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Risk Factors for Transplant Outcomes in Children and Adolescents with Non-Malignant Diseases Following Allogeneic Hematopoietic Stem Cell Transplantation

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1 Agnieszka Zaucha-Prażmo
BDE 2 Elżbieta Sadurska
BDE 3 Anna Pieczonka
BD 4 Jolanta Goździk
BD 5 Robert Dębski
BDE 1 Katarzyna Drabko
DE 1 Joanna Zawitkowska
BDF 1 Monika Lejman
DE 3 Jacek Wachowiak
ADE 5 Jan Styczyński
ADE 1 Jerzy R. Kowalczyk

1 Department of Pediatric Hematology, Oncology and Transplantology, Medical University of Lublin, University Children's Hospital, Lublin, Poland
2 Department of Pediatric Cardiology, Medical University of Lublin, University Children's Hospital, Lublin, Poland
3 Department of Pediatric Oncology, Hematology, and Transplantology, University of Medical Sciences, Poznań, Poland
4 Department of Transplantation, Clinical Immunology and Transplantation Polish-American Institute of Pediatrics, Jagiellonian University Medical College, Children's University Hospital, Cracow, Poland
5 Department of Pediatric Hematology and Oncology, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland

Corresponding Author: Agnieszka Zaucha-Prażmo, e-mail: a.prazmo@umlub.pl, a.zauchaprazmo@gmail.com
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Background: The objective of this study was the analysis of transplant outcomes and survival in children treated with allogeneic hematopoietic cell transplantation (alloHCT) for non-malignant disorders, with a focus on risk factor analysis of transplant-related mortality (TRM).

Material/Methods: The treatment outcome was analyzed retrospectively in 10 consecutive years in 4 pediatric transplant centers in Poland. To compare the outcomes, patient data were analyzed according to the diagnosis, age at transplant, donor type, stem cell source, conditioning regimens, transplanted CD34+ cells dose, and pediatric TRM score.

Results: From 183 analyzed patients, 27 (14.8%) died, all of them due to transplant-related complications. TRM occurred more frequently in matched unrelated donor (MUD) transplant recipients *vs.* matched sibling donor (MSD) transplant recipients (p=0.02); in peripheral blood (PB) recipients *vs.* bone marrow (BM) recipients (p=0.004); and in patients receiving >5×10^6/kg CD34+ cells (p<0.0001). OS differed significantly according to underlying disease comparing to other diagnoses. Lower survival was found in patients transplanted from MUD (p=0.02). OS was higher in patients receiving BM (p=0.001) and in those receiving ≤5×10^6/kg CD34+ cells (p<0.001). Multivariate analysis showed lower probability of TRM in BM recipients (p=0.04). The probability of TRM was higher in SCID patients (p=0.02) and in patients receiving >5×10^6/kg CD34+ cells (p=0.0001).

Conclusions: Underlying disease, stem cell source, and CD34+ dose higher than 5×10^6/kg were the most important risk factors for TRM, and they all affected OS.

MeSH Keywords: Adolescent • Child • Hematopoietic Stem Cell Transplantation • Risk Factors

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Background

Indications for allogeneic hematopoietic cell transplantation (alloHCT) for non-malignant disorders in pediatric patients are based on EBMT recommendations, which are published on a regular basis [1–4]. In severe aplastic anemia (SAA), alloHCT from a matched sibling donor (MSD) is a treatment of choice; matched unrelated donor (MUD) HCT is performed when previous immunosuppressive therapy has failed. In inherited bone marrow failure syndromes (IBMFS) such as Fanconi anemia (FA), Diamond-Blackfan anemia (DBA), hematologic manifestation of the disease and cancer predisposition can be cured with HCT. Primary immunodeficiencies are a heterogenous group of disorders. In severe combined immunodeficiency syndrome (SCID), alloHCT is the only feasible treatment. In other primary immunodeficiencies (PID), including Wiscott-Aldrich syndrome (WAS), autoimmune lymphoproliferative syndrome (ALPS), hemophagocytic lymphohistiocytosis (HLH), or DNA breakage repair disorders, and in some inborn errors of metabolism (IEM) such as mucopolysaccharidosis type I, or osteopetrosis, alloHCT may be effective and is recommended [1–4].

Indications for allogeneic HCT in non-malignant hematopoietic disorders in children are expanding because of improving results of HCT over the last decades [1–5]. Successful outcome of alloHCT may be influenced by various factors that can increase the incidence of serious procedure-related complications, and thereby affect overall survival. They may be related not only to transplant procedure, but also to the condition of the patient before HCT. Some children may have had previous infections or toxicities connected to the treatment before HCT, even if they do not have accompanying chronic diseases or organ dysfunctions [6–10]. The realistic estimation of survival probability after HCT compared to other treatment modalities may be helpful in the final decision of treatment method. The question is whether the transplant-related mortality (TRM) can be accurately predicted based on a risk assessment before HCT.

The aim of this study was to analyze risk factors for TRM to assess their effect on transplant outcome in children with non-malignant disorders, undergoing allogeneic HCT.

Design of the study

Treatment outcome was analyzed in a retrospective study on children with non-malignant diseases treated with allogeneic HCT in 10 consecutive years from 2006 to 2015 in 4 pediatric centers in Poland. Data were retrieved from institutional databases. All patients gave their consent for the individual transplant center to store the data. Approval for the study was given by the institutional committee. This study was a retrospective analysis of patient data. Given the retrospective nature of the study, the requirement for obtaining informed consent from each patient was waived.

To compare the outcome, patients were analyzed according to the diagnosis, age at transplant, donor type, stem cell source, conditioning regimens, transplanted CD34+ cells dose, and pediatric TRM score. This has been published by Matthes-Martin et al. and is defined as a sum of points depending on 3 risk factors: donor type, age at transplantation, and disease status (0 points for matched sibling donor, age ≤10 years at the time of HCT, and all non-malignant diseases; 1 point for alternative donors, age >10 years, and advanced malignant disease at the time of HCT) [5]. In non-malignant patients, such stratification results in 3 risk groups: low risk (score 0), intermediate risk (score 1), and high risk (score 3).

Material and Methods

All consecutive patients with non-malignant diseases treated with first allogeneic HCT over a 10-year period in 4 pediatric transplant departments in Poland were enrolled for analysis. Medical records of 183 children were analyzed. There were 112 boys (61.2%) and 71 girls (38.8%).

Transplant characteristics

Matched donors were specified as 10/10 and 9/10 match by HLA high-resolution typing. Conditioning regimens were in line with current EBMT recommendations [4]. Conditioning was considered myeloablative (MAC) when full-dose busulfan (4 mg/kg/day for 4 days) was used, and it was considered non-myeloablative (non-MAC) when fludarabine, cyclophosphamide, low-dose TBI (1-2 Gy), low-dose busulfan (1 mg/kg/day for 2–4 days), or ATG alone were used. Reduced-toxicity conditioning (RTC) was based on treosulfan (10–14 g/m^2 for 3 days, age-dependent). The diagnosis and management of GvHD, as well as supportive care and infections prophylaxis, were provided according to EBMT guidelines and center procedures.

Definitions

The main outcomes analyzed were transplant-related mortality (TRM) and overall survival (OS). TRM was defined as death resulting from any cause connected with transplant procedure. For estimating OS, death from any cause was considered an event. Surviving patients were censored at last follow-up.

Statistical methods

Statistical analysis was performed using SPSS IBM Statistics (Version 24) and R package version 3.4.1 (survival library version 2.41-3). Non-parametric tests used were Pearson's chi-square

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Table 1. Patient characteristics.

Diagnosis n (%)	Total	SAA n(%)	PID n (%)	IBMFS n (%)	CGD n (%)	SCID n (%)	IEM n (%)
	n=183 (100)	70 (38.3)	38 (20.8)	25 (13.7)	21 (11.5)	18 (9.8)	11 (6.0)
Age							
≤10 years	110 (60.1)	20 (28.6)	30 (78.9)	19 (76.0)	14 (66.7)	18 (100)	9 (81.8)
>10 years	73 (39.9)	50 (71.4)	8 (21.1)	6 (24.0)	7 (33.3)	0 (0.0)	2 (18.2)
Donor type							
MUD	125 (68.3)	40 (57.1)	26 (68.4)	22 (88.0)	18 85.7)	11 (61.1)	8 (72.7)
MSD	52 (28.4)	29 (41.5)	11 (28.9)	3 (12.0)	3 (14.3)	4 (22.2)	2 (18.2)
MMD	6 (3.3)	1 (1.4)	1 (2.7)	0 (0.0)	0 (0.0)	3 (16.7)	1 (9.1)
MMFD	5 (2.7)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	3 (16.7)	1 (9.1)
MMUD	1 (0.5)	0 (0.0)	1 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stem cell source							
BM	130 (71)	49 (70.0)	28 (73.7)	20 (80.0)	18 (85.7)	10 (55.6)	5 (45.5)
PB	48 (26.2)	21 (30.0)	7 (18.4)	5 (20.0)	3 (14.3)	8 (44.4)	4 (36.3)
CB	5 (2.7)	0 (0.0)	3 (7.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (18.2)
Stem cell dose							
>5×10⁶/kg	55 (30.0)	19 (27.1)	10 (26.3)	6 (24.0)	3 (14.3)	11 (61.1)	6 (54.5)
≤5×10⁶/kg	128 (70.0)	51 (72.9)	28 (73.7)	19 (76.0)	18 (85.7)	7 (38.9)	5 (45.5)
TRM score							
0	20 (10.9)	5 (7.1)	6 (15.8)	2 (8.0)	2 (9.5)	4 (22.2)	1 (9.1)
1	120 (65.6)	38 (54.3)	29 (76.3)	18 (72.0)	13 (61.9)	14 (77.8)	8 (72.7)
2	43 (23.5)	27 (38.6)	3 (7.9)	5 (20.0)	6 (28.6)	0 (0.0)	2 (18.2)

SAA – severe aplastic anaemia; PID – primary immune deficiency syndrome; IBMFS – inherited bone marrow failure syndrome; CGD – chronic granulomatous disease; IEM – inborn errors of metabolism; TRM – transplant related mortality; PB – peripheral blood, BM – bone marrow; CB – cord blood; MSD – matched sibling donor; MUD – matched unrelated donor; MMD – mismatched donor; MMFD – mis-matched family donor; MMUD – mis-matched unrelated donor; non-MAC – nonmyeloablative conditioning; MAC – myeloablative conditioning; RC – reduced toxicity conditioning.

test and the chi-square test with simulating p values, which are insensitive to small numbers, and the Kruskal-Wallis test was used for group comparison. OS was estimated using Kaplan-Meier method and log-rank tests. Multivariate analysis of OS was performed with a cause-specific proportional hazard model (Cox model). Statistical significance was considered $P<0.05$.

Results

Table 1 shows patient characteristics depending on age at transplant, donor type, stem cell source, conditioning type, stem cell dose, and TRM score. Detailed diagnoses of patients are presented in Table 2.

The median age of the analyzed patients was 7.8 years (range, 0.06–19.8). Median follow-up was 3.66 years (0.2–11.8 years). All of the SCID patients were younger than 10 years at time of HCT.

At the time of HCT, 6/18 (33.3%) SCID patients had an active infection: 1 had rotavirus infection, 1 had BCG-itis; 1 had interstitial pneumonia of unknown etiology; 1 had respiratory syncytial virus (RSV) pneumonia, candida infection, 1 had CMV, ADV, and norovirus infection, and 1 had CMV interstitial pneumonia. In 2 of these patients, sepsis occurred before transplantation and had already resolved before HCT.

Eighty-eight (48.0%) children received non-MAC, 57 (31.1%) received MAC, and 38 children received (20.8%) RTC. In 179 children (97.8%), cyclosporin was used as graft-versus host disease (GvHD) prophylaxis: alone (43 patients) or in combination with methotrexate (114 patients) or MMF (22 patients). Two patients received tacrolimus and 2 received MMF alone as GvHD prophylaxis. MUD transplant recipients received antithymocyte globulin (ATG) as T-cell depletion, and MMD transplant recipients received *ex-vivo* T-cell depleted grafts.

Transplant-related mortality

Depending on the donor type, TRM occurred more frequently in MUD and MMD HCT compared to MSD transplant recipients ($p=0.02$). TRM was more frequent in PB recipients compared to in BM recipients ($p=0.004$), and in patients who

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Table 2. Detailed diagnoses in analyzed patients.

Group of patients (n)	Detailed diagnoses	Numer of patients
All (183)		183
SAA (70)		70
PID (38)	Hemophagocytic lymphohistiocytosis (HLH)	17
	Wiscott-Aldrich syndrome (WAS)	9
	Hyper IgM syndrome	4
	Autoimmune lymphoproliferative syndrome (ALPS)	3
	Nijmegen Breakage syndrome (NBS)	3
	Common variable immunodeficiency (CVID)	1
	IL-10 receptor deficiency	1
IBMFS (25)	Fanconi anaemia	13
	Blackfan-Diamond anaemia	6
	Shwachman-Damond syndrome	3
	Congenital neutropenia	2
	Pure red cell aplasia	1
CGD (21)		21
SCID (18)	T (–), B (–), NK (+)	10
	Omenn syndrome	5
	T (–), B (+), NK (–)	3
IEM (11)	X-linked adrenolekodystrophy	6
	Osteopetrosis	4
	Mucopolisaccharidosis type 1	1

SAA – severe aplastic anaemia; PID – primary immunodeficiency; SCID – severe combined immunodeficiency; IBMFS – inherited bone marrow failure syndrome; CGD – chronic granulomatous disease; IEM – inborn errors of metabolism.

Table 3. Risk factors of transplant-related mortality.

Risk factor	All patients	Patients n	TRM n (%)		p-Value
		183	27	(14.8%)	
Diagnosis	SAA	70	8	(11.4%)	p=0.055
	PID	38	9	(27.9%)	
	IBMFS	25	2	(8.0%)	
	CGD	21	1	(4.8%)	
	SCID	18	6	(33.3%)	
	IEM	11	1	(9.1%)	
Age	≤10 years	110	16	(14.5%)	p=0.63
	>10 years	73	8	(11.0%)	
Donor type	MUD	125	24	(19.2%)	p=0.02
	MSD	52	2	(3.8%)	
	MMD	6	2	(33.3%)	
Stem cell source	BM	130	13	(9.2%)	p=0.004
	PB	48	14	(29.9%)	
	CB	5	0	(0.0%)	
Conditioning type	Non-MAC	88	13	(14.8%)	p=0.86
	MAC	57	7	(14.0%)	
	RTC	38	6	(16.7%)	
Stem cells dose	>5×10⁶/kg	55	17	(30.9%)	p<0.0001
	≤5×10⁶/kg	128	10	(7.9%)	
TRM score	0	20	1	(5.0%)	p=0.36
	1	120	19	(15.8%)	
	2	43	8	(18.6%)	

SAA – severe aplastic anaemia; PID – primary immune deficiency syndrome; IBMFS – inherited bone marrow failure syndrome; CGD – chronic granulomatous disease; IEM – inborn errors of metabolism; TRM – transplant related mortality; PB – peripheral blood, BM – bone marrow; CB – cord blood; MSD – matched sibling donor; MUD – matched unrelated donor; MMD – mis-matched donor; non-MAC – nonmyeloablative conditioning; MAC – myeloablative conditioning; RC – reduced toxicity conditioning.

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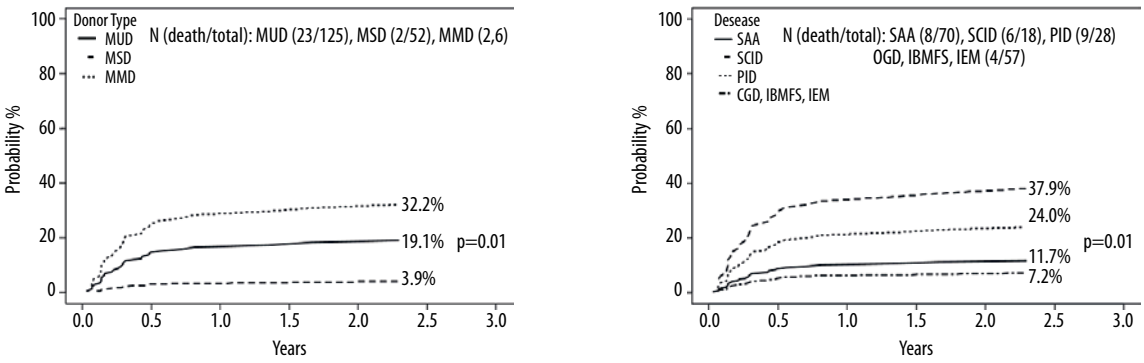

Figure 1. Prediction transplant-related mortality according to donor type and diagnosis. MUD – metched unrelated donor; MSD – metched related donor; MMD – mismatched donor; SAA – severe aplastic anaemia; PID – primary immune deficiency syndrome; IBMFS – inherited bone marrow failure syndrome; CGD – chronic granulomatous disease; IEM – inborn errors of methabolism.

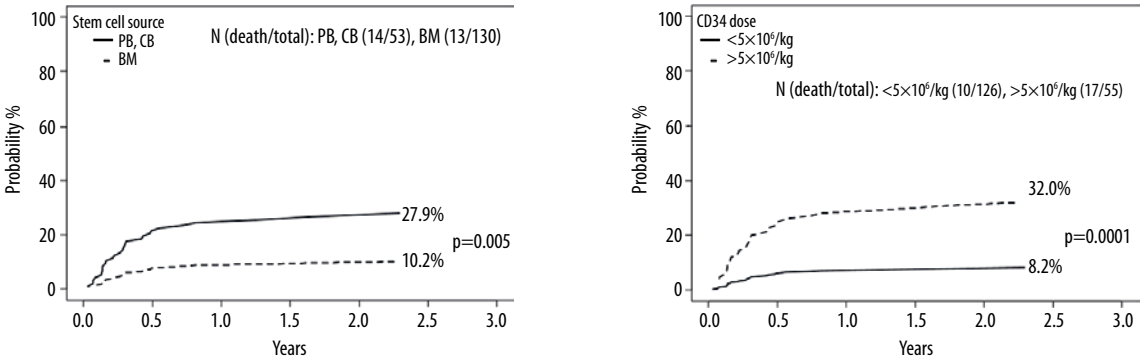

Figure 2. Prediction transplant-related mortality according to stem cel source and CD34+ cell dose. PB – peripheral blood; BM – bone marrow; CB – cord blood.

received >5×10⁶/kg CD34 in comparison to those who were given ≤5×10⁶/kg (p<0.0001).

TRM occurred more frequently in SCID patients compared to other diagnoses, but the difference was at the border of significance (p=0.055). SCID patients in most cases (61.1%) received >5×10⁶/kg CD34+ cells. There was no statistically significant difference in the occurrence of TRM depending on age at transplant, conditioning type, and pediatric TRM score. Risk factors for transplant-related mortality are shown in Table 3.

GvHD was diagnosed in 38 patients (20.8%): acute GvHD in 30 and chronic in 8. There was no statistically significant difference in acute and chronic GvHD occurrence depending on diagnosis, stem cell source, donor type, and CD34+ cells dose. Acute GvHD occurred more frequently in children age 10 years and younger at time of HCT: 4/110 (21.8%) children ≤10 years *vs.* 6/73 (8.2%) >10 years (p=0.01). None of the patients age >10 years developed cGvHD, and it was diagnosed in 8/110 children age ≤10 years (p=0.015).

Survival

Overall survival (OS) in the entire group of patients was 85% at the median observation time of 3.66 years, as well as at the maximum (11.23 years) observation time. OS differed significantly according to underlying disease, and was 95% in CGD patients, 92% in IBMFS patients, 91% in IEM patients; 89% in SAA patients; 75% in non-SCID PID patients, and 65% in SCID patients (p=0.022).

Significantly lower survival was observed in patients transplanted from MMD (67%) and MUD (81%) compared to those transplanted from MSD (96%) (p=0.02). After excluding 6 patients transplanted from MMD, the OS was also significantly lower in patients transplanted from MUD compared to MSD (p=0.012). OS was significantly higher in patients receiving BM as a graft source

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Table 4. Cox multiple regression for transplant-related mortality.

ID	Independent variables (all but age dichotomized)	HR	95% confidence interval for HR		p	Cox regression
			Lower	Upper		p
	Donor Type: MSD	0.11	0.01	1.63	0.10	
	Donor Type: MMD	0.84	0.17	4.18	0.83	
	Sex: M	0.99	0.45	2.12	0.99	
	Pediatric TRM score: 1	0.53	0.02	13.15	0.70	
	Pediatric TRM score: 2	0.39	0.01	28.49	0.67	
1	Age	1.07	0.91	1.26	0.38	**0.004**
	Disease: SCID	6.02	1.34	26.95	**0.02**	
	Disease: PID	2.74	0.82	9.12	0.10	
	Disease: Others	0.56	0.15	2.02	0.38	
	Stem Cell Source: BM	0.44	0.12	0.96	**0.04**	
	CD 34+ cells: >5×10^6/kg	4.53	2.07	9.9	**0.0001**	

Input variables: Donor Type + Sex + Pediatric TRM score + Age + Desease + Stem Cell Source+ CD 34+ cells dose.

compared to those who received PB (89.6% and 69.8%, respectively) (p=0. 0007). CB transplants were excluded from the analysis due to the small number of such patients. Statistically higher OS was observed in patients receiving ≤5×10^6/kg CD34+ cells (92%) compared to those receiving >5×10^6/kg (68%) (p<0.001). OS did not differ according to sex and age at HCT or according to conditioning type and TRM score stratification.

Risk factor analysis

In univariate analysis, the probability of TRM was significantly lower: HR 0.19 for MSD recipients (95% CI 0.04–0.80) (p=0.02), HR 0.33 in patients receiving BM as stem cell source (95% CI 0.16–0.70) (p=0.004), and HR 4.53 in patients receiving ≤5×10^6/kg CD34+ cells (95% CI 2.07–9.9) (p=0.0001). For patients diagnosed with SCID, predicted TRM was HR 3.84, which was higher than in patients with other diagnoses (95% CI 1.33–11.06) (p=0.01). Prediction of TRM events according to diagnosis, donor type, stem cell source, and CD34+ cells dose is presented in Figures 1 and 2. Multivariate analysis showed that 3 factors affect TRM: (1) stem cell source, with lower probability of TRM in BM recipients: HR 0.44 (95% CI 0.2–0.96) (p=0.04); (2) diagnosis, with higher probability of TRM in SCID: HR 6.02 (95% CI 1.34–26.95) (p=0.02); and (3) CD34+ cell dose, with higher probability of TRM in recipients of >5×10^6 138 cells/kg: HR 4.53 (95% CI 2.07–9.9) (p=0.0001) (Table 4).

Causes of deaths

There were 156 patients still alive at the end of the study (85.2%), and 27 patients (14.8%) had died, all due to transplant-related complications. The causes of death with patient details are presented in Table 5.

Discussion

Patients with non-malignant diseases treated with HCT constitute a heterogenous group in terms of diagnoses. In our cohort of patients, TRM was observed more frequently in patients with SCID, and these children had the lowest survival. According to Gennery et al., significantly lower survival was observed in SCID patients transplanted from unrelated and mismatched related donors (69% and 66%, respectively) compared to matched related donors (90%) [6]. In the same study, the absence of respiratory impairment, or viral infection before transplantation, were associated with better prognosis on multivariate analysis [6]. According to an analysis of SCID patients by Heimall et al., the average survival for patients who underwent HCT was about 70% at 3 years after transplantation [7]. This may be the consequence of prolonged immunosuppression and previous life-threatening infections, observed especially in severely immunocompromised patients. In another study of this same group, 2-year overall survival in SCID patients was lower in those transplanted with active infection [8]. In our analysis, 6/18 patients (33.3%) with SCID had active infection at the time of HCT, and 2 patients with SCID died due to infections. Infection was the most common cause of death in the whole analyzed cohort.

In our patients, TRM occurred more frequently in PB recipients compared to BM recipients, with significantly higher OS in

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Table 5. Causes of mortality in analyzed patients.

No.	sex	Age at HCT years	Diagnosis	Donor type	Stem cell source	CD34+ cells dose ×10⁶/kg	Cause of death	Accompanying complications
1	M	0.3	SCID-Ommen s.	MUD	PB	9.3	Organ failure	Renal failure, IFI
2	F	7.5	SAA	MUD	BM	8.5	Infection	bacterial infection (unknown pathogen), graft failure
3	F	8	SAA	MUD	PB	13	Infection	fungal infection of CNS
4	F	10.2	PID– NBS	MSD	BM	3.5	Infection	CMV reactivation, graft failure
5	F	0.6	SCID– T–, B– NK+	MUD	PB	7.9	Infection	Idiopatic pneumonia
6	F	14.5	PID– NBS	MUD	BM	1.7	Infection	CMV reactivation
7	M	0.3	SCID– Ommen s.	MMFD	PB	14	Organ failure	respiratory failure, EBV, IFI
8	M	13.2	IBMFS– FA	MUD	PB	5.9	Infection	Bacterial sepsis (unknown pathogen)
9	M	10.5	PID– HLH	MMUD	BM	4.4	Organ failure	CNS bleeding, CMV reactivation
10	M	7.6	SAA	MUD	BM	1.84	Infection	CMV reactivation
11	F	1.4	SCID– T–, B– NK+	MUD	PB	9.06	Infection	Sepsis (pseudomonas)
12	M	4.5	SCID– T–, B– NK+	MUD	PB	6.09	Organ failure	CNS bleeding
13	F	11.3	SAA	MUD	PB	15	Organ failure	Encephalopathy
14	M	13.3	SAA	MUD	PB	7	Infection	Pulmonary aspergillosis
15	M	10.8	SAA	MUD	BM	1.9	GvHD IIIo	Renal failure, CMV reactivation
16	F	0.4	IEM– osteopetrosis	MUD	BM	6.6	GvHD IVo	Infection (unknown pathogen)
17	M	9	CGD	MUD	BM	2.6	Infection	IFI
18	M	0.25	PID– HLH	MUD	BM	4.0	GvHD IIIo	CMV reactivation, VOD
19	F	2	SCID– T–, B– NK+	MUD	BM	5.42	Organ failure	GvHD IIo
20	F	15	PID– hiper IgM syndr.	MSD	BM	4.26	Infection	Bacterial sepsis (*Klebsiella pneumoniae*)
21	F	17	SAA	MUD	PB	4.32	Organ failure	VOD, gastrointestinal (GI) bleeding
22	M	15.5	SAA	MUD	PB	7.5	Infection	Pneumonia (unknown pathogen)
23	M	1.8	PID– WAS	MUD	PB	5.6	Infection	Pneumonia (unknown pathogen)
24	M	0.8	PID– WAS	MUD	PB	7.8	cGvHD	IFI, pneumonia
25	M	1.5	PID– HLH	MUD	PB	6.5	Organ failure	Respiratory failure, renal failure, GvHD
26	F	7	IBMFS– FA	MUD	BM	1.8	Organ failure	Respiratory failure, renal failure, GvHD
27	M	1.5	PID– HLH	MUD	BM	5.3	Infection	Viral infection, RSV pneumonia

SAA – severe aplastic anaemia; PID – primary immune deficiency syndrome; IBMFS – inherited bone marrow failure syndrome; CGD – chronic granulomatous disease; IEM – inborn errors of methabolism; NBS – Nijmegen Breckage Syndrome; FA – Fanconi anaemia; WAS – Wscott-Aldrich syndrome; HLH – limphohistiocytosis; CNS – central nervous system; GvHD – graft versus host disease; IFI – invasive fungal infection, CMV – cytomegalovirus; RSV – respiratory syncytial virus; VOD – venoclusive disease; PB – peripheral blood; BM – bone marrow; MSD – matched sibling donor; MUD – matched unrelated donor; MMFD – mis-matched family donor; MMUD – mis-matched unrelated donor.

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patients receiving BM. Bacigalupo et al. reported that PB as the stem cell source was a negative predictor of survival in patients transplanted for SAA [9]. Studies by Eapen et al. on SAA patients showed that stem cell source was an important risk factor for survival, and BM was the preferred graft source in SAA patients, with lower mortality after BM compared to PB [10,11]. Several analyses show that PB stem cells and higher CD34+ dose tend to be associated with increased mortality and lower survival due to GvHD [12,13]. In our analysis, CD34+ cells dose, stem cell source, and underlying disease had no effect on acute and chronic GvHD, although CD34+ cells dose >5×10^6/kg was associated with higher incidence of TRM and lower OS. Many studies found that higher CD34+ cell dose improved engraftment and had no effect on severe GvHD and TRM in children [14–16], but other studies found a correlation between low CD34+ dose and worse survival [17,18]. According to Remberger et al., in patients treated for malignancies, those given a very high CD34+ cell dose (≥11×10^6/kg) had decreased rates of survival [19]; stem cell dose was an important risk factor for survival when connected with graft source. Patients who received PB containing <11.0×10^6/kg CD34+ cells had significantly better OS compared with those receiving BM, regardless of cell dose. The study found that PB CD34+ cell dose ≥11×10^6/kg was correlated with reduced OS and increased mortality rate [19].

In our cohort, univariate analysis showed that OS was significantly lower in children transplanted from MUD compared to MSD. Several authors showed that patients transplanted from unrelated donors have lower survival and higher TRM [17–20]. Locatelli et al. reported an estimated OS of 87% in patients with FA when the donor was an HLA-identical sibling *vs.* 40% in MUD transplants [21]. Roy et al. reported outcomes of 61 transplanted BDA patients, with 76% 3-year OS after MSD HSCT, and 39% OS after MUD HSCT [20]. In SAA patients, the OS was 89% in our cohort, which is in line with other studies, in which OS varied from 91% to 86% after MSD HCT. In patients after failed immunosuppressive therapy (IST) treated with MUD HCT, OS was lower but still improving [22–24].

Recommended conditioning regimens have changed in recent years and now differ. In our cohort, conditioning type had no effect on TRM and OS. The results an analysis by Burroughs et al. of patients with non-malignant diseases indicate that RTC conditioning is effective and improves survival due to its lower toxicity [25]. However, Al Mulla et al. showed that reduced-toxicity conditioning was not significantly less toxic than myeloablative in pediatric and adolescent patients undergoing allogeneic HCT [26]. In our study, pediatric TRM score had no effect on TRM and OS, probably because the type of non-malignant disease was not included in the TRM stratification, and according to our analysis, the underlying disease affected survival after HCT.

This study has some limitations. The population was not homogeneous, as the underlying disease varied among the analyzed groups. The retrospective nature of the study, as well as the extended time of data collection and hence the changes of guidelines and standards of care during that time, could also have affected the results. Nevertheless, our results should be of value in investigating the causes of TRM in children with non-malignant diseases undergoing allogeneic HCT. Further research is needed to assess the effects of different risk factors on HCT outcome. In addition, prospective studies would allow gathering larger and more homogeneous populations of patients.

Predicting the outcome of HCT based on pretransplant factors is important for clinical practice. Despite the introduction of procedures that reduce the risk of TRM, it is necessary to assess such a risk individually before making a transplant decision.

Conclusions

In our study, SCID diagnosis, PB as stem cell source, and CD34+ dose higher than 5×10^6/kg were the most important risk factors for TRM in patients with non-malignant diseases treated with HCT, and they all appear to affect OS.

References:

1. Sureda A, Bader P, Cesaro S et al: Indications for allo- and auto-SCT for haematological diseases, solid tumours and immune disorders: Current practice in Europe, 2015. Bone Marrow Transplant, 2015; 50: 1037–56
2. Ljungman P, Bregni M, Brune M et al: Allogeneic and autologous transplantation for haematological diseases, solid tumours and immune disorders: Current practice in Europe 2009. Bone Marrow Transplant, 2010: 45: 219–34
3. Ljungman P, Urbano-Ispizua A, Cavazzana-Calvo M et al: Allogeneic and autologous transplantation for haematological diseases, solid tumours and immune disorders: Definitions current practice in Europe. Bone Marrow Transplant, 2006; 37: 439–49
4. EBMT-ESH Handbook on Haematopoietic Stem Cell Transplantation. 2012. Apperley J, Carreras E, Gluckman E, Masszi T (eds.)
5. Matthes-Martin S, Potschger U, Bergmann K et al: Risk-adjusted outcome measurements in pediatric allogeneic stem cell transplantation. Biol Blood Marrow Transplant, 2008; 14: 335–43
6. Gennery AM, Slatter MA, Grandin M et al: Transplantation of hematopoietic stem cells and long-term survival for primary immunodeficiencies in Europe: Entering a new century, do we do better? J Allergy Clin Immunol, 2010; 126(3): 602–10
7. Heimall J, Puck J, Buckley R et al: Current knowledge and priorities for future research in late effects after hematopoietic cell transplantation (HCT) for severe combined immunodeficiency patients: A consensus statement from the Second Pediatric Blood and Marrow Transplant Consortium International Conference on Late Effects after Pediatric HCT. Biol Blood Marrow Transplant, 2017; 23(3): 379–87
8. Heimall J, Logan BR, Cowan MJ et al: Immune reconstitution and survival in 100 SCID patients post-hematopoietic cell transplant: A PIDTC natural history study. Blood, 2017; 130(25): 2718–27
9. Bacigalupo A, Socie G, Hamladij RM et al: Current outcome of HLA identical sibling *vs.* unrelated donor transplants in severe aplastic anaemia: An EBMT analysis. Haematologica, 2015; 100: 696–702

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

10. Eapen M, Rademacher JL, Antin JH et al: Effect on stem cell source on outcomes after unrelated donor transplantation in severe aplastic anaemia. Blood, 2011; 118(9): 2618–21
11. Eapen M, Logan BR, Confer DL et al: Peripheral blood grafts from unrelated donors are associated with increased acute and chronic graft-versus-host disease without improved survival. Biol Blood Marrow Transplant, 2007; 13(12): 1461–68
12. Levine JE, Wiley J, Kletzel M et al: Cytokine-mobilized allogeneic peripheral blood stem cell transplants in children result in rapid engraftment and a high incidence of chronic GVHD. Bone Marrow Transplant, 2000; 25: 13–18
13. Mohty M, Bilger K, Jourdan E et al: Higher doses of CD34+ peripheral blood stem cells are associated with increased mortality from chronic graft-versus-host disease after allogeneic HLA-identical sibling transplantation. Leukemia, 2003; 17: 869–75
14. Pichler H, Volker W, Winter E et al: No impact of total or myeloid CD34+ cell numbers on neutrophil engraftment and transplantation-related mortality after allogeneic pediatric bone marrow transplantation. Biol Blood Marrow Transplant, 2014; 20(5): 676–83
15. Kałwak K, Porwolik J, Mielcarek M et al: Higher CD34(+) and CD3(+) doses in the graft promote long-term survival and have no impact on the incidence of severe acute or chronic graft-versus-host disease after *in-vivo* T-cell depleted unrelated donor hematopoietic stem cell transplantation in children. Biol Blood Marrow Transplant, 2010; 16(10): 1388–401
16. Pulsipher MA, Chitphakdithai P, Logan BR et al: Donor, recipient and transplant characteristics as risk factors after unrelated donor PBSC transplantation: beneficial effects of higher CD34+ cell dose. Blood, 2009; 114(13): 2606–16
17. Törlén J, Ringdén O, Le Rademacher J et al: Low CD34 dose is associated with poor survival after reduced-intensity conditioning allogeneic transplantation for acute myeloid leukemia and myelodysplastic syndrome. Biol Blood Marrow Transplant, 2014; 20(9): 1418–25
18. Basquiera AL, Abichaín P, Damonte JC, García JJ: CD34+ cell dose in allogeneic transplantation: weight considerations. Biol Blood Marrow Transplant, 2015; 21(1): 196
19. Remberger M, Törlén J, Ringdén O et al: Effect of total nucleated and CD34(+) cell dose on outcome after allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant, 2015; 21(5): 889–93
20. Roy V, Perez WS, Eapen M et al: Bone marrow transplantation for Diamond-Blackfan Anaemia. Biol Blood Marrow Transplant, 2005; 11(8): 600–8
21. Locatelli F, Zecca M, Pession A et al: The outcome of children with Fanconi anaemia given hematopoietic stem cell transplantation and the influence of fludarabine in the conditioning regimen: A report from the Italian pediatric group. Haematologica, 2007; 92(10): 1381–88
22. Dufour C, Pillon M, Socie G et al: Outcome of aplastic anaemia in children. A study by the severe aplastic anaemia and pediatric disease working parties of the European group blood and marrow transplantation. Br J Haematol, 2015; 169: 565–73
23. Bacigalupo A: Bone marrow transplantation for acquired severe aplastic anaemia. Hematol Oncology Clin North Am, 2014; 28(6): 1145–55
24. Dietz AC, Luccini G, Samarasinghe S, Pulsipher MA: Evolving hematopoietic stem cell transplantation strategies in severe aplastic anaemia. Curr Opin Pediatr, 2016; 28(1): 3–11
25. Burroughs LM, Nemecek ER, Torgerson TR et al: Treosulfan-based conditioning and hematopoietic cell transplantation for nonmalignant diseases: A prospective multicenter trial. Biol Blood Marrow Transplant, 2014; 20(12): 1996–2003
26. Al Mulla N, Kahn JM, Jin Z et al: Survival impact of early post-transplant toxicities in pediatric and adolescent patients undergoing allogeneic hematopoietic cell transplantation for malignant and nonmalignant diseases: recognizing risks and optimizing outcomes. Biol Blood Marrow Transplant, 2016; 22(8): 1525–30

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