Alternative Donor Hematopoietic Stem Cell Transplantation for Sickle Cell Disease in Europe

Barbara Cappelli, Graziana Maria Scigliuolo, Fernanda Volt, Selim Corbacioglu, Josu de la Fuente, Nathalie Dhedin, Corinne Pondarré, Juergen Foell, Farah O' Boyle, Arjan Lankester, Elisabetta Calore, Stefania Varotto, Marco Zecca, Amal Al-Seraihy, Mahmoud D Aljurf, Anders Fasth, Sonia Bonanomi, Maria Carmen Addari, Franco Locatelli, Alina Ferster, Veerle Labarque, Peter Bader, Belinda Pinto Simões, Karina Tozatto-Maio, Vanderson Rocha, Mathieu Kuentz, Hanadi Elayoubi, Annalisa Ruggeri, Francoise Bernaudin and Eliane Gluckman on behalf of Eurocord, Monacord and Paediatric Diseases Working Party (PDWP) of EBMT

Background:

Hematopoietic stem cell transplantation (HSCT) from an HLA identical sibling is a well-established curative therapy for sickle cell disease (SCD). HSCT from an unrelated donor is a treatment option, but the likelihood of finding a donor varies according to ethnicity and results are still limited. HLA haploidentical relatives can be alternatively used but, to date, only small series of patients have been described.

Methods:

- European, retrospective, registry (EBMT, Eurocord) based survey on 64 SCD patients (children and adults) transplanted with alternative donor grafts;
- HSCTs performed between 1991 and 2017 in 22 EBMT centers;
- Primary endpoint: 3-year overall survival (OS);
- Secondary endpoints:
  - 3 year event free survival (EFS),
  - engraftment,
  - acute and chronic GVHD.

Patient Characteristics:

	Total (N = 64)	Haplo (N = 40)	UD (N = 24)
Follow-up, months, median (range)	28.7 (1.6 -156)	29.6 (2.1 – 133.5)	24.6 (1.6 –156)
Age, years, median (range)	11.3 (2.1 – 42.8)	14.2 (3– 31.7)	11.8 (2.14 – 42.8)
Sex: Female / Male, %*	42.2/57.8	47.5/52.5	33.3/66.7
HB Genotype, %*			
HbSS	88.5	90.6	85
HbSb0	3.8	---	10
HBSb+	5.8	9.4	---
HBSD Punjab	1.9	---	5
Median year of transplant (range)	2014 (1991 – 2017)	2014 (1991 – 2017)	2011 (2004 - 2015)
Source of HSC, %*			
BM	54.7	52.5	58.3
PBSC	37.5	47.5	20.8
CB	7.8	---	20.8
Performance status pre-HSCT > 80, %*	92.7	90.5	95
CMV patient - / donor + (N)	10	7	3
HU before HSCT, %*	67.9	67.66	68.2
RBC transfusions before HSCT, %*			
No	3.7	6.1	---
Yes, < 20	35.2	33.3	38.1
Yes, ≥ 20	61.1	60.6	61.9
RBC alloimmunization, %* (evaluable % in transfused)	13.7	16.1	10

Abbreviations: CMV = cytomegalovirus; Haplo, haploidentical relative; HB = hemoglobin; HSCT, hematopoietic stem cell transplantation; HU = hydroxyurea; RBC= red blood cells; UD, unrelated donor.

%* of evaluable patients

HSCT donor type	N = 64
Haploidentical related donors	40
Haplo CYPT	16
Haplo BT depleted	15
Haplo other	9
Unrelated donors	24
Adult UD	19
CB UD	5

Abbreviations: CB, cord blood; CYPT cyclophosphamide post transplantation; UD, unrelated donor

Indications for HSCT, N	Total (N = 64)	Haplo (N = 40)	UD (N = 24)
Vaso-occlusive crisis	33	16	17
Cerebral vasculopathy	18	15	3
Other	4	2	2
Missing	9	7	2

Transplantation characteristics:

	All Patients (N=64)	All Haplo (N=40)	Haplo CYPT (N=16)	Haplo BT depleted (N=15)	All UD (N=24)	Adult UD (N=19)	CB UD (N=5)
Conditioning type, N (%)							
MAC	55 (86)	35 (70)	14 (87.5)	14 (93.3)	20 (83)	16 (84)	4(80)
RIC	9 (14)	5 (30)	2 (12.5)	1 (7.7)	4 (17)	3 (16)	1 (20)
Conditioning regimen, N							
BuCy +- other	10	4	-	-	6	2	4
FluBu +- other	1	-	-	-	1	1	-
FluMel +- other	3	2	-	1	1	1	-
FluTreoThio +- other	31	18	1	14	13	13	-
TBI or TLI based	17	15	15	-	2	1	1
other	1	1	-	-	-	-	-
Missing	1	-	-	-	1	1	-
In vivo TCD, N							
No	2	1	-	-	1	-	1
ATG	57	37	16	14	20	16	4
Campath	3	1	-	1	2	2	-
Missing	2	1	-	-	1	1	-
GVHD prophylaxis, N							
CSA	3	2	-	2	1	-	1
CSA+ MTX	12	1	-	-	11	11	-
CSA + MMF	12	9	-	8	3	3	-
MMF + sirolimus	16	16	16	-	-	-	-
others	10	3	-	3	7	3	4
Missing	11	9	-	2	2	2	-

Abbreviations: ATG, anti-thymocyte globulin; BT, lymphocytes B and T; Bu, busulfan; CB, cord blood; Cy, cyclophosphamide; CYPT, cyclophosphamide post transplantation; CSA, cyclosporin A; Flu, fludarabine; GVHD, graft versus host disease; Haplo, haploidentical related donor; MAC, myeloablative conditioning; Mel, melphalan; MMF, mycophenolate mofetil; MTX, methotrexate; RIC, reduced intensity conditioning; TBI, total body irradiation; Thio, thiotepa; TLI, total lymphoid irradiation; Treo, treosulfan; TCD, T cell depletion; UD, unrelated donor.

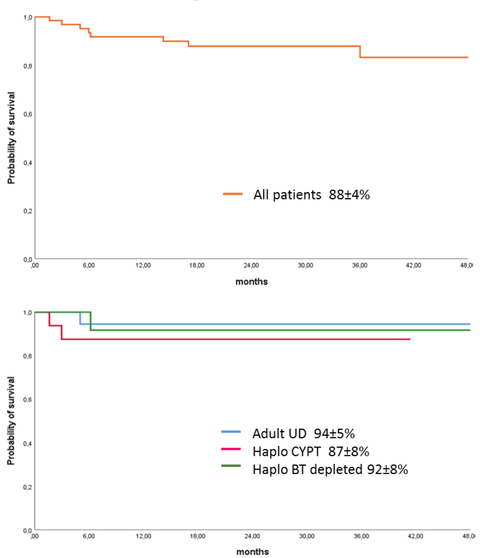
Results:

Outcomes:

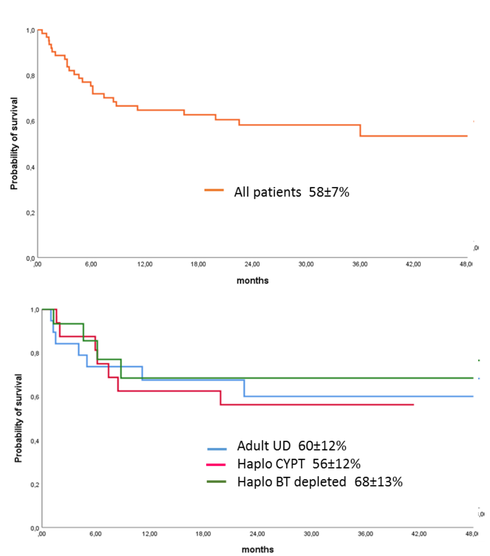
	All patients (N= 64)	All Haplo (N= 40)	Haplo CYPT (N= 16)	Haplo BT depleted (N= 15)	Adult UD[2] (N= 19)
3y OS	88± 4%	89±5%	87±8%	92±8%	94±5%
3y EFS[1]	58±7%	60±8%	56±12%	68±13%	60±12%
Engrafted (N)	55	35	16	14	16
Primary graft failure (N)	7	3	0	1	3
Late graft failure (N)	5	4	3	1	1
Second transplant (N)	6	5	-	2	1
aGVHD >= 2 (N)	16	10	5	3	4
aGVHD 3 - 4 (N)	7	3	2	0	2
cGVHD (N)					
limited	7	5	1	2	1
extensive	9	5	3	1	2
Death (N)	8	5	2	1	1
Cause of death (N)					
TRM - GVHD	1	1	1		
TRM - Infection	4	2	1	1	1
Unknown	3	2			

[1] EFS = death from any cause, primary or secondary graft failure and extensive chronic GVHD were considered events.
[2] CB UD were not calculated because they were only 5 patients

3-year OS



3-year EFS



Conclusions:

This preliminary analysis shows that, despite an acceptable 3 year OS of 88%, rejection and chronic GvHD are still of concern for alternative donor HSCTs, resulting in a 3 year EFS of 58%. Alternative donor transplantation for SCD should, therefore, be performed in experienced centers with the aim of improving success rate, decreasing toxicity and increasing the number of SCD patients eligible for HSCT.

There are no conflicts of interest to disclose.

For more information please contact us at: monacord@centrescientifique.mc