COMPARATIVE EFFECTIVENESS OF ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATIONS (ALLO-HSCT) FROM DIFFERENT GRAFT SOURCES IN ACUTE MYELOID LEUKEMIA (AML): RESULTS OF A SYSTEMATIC LITERATURE REVIEW

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BACKGROUND

- Acute myeloid leukemia (AML) is a rare disease with an annual incidence of cases 4.1 per 100,000 individuals in the US [1].
- AML patients have a poor prognosis, as demonstrated by a 5-year survival rate of 27.4%, experience reduced quality of life and produce significant costs levying a heavy economic burden on the healthcare system [2].
- Allogeneic hematopoietic stem cell transplantation (HSCT) is a potentially curative treatment option with a total of 7,463 allo-HSCTs performed in the US in 2015 across all indications including AML [3].
- The success of allo-HSCT is heavily influenced by the human leukocyte antigen (HLA) matching between the donor and the recipient and poor HLA matching can lead to serious complications such as graft-versus-host disease or death.
- In the US, the probability of finding an 8/8 HLA-matched adult donor varies from 19-75% based on patient characteristics such as race [4].
- As numerous patients do not have HLA-matched donors, there is a significant use of mismatched grafts derived from peripheral blood (PB), bone marrow (BM) or umbilical cord blood (UCB).
- There is limited published data concerning the comparative effectiveness of allo-HSCT across different graft sources.

OBJECTIVES

We reviewed published clinical evidence to compare outcomes of mismatched (<8/8 HLA) allo-HSCT in AML patients.

RESULTS

- A total of 1,335 records were reviewed and 10 satisfied inclusion criteria (5 allo-HSCT, 1 unmanipulated UCB, 4 manipulated UCB).
- No relevant studies were identified in the congress search.
- Baseline characteristics were generally comparable between studies.
- Patients receiving unmanipulated UCB took longer to achieve neutrophil engraftment (defined as ≥0.5x10^9/L); 36 versus 18 days compared to UM171-expanded UCB and ranged from 12-19 days with PB-based grafts.
- OS at 12 months was 63.7% with unmanipulated UCB compared with 95.3% with UM171-expanded UCB and ranged from 41.0-49.8% with other mismatched graft sources (Figure 2).
- OS at 24 months was 83.2%, 50.8% and 57.0% with UM171-expanded UCB, NiCord®-expanded UCB and unmmanipulated UCB, respectively, and ranged from 28.0-39.1% with other mismatched graft sources (Figure 3).
- PFS at 12 months was 76.8% for UM171-expanded UCB, 55.0% with unmanipulated UCB and 34.0% with PB-based grafts (Figure 4).
- Relapse at 24 months was 18.0% with UM171-expanded UCB, 27.0% with NiCord®-expanded UCB and ranged from 31.0-39.0% with other graft sources (Figure 5).
- Approximately half of all AML patients (excluding those treated with UM171-expanded UCB) from the identified studies died within 1 year, demonstrating a significant clinical burden and unmet need in the population without a HLA-matched graft donor.
- Patients treated with UM171-expanded UCB were shown to experience better outcomes (OS, PFS, relapse) relative to patients treated with alternative UCB and mismatched allo-HSCT graft sources.
- Better outcomes with mismatched graft sources may improve access of allo-HSCT to patients who would have otherwise been considered ineligible due to poor pre-transplant condition, ultimately giving this subset of patients a chance at potentially curative treatment, however, the analysis in this subpopulation warrants further investigation.

CONCLUSIONS

- Our review demonstrates that for AML patients without matched stem cells, UM171-expanded UCB may offer improved outcomes relative to other sources.
- Additionally, there is a significant unmet need demonstrated by the resulting limited survival where approximately half of AML patients treated mismatched allo-HSCT graft sources die within a year.

LIMITATIONS

- One limitation associated with naïve comparisons is the lack of statistical adjustment for potentially heterogenous patient populations and confounding variables.
- As such, statistical adjustment for baseline characteristics is required to further validate the findings of the naïve comparisons.

MATERIALS & METHODS

- A systematic literature review was performed in November of 2018 following the Preferred Reporting Item for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, using the Population, Interventions, Comparators, Outcomes and Study Design (PICOS) criteria and following the Cochrane Collaboration Guidelines for Systematic Reviews.
- Studies were identified based on a systematic search using key biomedical literature databases: EMBASE®, MEDLINE® and Cochrane.
- The search was limited to records published 2008-2018 and all non-English studies were excluded.
- The patient population included any adult patients with AML.
- The interventions included mismatched allo-HSCT (HLA-matching <8/8), as well as UCB transplants.
- Outcomes such as overall survival (OS), progression-free survival (PFS), time to neutrophil engraftment and relapse were collected.
- Prospective interventional studies, such as randomized clinical trials and single-arm trials, were collected for the subsequent screening phase.
- All other study types, such as retrospective real-world evidence, non-interventional studies, case series, case studies and case reports, were excluded in an attempt to limit the amount of bias in cross-study comparisons.
- Relevant congress abstracts (ASH, ASCO) published between 2015-2018 were also reviewed.
- Two independent reviewers screened all citations and full-text articles using PICOS-based criteria; inconsistencies were resolved through roundtable discussion with a third analyst.
- Survival curves were digitized to obtain additional numerical data, when available.
- Data were extracted into a predefined template for meta-analysis and summarized using the PRISMA flow diagram (Figure 1).

REFERENCES