Comparative effectiveness and safety of omidubicel versus other current allogeneic hematopoietic stem cell donor sources using network meta-analysis

Smitha Sivaraman[1], Shruti Nambiar[2], Ronit Simantov[1], Rocio Manghani[1], Yuan Yuan[2], Jeffrey R. Skaar[2]
[1]Gamida Cell Ltd., Boston, MA, USA; [2]Trinity Life Sciences, Waltham, MA, USA

BACKGROUND

- Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially curative procedure for a variety of hematologic malignancies [1]
- The number of allo-HSCTs each year in the United States (US) has increased from approximately 8,000 in 2013 to more than 9,000 in 2018 [2,3]
- Donor sources for allo-HSCTs may include matched related donors (MRD), matched unrelated donors (MUD), mismatched unrelated donors (MMUD), unrelated donors (UD) that can either be matched or mismatched, half-matched/haploidentical donors (Haplo), and umbilical cord blood (UCB). Among these different modalities, MRDs are the most preferred due to better compatibility [i.e., lower incidence of graft-versus-host-disease (GVHD)] and ease of access to donor, though the donor needs to be appropriate (e.g., right age, absence of comorbidities, etc.) [4]
- Only 15-30% patients find suitable MRDs, and many patients may not find a suitable donor of any type [1]. Sometimes, even if a suitable donor is identified, they may not be readily available for sample collection when needed [5]
- Non-MRD donor sources are associated with multiple limitations, including increased risk of GVHD, slow immune reconstitution, and lack of donors for minority populations; there is no clear indication of superior clinical benefit associated with any non-MRD allo-HSCT donor source [6-9]
- Omidubicel is an advanced cell therapy for allo-HSCT with nicotinamide-based proprietary technology that creates a high number of functionally optimized cells with improved migration, homing, and engraftment. It was studied in two clinical trials in patients with hematologic malignancies who required an allo-HSCT and did not have a suitable donor available [10,11]. Omidubicel can be matched more easily in diverse patients than other sources like MRD, as reflected in the clinical trial populations
- In both Phase 2 (NCT01221857) and Phase 3 (NCT02730299) clinical trials comparing omidubicel vs. standard UCB, omidubicel was associated with statistically significantly improved time to neutrophil engraftment, prompt immune reconstitution, fewer days in hospital, and a reduced rate of serious infections [10,11]
- There are no clinical studies directly evaluating the efficacy and safety of omidubicel compared to non-UCB allo-HSCT donor sources

OBJECTIVE

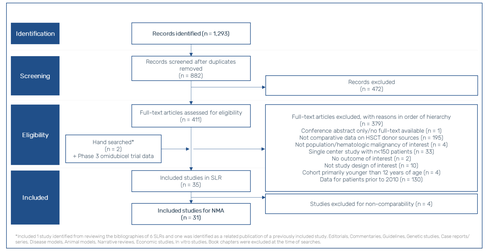
- To conduct a systematic literature review and network meta-analysis (NMA) to evaluate the comparative efficacy and safety of omidubicel versus all currently available allo-HSCT donor sources, including MRD, MUD, MMUD, UD, Haplo, and UCB

METHODS

- A systematic literature review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines
- Searches were conducted in PubMed and Embase for publications from 2010 to February 2021 using relevant medical subject headings and free text terms to identify randomized controlled or observational studies comparing allo-HSCT donor sources used in any hematological malignancies
  - Bibliographies of previously published systematic reviews were also examined to ensure full capture of clinical studies that were not identified in the primary search
- Titles and abstracts were screened by multiple researchers, and subsequently, full-text articles were screened by two, independent researchers for relevance based on pre-determined eligibility criteria
  - Studies were required to include comparison(s) of two or more allo-HSCT donor sources with each other and evaluate at least one of the following outcomes of interest: overall survival (OS), non-relapse mortality (NRM), infections, time to neutrophil engraftment, time to platelet engraftment, acute GVHD, chronic GVHD, or other adverse events
  - UD arm included studies that combined matched and mismatched unrelated donors as a single group
  - Exclusion criteria are highlighted in the PRISMA flow diagram (Figure 1)
- Data from the Phase 3 clinical trial of omidubicel were available on file and provided by the study sponsor for inclusion into the study [11]
- A formal feasibility assessment was conducted to establish the parameters and outcomes available for a network meta-analysis (NMA) comparing omidubicel with all other allo-HSCT donor sources, including potential sources of heterogeneity
  - OS, NRM, acute GVHD, and chronic GVHD were determined to be feasible for analysis in the NMA
  - Base case analyses included the following analyses: OS at 6 months, OS at 1 year, OS at 2 years, NRM at 1 year, NRM at 2 years, acute GVHD at any time point, chronic GVHD at any time point
- A Bayesian random-effects NMA was conducted using the R 'pcnetmeta' package
  - Model convergence was evaluated through the Markov Chain Monte Carlo (MCMC) simulation
  - The pooled effect estimates for all outcomes that were feasible for analysis were presented as odds ratios (OR) and 95% credible intervals (CrI)

RESULTS

FIGURE 1. PRISMA FLOW DIAGRAM



- The systematic literature identified 31 studies including the published Phase 2 omidubicel clinical trial data
- Five of the included studies were multicenter, international studies, and almost half of the remaining studies were in sites in Asia
- Across all included studies (and the omidubicel clinical trials), the total number of patients was 59,499, with patient ages ranging from 2-74 years

FIGURE 2. STUDY DESIGN AND SAMPLE SIZE RANGES OF INCLUDED STUDIES

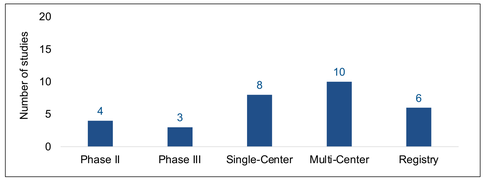
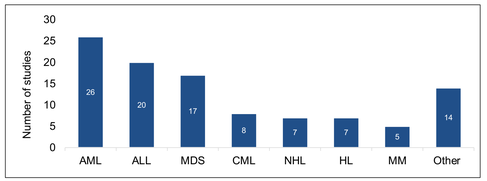
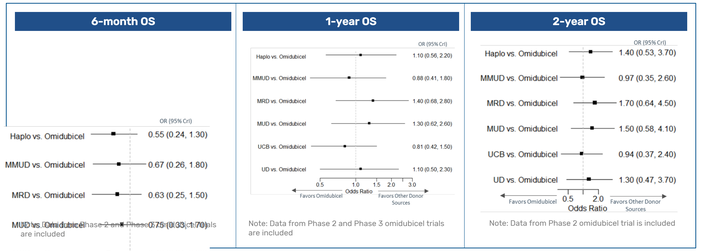


FIGURE 3. TYPES OF HEMATOLOGIC MALIGNANCIES IN INCLUDED STUDIES



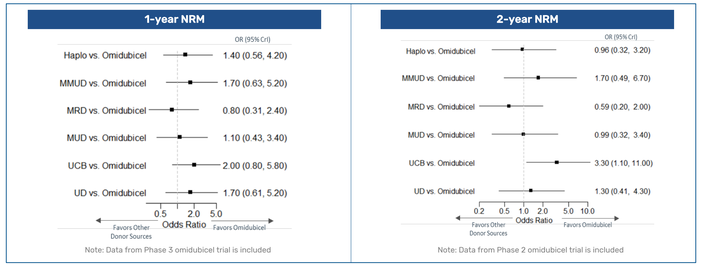
- The majority of included studies were observational in nature (74%), and the remaining studies were Phase 2 or 3 clinical trials comparing different donor sources (Figure 2)
- Although most studies included patients with different types of hematologic malignancies, studies including patients with acute myeloid leukemia or acute lymphocytic leukemia were highly represented (Figure 3)
  - Notably, the omidubicel phase III clinical trial was also comprised mostly of patients with acute myeloid leukemia or acute lymphocytic leukemia

FIGURE 4. FOREST PLOTS FOR POOLED EFFECT ESTIMATES FOR OS AT DIFFERENT TIMEPOINTS



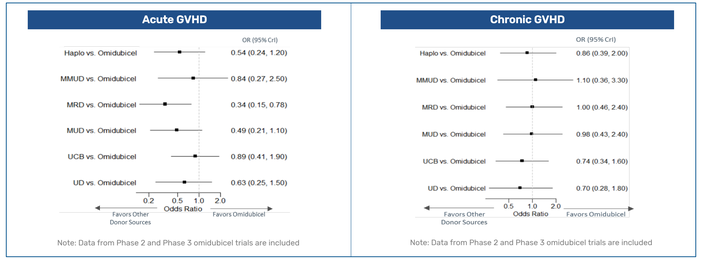
- Omidubicel demonstrated statistically improved or equivalent OS at all time points examined versus all other donor sources
  - At 6 months, omidubicel showed statistically significant improvement over standard UCB in OS
  - At the 1- and 2-year timepoints, OS with omidubicel was comparable with other donor sources

FIGURE 5. FOREST PLOTS FOR POOLED EFFECT ESTIMATES FOR NRM AT DIFFERENT TIMEPOINTS



- Omidubicel demonstrated statistically improved or equivalent NRM at all time points examined versus all other donor sources
  - At 2 years, omidubicel showed statistically significant improvement in NRM over standard UCB

FIGURE 6. FOREST PLOTS FOR POOLED EFFECT ESTIMATES FOR GVHD



- Omidubicel demonstrated statistically equivalent rates of acute GVHD versus all other donor sources except for MRD
- Omidubicel demonstrated statistically equivalent rates of chronic GVHD versus all other donor sources

LIMITATIONS

- The data analyzed were dependent upon the available published data (i.e., outcomes reported, sample sizes, patient demographics/characteristics, quality of data, etc.)
- As indicated by wide credible intervals of the pooled effect estimates, there was substantial heterogeneity across the included studies that could result from inherent differences in study designs and populations that could not be adjusted for adequately in the NMA
  - However, despite the heterogeneity, omidubicel shows statistical equivalence (i.e., non-inferiority) or superiority
- When necessary due to insufficient follow-up periods , some estimates were extracted from Kaplan-Meier curve extrapolations as opposed to observed event rates
  - Evolving data from the omidubicel Phase 3 trial was included, and longer-term endpoints have the potential to change as the data mature
- The examination of multiple safety and tolerability outcomes was not possible due to insufficient capture with retrospective studies using data sources such as patient registries

CONCLUSIONS

- In this NMA, omidubicel was demonstrated to be statistically equivalent to other donor sources in efficacy (i.e., OS, NRM) and safety (i.e., acute GVHD, and chronic GVHD)
  - Previously, omidubicel was only compared directly to UCB in the clinical trial program, and this study is the first comparing omidubicel to other donor sources
  - Omidubicel was also demonstrated to have statistically significant improvement in OS at 6 months and reduced risk of NRM at 2 years compared to standard UCB
- The clinical equivalence of omidubicel to other donor sources supports its broad use in patients with hematological malignancies without concerns of lower efficacy or increased safety issues
  - Omidubicel's comparable efficacy and safety also makes it an option for patients who lack suitable donors but need an allo-HSCT
- The ability to use omidubicel in place of other donor sources has the potential to decrease delays in transplants associated with searches for acceptable donor sources, which may positively impact patients' chances of survival

REFERENCES

1. Gyurkocza, B., A. Rezvani, and R.F. Storb, Allogeneic hematopoietic cell transplantation: the state of the art. Expert Rev Hematol, 2010. 3(3): p. 285–99.
2. Besse, K.L., et al., Estimating demand and unmet need for allogeneic hematopoietic cell transplantation in the United States using geographic information systems. J Oncol Pract, 2015. 11(2): p. e120-30.
3. D'Souza, A., et al., Current Use of and Trends in Hematopoietic Cell Transplantation in the United States. Biol Blood Marrow Transplant, 2020. 26(8): p. e177–e182.
4. Tiercy, J.M., How to select the best available related or unrelated donor of hematopoietic stem cells? Haematologica, 2016. 101(6): p. 680–7.
5. National Marrow Donor Program, National Marrow Donor Program /Be The Match® 24th Edition Standards And Glossary. 2018.
6. Ballen, K.K., et al., Selection of optimal alternative graft source: mismatched unrelated donor, umbilical cord blood, or haploidentical transplant. Blood, 2012. 119(9): p. 1972–80.
7. Lozano Cerrada, S., S.Y. Altaf, and E. Olavarria, Allogeneic stem cell transplantation from unrelated donors in acute leukaemia. Curr Opin Oncol, 2018. 30(6): p. 418–424.
8. Piemontese, S., et al., A comparison between allogeneic stem cell transplantation from unmanipulated haploidentical and unrelated donors in acute leukemia. J Hematol Oncol, 2017. 10(1): p. 24.
9. Solh, M., Haploidentical vs cord blood transplantation for adults with acute myelogenous leukemia. World J Stem Cells, 2014. 6(4): p. 371–9.
10. Anand, S., et al., Transplantation of Ex Vivo Expanded Umbilical Cord Blood (NiCord) Decreases Early Infection and Hospitalization. Biol Blood Marrow Transplant, 2017. 23(7): p. 1151–1157.
11. Horwitz, M.E., et al., Omidubicel Versus Standard Myeloablative Umbilical Cord Blood Transplantation: Results of a Phase III Randomized Study. Blood, 2021.

DISCLOSURES AND ACKNOWLEDGEMENTS

This study was sponsored by Gamida Cell, Ltd. SS, RS, and RM are employees of Gamida Cell, Ltd. YY and JRS are employees of Trinity Life Sciences, which was contracted for these analyses by Gamida Cell, Ltd. JRS also holds equity in Trinity Life Sciences. SN was also an employee of Trinity Life Sciences at the time of completion of this study.

The authors wish to acknowledge Ben Miao, Nicole Hilton, Mahfuza Ahmed, and Marie Ng for their support in execution of the systematic review.

PRESENTED AT AMCP NEXUS 2021 · OCTOBER 18-21, 2021, DENVER, CO, USA