Results of Unrelated Donor Hematopoietic Stem Cell Transplantation for Sickle Cell Disease in Europe

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Background

Allogeneic hematopoietic stem cell transplantation (HSCT) is, to date, the only curative treatment for sickle cell disease (SCD). Because a human leukocyte antigen (HLA) matched sibling donor is not always available, alternative stem cell sources such as unrelated or haploidentical related donors have been explored. The likelihood of finding a 10/10 (HLA-A, B, C, DRB1 and DQB1) matched donor varies among ethnic groups. To date, few series of SCD patients transplanted with an unrelated donor (UD) have been reported.

Methods

- European, retrospective, registry (EBMT, Eurocord) based survey on 71 SCD patients transplanted with an unrelated donor
- HSCTs performed between 2005 and 2017 in 23 EBMT centers;
- Primary endpoint: 3-year overall survival (OS);
- Secondary endpoints:
  - 3-year event free survival (EFS), considering death and graft failure as events;
  - engraftment;
  - acute and chronic GVHD.

Patient Characteristics N=71

Follow-up, months, median (range)	38 (2 - 154)
Age, years, median (range)	9,3 (2–43)
Children (≤16y), N (%)	62 (87%)
Adults (>16y), N (%)	9 (13%)
Sex: Female / Male, N (%)	31/40 (44% /56%)
HB Genotype, N (%)*	
HbSS	55 (79%)
HbSb0	9 (13%)
HBSC	1 (1%)
HBSD Punjab	2 (3%)
Other	3 (4%)
Missing	1
Median year of transplant (range)	2015 (2005 -2017)
KPS ≥ 80, N (%)*	61 (98%)
CMV positive, N (%)*	55 (79%)
HU treatment before HSCT, N (%)*	40 (65%)
RBC transfusions before HSCT,*	
None or < 20	30 (47%)
≥ 20	34 (53%)
RBC alloimmunization N, (% in transfused)*	8 (14%)

* N (% of evaluable patients)

Abbreviations: CMV = cytomegalovirus; Haplo, haploidentical relative; HB = hemoglobin; HSCT, hematopoietic stem cell transplantation; HU = hydroxyurea; KPS, Karnofsky performance status; RBC= red blood cells.

Indications for HSCT	N (% of N tot)
Vaso-occlusive crisis	58 (82%)
Acute Chest Syndrome	24 (34%)
Cerebral vasculopathy	23 (32%)
Osteonecrosis	13 (18%)
Other	11 (15%)

Recipient – donor matching	N = 71
HR 10/10 (HLA-A, B, C, DRB1 and DQB1)	31
HR 9/10 (HLA-A, B, C, DRB1 and DQB1)	20
MM A	10
MM B	3
MM C	5
MM DQB1	2
HR 8/10 (HLA-A, B, C, DRB1 and DQB1)	4
MM B and C	2
MM in C and DRB1	1
MM in DRB1 and DQB1	1
HR 8/8 (HLA-A, B, C, DRB1)	1
ILR 10/10 or 9/10 (HLA-A, B, C, DRB1 and DQB1)	10
Missing HLA data	5

Abbreviations: HR= high resolution typing, ILR= intermediate or low resolution typing, MM= mismatch

Transplantation characteristics

Source of HSC, N (%)*	BM	56 (79%)
	PBSC	15 (21%)
Conditioning regimen*	FluTreoThio	45 (64%)
	BuCy ± other	8 (12%)
	FluMel ± other	7 (10%)
	Other	10 (14%)
	missing	1
Conditioning regimen including TBI (2Gy)*		3 (4%)
In vivo T-Cell Depletion*	No	1 (1%)
	ATG	63 (90%)
	Alemtuzumab	6 (9%)
	missing	1
GvHD prophylaxis*	CSA+ MTX	42 (60%)
	CSA + MMF	16 (23%)
	Other	12 (17%)
	missing	1
Ex-vivo T cell depletion*		6 (9%)
Cyclophosphamide Post-HSCT*		3 (5%)
N. Infused cells– median (range) if BM source (N=56) :		
	TNC X 10^8	3,5 (0,04-13,8)
	CD34 X 10^6	4,5 (0,1– 15)
N. infused cells– median(range) if PBSC source (N=15):		
	TNC X 10^8	7,1 (3,3 – 20,8)
	CD34 X 10^6	8,3 (4,7– 13)

Abbreviations: ATG, anti-thymocyte globulin; BM, bone marrow; Bu, busulfan; Cy, cyclophosphamide; CSA, cyclosporin A; Flu, fludarabine; GvHD, graft versus host disease; HLA, human leukocyte antigen; HSC, Hematopoietic Stem Cell; HR, High resolution typing; IR, intermediate resolution typing; Mel, melphalan; MMF, mycophenolate mofetil; MTX, methotrexate; N., Number; PBSC , peripheral blood stem cells; TBI, total body irradiation; Thio, thiotepa; TNC, total nucleated cells; Treo, treosulfan; TCD, T cell depletion.

* N (% of evaluable patients)

Outcomes

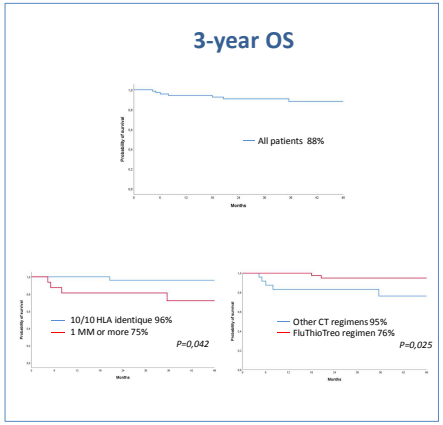
Chimerism at 100 days*		
	Full Donor >95%	51 (77%)
	Mixed 5-94%	9 (14%)
	Autologous Recovery <5%	6 (9%)
Chimerism at last follow-up*		
	Full Donor >95%	40 (63%)
	Mixed 5-94%	13 (23%)
	Autologous Recovery <5%	11 (17%)
Graft failure*	Primary	6 (8%)
	Late	5 (7%)
Second HSCT*		7 (11%)
Acute GvHD*	Grade >= 2	16 (23 %)
	Grade 3 - 4	8 (11%)
Chronic GvHD*	Limited	7 (44%)
	Extensive	9 (56%)
Death*		7 (10%)

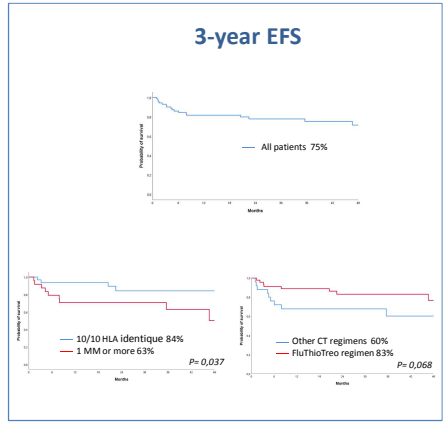
* N (% evaluable pts)

3-year OS	88% (95% CI 78-94%)
3-year EFS[1]	75% (95% CI 62-85%)
Neutrophil engraftment (60 days)	92% (95% CI 85-99)
Platelet engraftment (180 days)	89% (95% CI 82-97)

Abbreviations: CT regimen, Conditioning Regimen; Flu Thio Treo, Fludarabine, Thiotepa, Treosulfan; EFS, event free survival; HSCT, hematopoietic stem cell transplantation; GvHD, graft versus host disease ; MM, Mismatched; OS, overall survival, UD, Unrelated Donor.

[1] EFS = death from any cause and primary or late graft failure were considered events.





Conclusions

UD HSCT is a valid option for SCD patients who lack an HLA-identical sibling donor. Nevertheless, efforts are still needed to improve outcomes after UD HSCT. Our results indicate that using a 10/10 HLA matched UD improves both OS and EFS compared to donors with 1 or more mismatches; when such a matched unrelated donor is not found, using an haplo relative or an unrelated cord blood as donor source could be evaluated. Moreover, the use of Flu Treo Thio as conditioning regimen is associated to better EFS and OS.

There are no conflicts of interest to disclose.
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