PMU145

Systematic review of paediatric allogeneic haematopoietic stem cell transplantation: donor availability, quality of life and economic implications

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BACKGROUND

- Allogeneic haematopoietic stem cell transplantation (allo-HSCT) is indicated for various paediatric malignant and non-malignant haematological disorders. In the absence of a matched sibling donor (MSD), choice of alternative donor source and grafting technique is influenced by multiple clinical and non-clinical factors
- To our knowledge, there are no systematic reviews of paediatric allo-HSCT techniques in current practice
- The objective of this study was to systematically review published reports of clinical outcomes, health-related quality of life (HRQoL), donor availability, and economic factors in paediatric allo-HSCT

METHODS

A systematic search of the literature was conducted to identify real-world evidence relating to paediatric allo-HSCT that met inclusion criteria as detailed in the PICOS elements (Table 1). Searches of PubMed, Embase, and Evidence Based Medicine Reviews through Ovid were supplemented with hand-searches of key grey literature.

Table 1. PICOS elements

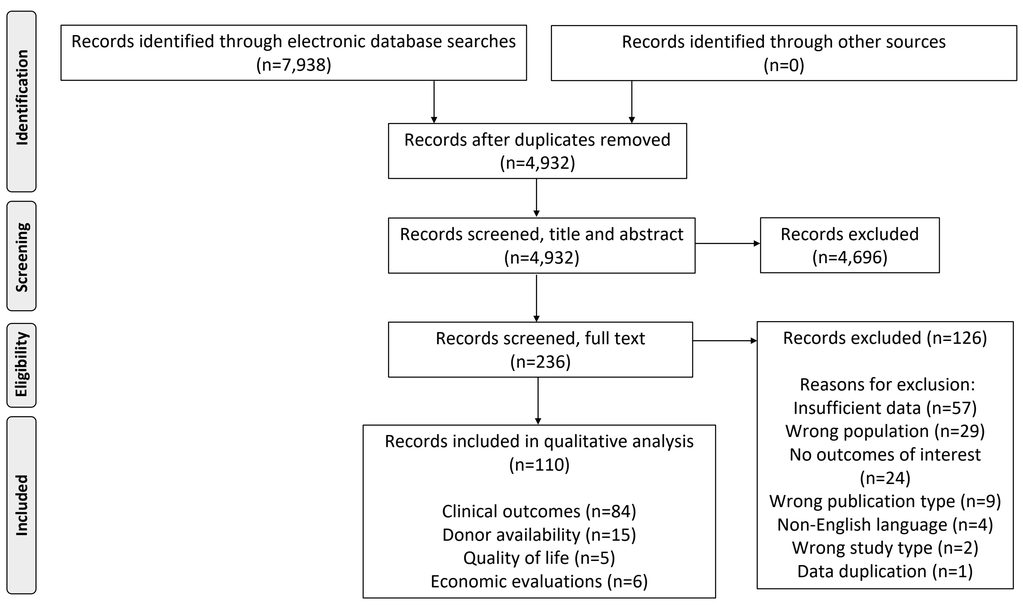
Population	Paediatric[a] allo-HSCT patients[b]	
Intervention	Allo-HSCT: all donor types, all stem cell sources, all preparatory and prophylaxis regimens	
Comparator	No specified comparator	
Outcomes	Clinical	Survival, relapse, GvHD, infection, haematological recovery
	HRQoL	Utilities, patient-reported outcomes, factors associated with HRQoL
	Donor availability	HLA match rates, time to graft acquisition, treatment rates
	Economic data	Budget impact, resource utilisation, cost-effectiveness
Study design	Clinical trials, cohort studies, case-control studies, case series, economic evaluations, costing studies	
Date	January 1 2009 to February 25, 2019	
Language	English	
Country	No restriction	

Key: allo-HSCT, allogeneic haematopoietic stem cell transplant; GvHD, graft-versus-host disease; HLA, human leukocyte antigen; HRQoL, health-related quality of life; [a] As defined by author; [b] Studies reporting on adult allo-HSCT patients were included when ≤15 studies per outcome category (e.g., HRQoL) were identified

RESULTS

- Of 4,932 unique records screened, 110 met the inclusion criteria (Figure 1)
- We report the analysis of the HRQoL, donor availability, and economic sub-sets (26 included records):
  - 17 (65%) were full text articles (marked yellow) and 9 (35%) were abstracts (marked blue)
  - Half (12/26, 46%) were conducted in The Americas, 31% of studies in Europe, 19% in Asia, and 3.8% in Australia

Figure 1. PRISMA flow



Note: Final inclusion numbers updated from abstract

Among included HRQoL reports (Table 2):

- Only 3 studies were specific to paediatric allo-HSCT patients[1–3]
- Post-HSCT HRQoL outcomes varied between studies and domains
- Generalisable themes were difficult to draw
- Long-term HRQoL was not significantly affected by human leukocyte antigen (HLA) disparity[3]
- Infection and graft-versus-host disease (GvHD) were noted as significant HRQoL drivers[2,4,5]
- HRQoL tools were:
  - All validated
  - All self-reported, except 2 completed by caregivers/parent proxy[1, 3]
  - Not specific to transplantation, except FACT-BMT (Functional Assessment of Cancer Therapy – Bone Marrow Transplantation scale) used for a study of adult patients[4]

Table 2. Key characteristics of HRQoL studies

Authors, year	Country	No. of patients	Age	Background disease status	Donor types	HRQoL measure
Bhatia, 2015[1]	USA	23	Paediatric	Non-malignant	MSD, UCB	PedsQoL v4.0
Kisch, 2012[4]	Sweden	75	Adult	Mixed	MSD, URD[a], haplo	FACT-BMT, FACIT-Sp
Mo, 2012[5]	China	350	Adult	Mixed	MSD, haplo	SF-36
Oberg, 2012[2]	USA	80	Paediatric	Mixed	MUD, MRD[b]	PedsQoL v4.0
Visentin, 2016[3]	France	341	Paediatric	Malignant	MSD, MUD, UCB	VSPA, VSPAe, VSP-Ap, SF-36

Key: FACIT-Sp, Functional Assessment of Chronic Illness – Spiritual Wellbeing subscale; FACT-BMT, Functional Assessment of Cancer Therapy – Bone Marrow Transplantation scale; haplo, haploidentical; MUD, matched unrelated donor; MSD, matched sibling donor; MRD, matched related donor; PedsQoL, Pediatric Quality of Life Inventory; SF-36, Short Form (36) Health Survey; UCB, umbilical cord blood; URD, unrelated donor; VSPA, Vécu et Santé Perçue de l'Adolescent (Quality of Life of Adolescents); VSPAe, Vécu et Santé Perçue de l'Enfant (Quality of Life of Children); VSP-Ap, Vécu et Santé Perçue de l'Enfant et de l'Adolescent rapportés par les parents (Quality of Life of Children and Adolescents, as reported by parents); [a] HLA match unspecified; [b] Relationship unspecified; Full text articles labelled in yellow

Among included reports on donor availability (Table 3):

- Finding an MSD:
  - depends on family size, age, race/ethnicity[6–9]
  - is less likely for younger patients[7, 9]
- Finding a matched unrelated donor (MUD) and receiving transplant:
  - depends on race, haplotype frequency, disease status, and time between diagnosis and start of donor search[10,11]
  - Non-white patients are significantly less likely to have suitable living unrelated donors than white[12,13]
  - Age and sex influence selection of donors[13]
- There is high unmet demand for allo-HSCTs from sources other than unrelated donors[6,7,9,14–16]

Table 3. Key characteristics of donor availability studies

Authors, year (Full text/Abstract)	Country	No. of patients	Age, median years (range)	Background disease status	Outcomes reported: Factors affecting likelihood of donor selection	Outcomes reported: Length of donor search	Outcomes reported: Centre experience of HSCT
Acevedo, 2018[6]	USA	161	24 (3.8–68)	Non-malignant	✓	✓	✗
Besse, 2016[7]	USA	>26,000	NR (0–80)	NR	✓	✗	✗
Ciurea, 2018[10]	USA	242	58 (9–80)	Malignant	✓	✓	✓
DiLabio, 2015[12]	Canada	252	7 (2–12)	Mixed	✓	✗	✗
Greco-Stewart, 2017[13]	Canada	332	NR	NR	✓	✗	✓
Hussein, 2012[8]	Jordan	341	9 (0.3–32)	Non-malignant	✓	✗	✓
Jawdat, 2009[9]	S. Arabia	421	(0–>20)	NR	✓	✗	✓
Justus, 2015[14]	USA	85	10.6 (1–21)	Non-malignant	✓	✗	✓
Kawashima, 2018[15]	Japan	340	NR (15–68)	Malignant	✓	✓	✗
Nestorowicz, 2015[17]	Poland	418	NR	Mixed	✓	✓	✓
Pérez, 2016[18]	Spain	263	46 (0.4–69)	Mixed	✓	✓	✓
Radojska, 2016[19]	Germany	191	NR	NR	✓	✗	✓
Rosenmayr, 2011[11]	Austria	1586	Mixed	Mixed	✓	✓	✗
Schetelig, 2011[16]	Germany	852	NR	NR	✓	✓	✓
Switzer, 2013[20]	USA	83[a]	NR (18–60)[a]	NA	✓	✗	✗

Key: NA, not applicable; NR, not reported; [a] Numbers correlate to donor registrants; Full text articles labelled in yellow, abstracts in blue

Among included economic reports (Table 4):

- Only three studies were specific to paediatric allo-HSCT patients[21–23]
- Cost burden was higher among patients developing GvHD due to greater clinical complications and additional cost of treatment[24]
- Length of hospital stay was:
  - A major driver of early post-HSCT costs[21]
  - Reported to vary by graft source (e.g. longer for umbilical cord blood [UCB] than for MUD)[21, 25]
- MUD was associated with:
  - Higher total healthcare and resource utilisation costs than MSD (paediatric patients)[21]
  - Higher incremental costs per quality-adjusted life year (QALY) when indirectly compared with MRD vs transfusion chelation in thalassaemia[22]

Table 4. Key characteristics of economic studies

Authors, year	Country	No. of patients	Age	Donor types	Background disease status	Costing perspective	Study types
Arnold, 2016[21]	USA	797	Paediatric	MSD, MUD, MMUD, UCB	Malignant	Healthcare	Economic evaluation
Ballen, 2014[25]	USA	1577	Mixed	UCB, MUD, MMUD	Malignant	Healthcare	Retrospective study
Foley, 2017[26]	USA	269	Adult	MRD[a], URD[b], haplo, UCB	NR	Societal	Retrospective study
John, 2018[22]	India	1000[c]	Paediatric	MRD[a], MUD	Non-malignant	Societal	Economic evaluation
Lupo-Stanghellini, 2017[24]	Italy	15	NR	URD[b], MSD, haplo	Malignant[d]	Healthcare	Retrospective study
Van Sambeek, 2018[23]	Australia	NA	Paediatric	Haplo, MUD	NR	Healthcare	Economic evaluation

Key: haplo, haploidentical; MMUD, mismatched unrelated donor; MRD, matched related donor; MSD, matched sibling donor; MUD, matched unrelated donor; NA, not applicable; NR, not reported; UCB, umbilical cord blood; URD, unrelated donor; [a] Relationship unspecified; [b] HLA match unspecified; [c] Hypothetical cohort used in model; [d] Majority; Full text articles labelled in yellow, abstracts in blue

CONCLUSIONS

- The scarcity and heterogeneity of published literature on donor availability, HRQoL and economic evaluations relating to paediatric allo-HSCT is striking considering the complexity of decision-making, albeit in a relatively small paediatric patient population
- Nevertheless, the handful of included studies suggest that
  - locating unrelated donors is challenging, especially for mixed/non-Caucasian ethnic groups
  - GvHD is a driver for poor HRQoL outcomes and increased economic burden
- Interpretation of available evidence is confounded by wide variation in practices regardless of donor source – e.g., pre-/post-HSCT treatments, definition of donor match
- Further research is needed to generate high quality evidence quantifying the relative merits of paediatric allo-HSCT treatment choices

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