ACCADEMIA NAZIONALE DI MEDICINA

AIEOP
ASSOCIAZIONE ITALIANA EMATOLOGIA ONCOLOGIA PEDIATRICA

AIEOP YOUNG PRECEPTORSHIP 2026
Nuovi approcci terapeutici in Ematologia pediatrica non oncologica

Considerazioni pratiche sull'uso del TCSE allogenico nell'anemia falciforme

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Disclosure

Il sottoscritto Marco Zecca

in qualità di docente/moderatore/relatore/tutor, ai sensi dell'art. 76, comma 4 dell'Accordo Stato-Regioni del 2 febbraio 2017 e del paragrafo 4.5. del Manuale nazionale di accreditamento per l'erogazione di eventi ECM

Dichiara

che negli ultimi due anni ha avuto i seguenti rapporti con soggetti portatori di interessi commerciali in ambito sanitario:

Company name	Research support	Employee	Consultant	Shareholder	Speakers' bureau	Advisory board	Other
AMGEN					X		
CLINIGEN						X	
GRIFOLS						X	
MEDAC	X				X	X	
NOVARTIS						X	
NOVO NORDISK						X	
VERTEX					X	X	

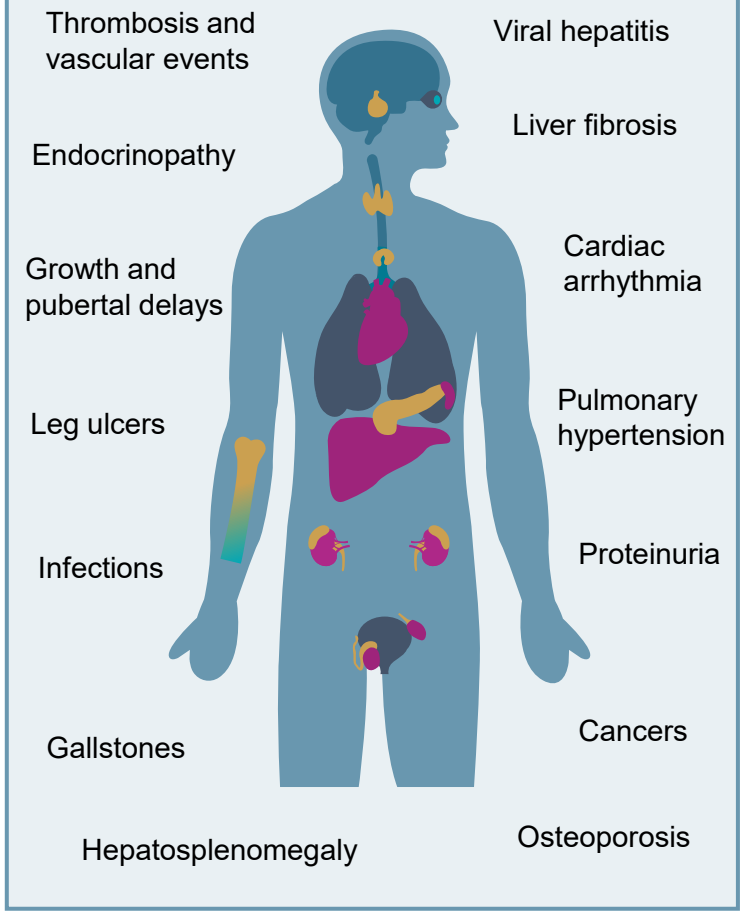
Why an MDT is essential

Haemoglobinopathies are lifelong multisystem disorders

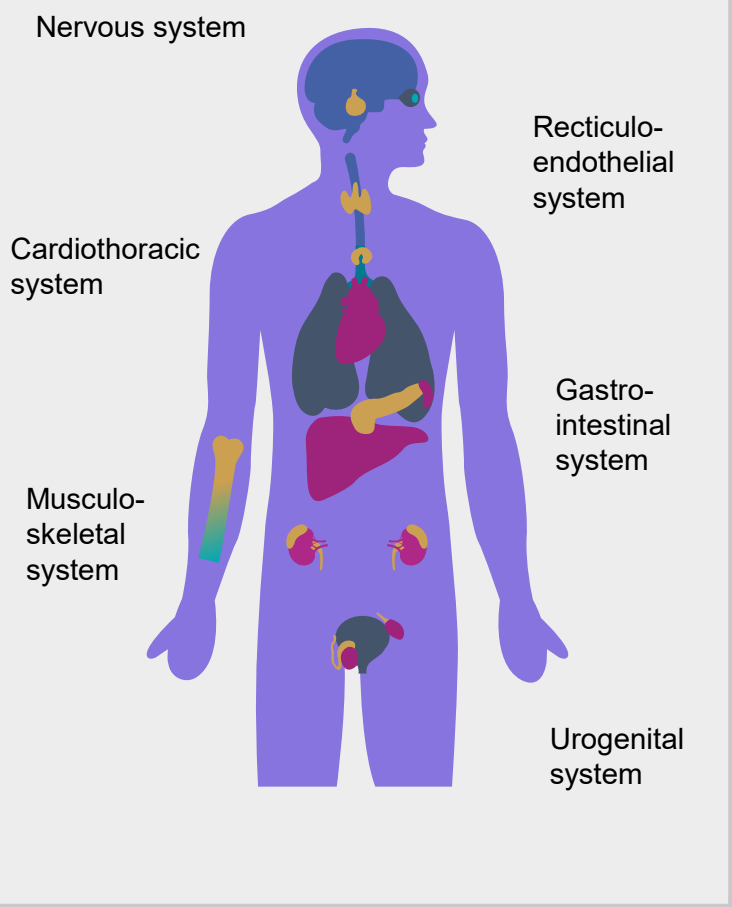
- They require comprehensive, coordinated management
- Transfusion and chelation remain essential but address only part of the disease burden
- A structured, proactive multidisciplinary approach anticipates complications
- Integration of an MDT practice improves survival, adherence, and quality of life, while ensuring equitable access to expertise[1]

Multidisciplinary care should be continuous, coordinated, and centred on the patient, rather than a sequence of isolated consultations

Thalassaemia complications[2]



Sickle cell disease complications[3]

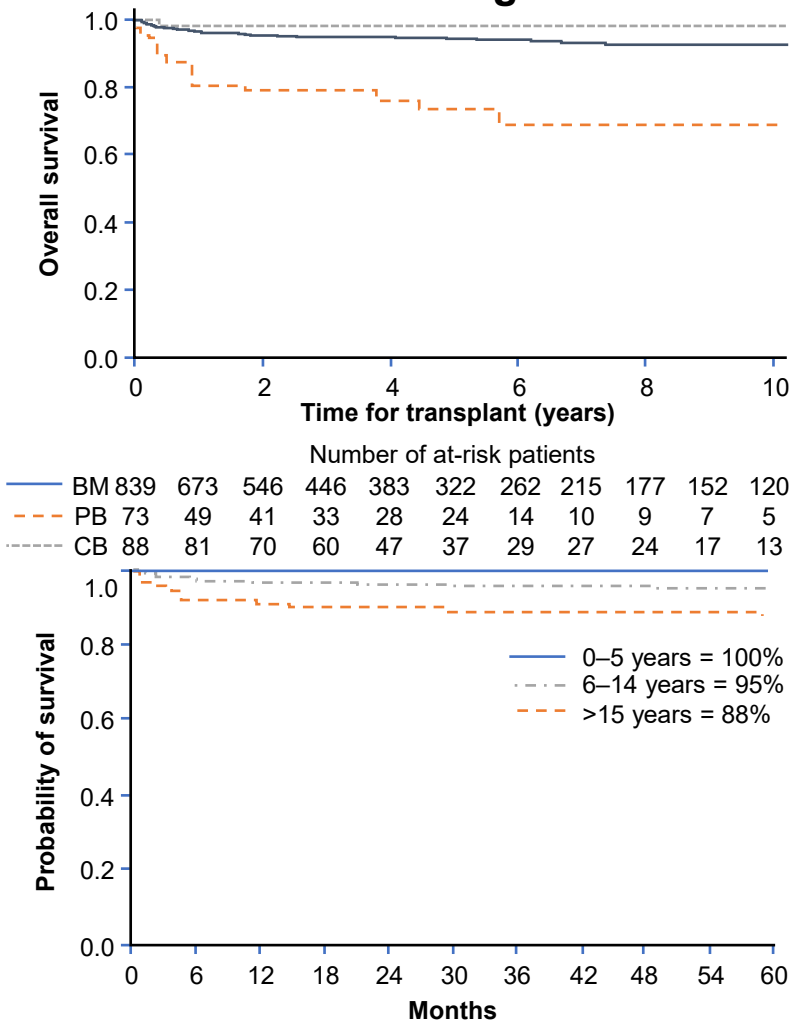


MDT, multidisciplinary team.

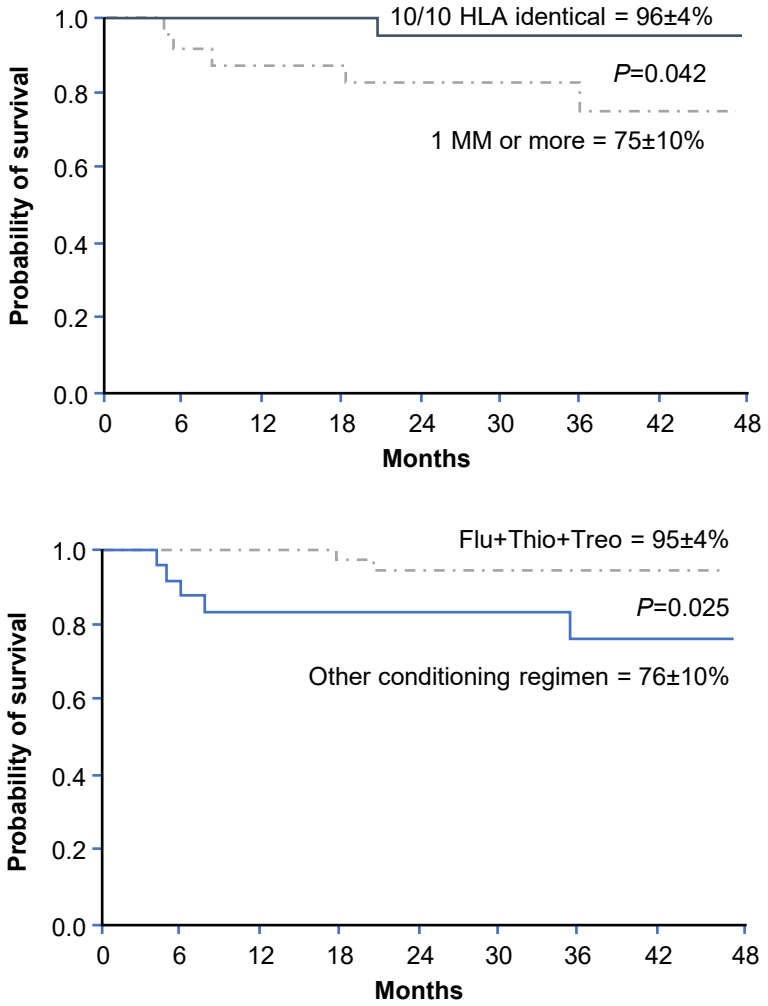
1. 2025 Guidelines for the management of transfusion dependent thalassemia (5th edition). Eds.: Taher A, Farmakis D, Porter JB, Cappellini MD, Musallam KM. Publisher: Thalassaemia International Federation; 2. Taher AT, et al. *N Engl J Med*. 2021; 384:727–743; 3. Piel FB, et al. *N Engl J Med*. 2017;376:1561–1573.

HSCT for SCD: State of the art

Matched sibling donor[1,2]



Matched unrelated donor[3]

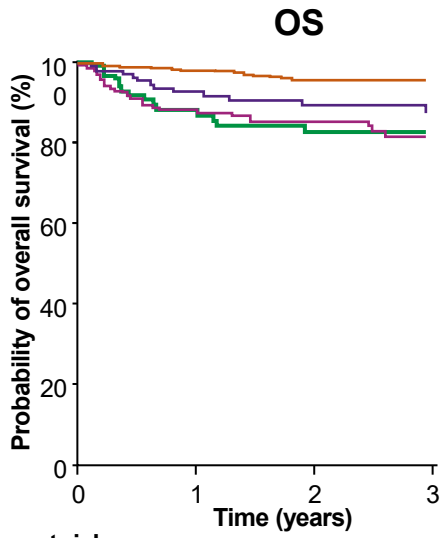


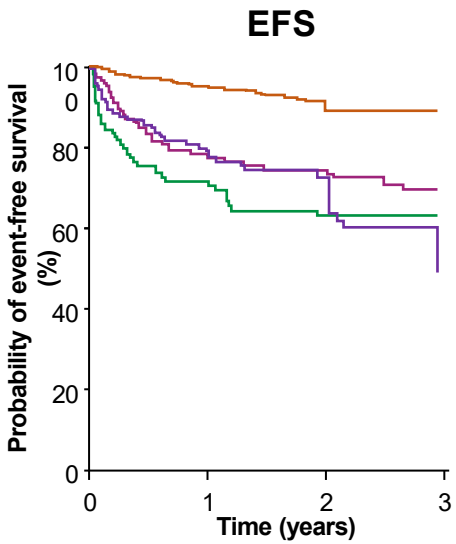
- Outcomes are better with BM or CB than PBSCs[1]
- Younger patients have a better survival probability[1,2]
- Outcomes are affected by HLA compatibility[3]
- Outcomes are better with Treo conditioning regimen than others[3]

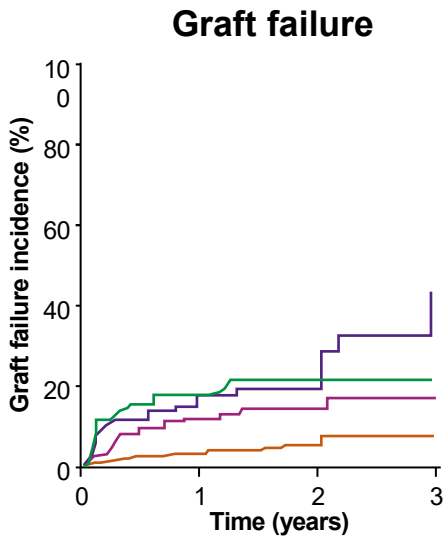
BM, bone marrow; CB, umbilical cord blood; Flu, fludarabine; HLA, human leukocyte antigen; HSCT, haematopoietic stem cell transplantation; MM, mismatch; PBSC, peripheral blood stem cell; SCD, sickle cell disease; Thio, thiotepa; Treo, treosulfan.

1. Gluckman E, et al. *Blood*. 2016;129:1548–1556; 2. Cappelli B, et al. *Haematologica*. 2019;104:e545; 3. Gluckman E, et al. *Bone Marrow Transplant*. 2020;55:1946–1954.

HSCT for SCD: State of the art







Number at risk			
HLA-matched sibling	460 (86)	62 (175)	276 (261)
Haploidentical relative	97 (31)	71 (54)	50 (74)
HLA-matched unrelated donor	79 (14)	63 (27)	45 (42)
HLA-mismatched unrelated donor	82 (11)	64 (25)	52 (37)

444 (86)	349 (165)	261 (245)
85 (28)	61 (47)	33 (60)
72 (11)	57 (22)	40 (35)
61 (11)	42 (23)	36 (29)

557 (0)	444 (97)	62 (185)	276 (265)
137 (0)	85 (34)	61 (56)	32 (69)
111 (0)	72 (27)	57 (40)	40 (55)
104 (0)	61 (18)	42 (33)	36 (39)

910 patients with SCD who underwent allogeneic HSCT in the USA between 2008–2017

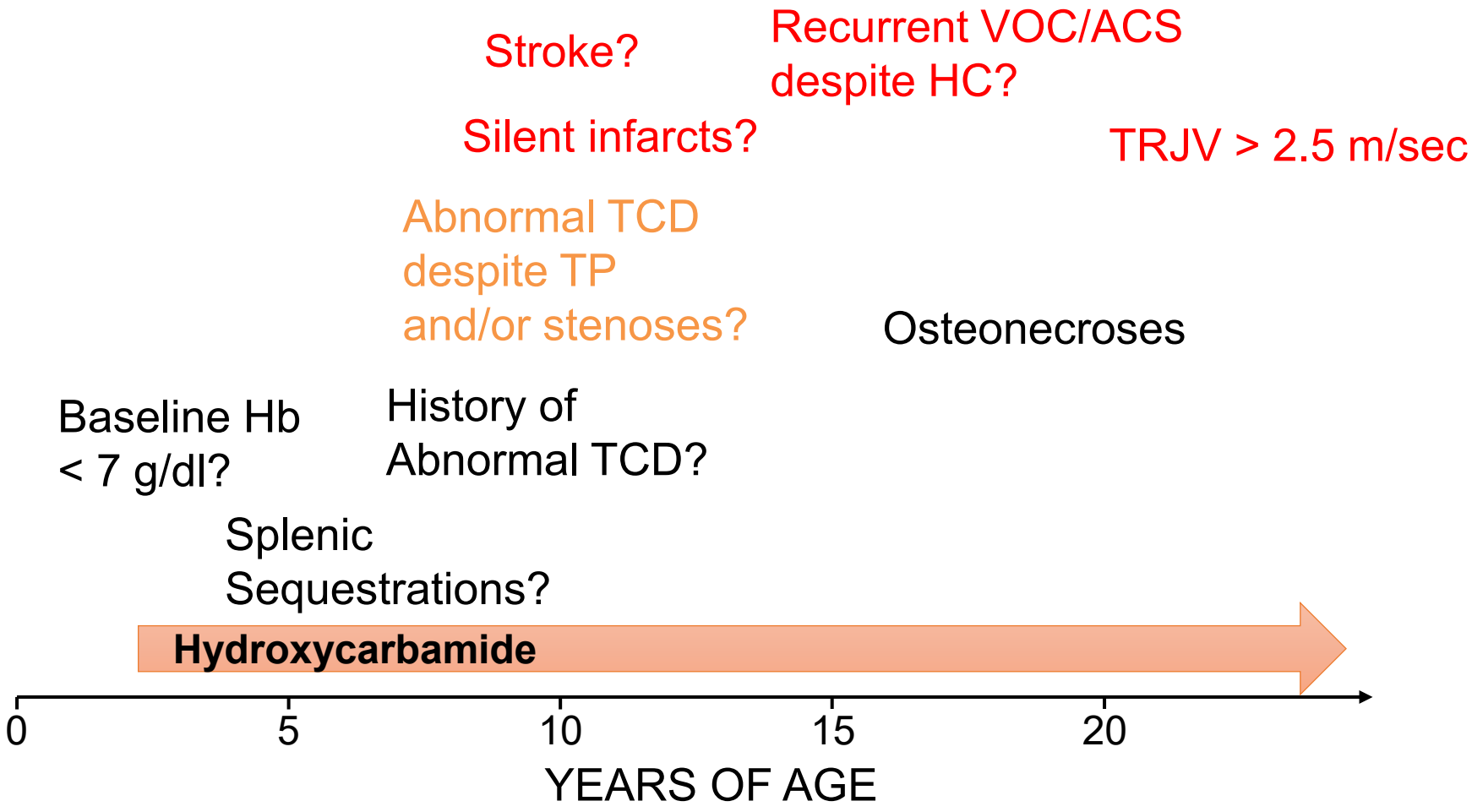
- Transplant should be offered early (≤12 years)
- Poorer outcome in unrelated and mismatched donors
- Graft failure is higher in mismatched donors

Event-free survival		Events / patients	Hazard ratio (95% CI)	*P*-value
Age, years	≤12	72 / 491	1 (ref)	
	13–49	102 / 418	1.74 (1.24, 2.45)	0.0014
Donor type	Matched sibling	52 / 557	1 (ref)	
	Haploidentical	45 / 137	5.30 (3.17, 8.86)	<0.0001
	MUD	38 / 111	3.71 (2.39, 5.75)	<0.0001
	Mismatched-MUD	39 / 104	4.34 (2.58, 7.32)	<0.0001

CI, confidence interval; EFS, event-free survival; HLA, human leukocyte antigen; HSCT, haematopoietic stem cell transplantation; MUD, matched unrelated donor; OS, overall survival; ref, reference; SCD, sickle cell disease.

Eapen M, et al. *Lancet Haematol.* 2019;6:e585-e596 (table adapted).

The decision: when and why?



Silent Cerebral Infarcts

- Prevalence approximately 33% (higher than abnormal TCD)
  - 13% at 1 year — Pediatr Blood Cancer 2008; 51:643-6.
  - 27% at 6 years — Br J Haematol 2009; 146:300-5.
  - 37% at 14 years — Blood 2011; 117:1130-40.
- Cognitive deterioration:
  - IQ scores 5 points lower — Am J Haematol 2014; 89:162-7.
  - 10% reduction in annual income when adults — Intelligence 2007; 35:489-501.
- Benefit of regular transfusion therapy for secondary prevention:
  - How long ?

Patients attitude to HCT

A survey on patient perception of reduced-intensity transplantation in adults with sickle cell disease

S Chakrabarti[1] and D Bareford[2]

[1]Department of Haematology and Bone Marrow Transplantation, St George's Hospital, London, UK and [2]Department of Haematology, City Hospital, Birmingham, UK

Bone Marrow Transplantation (2007) 39, 447–451

www.nature.com/bmt

Which is the TRM you would you accept in lieu of a cure of your condition with RIC alloHSCT?

- 30 adult patients with SCD (HbSS or HbC)
- 20 women and 10 men
- Median age 29 years (range, 18 – 56 years)

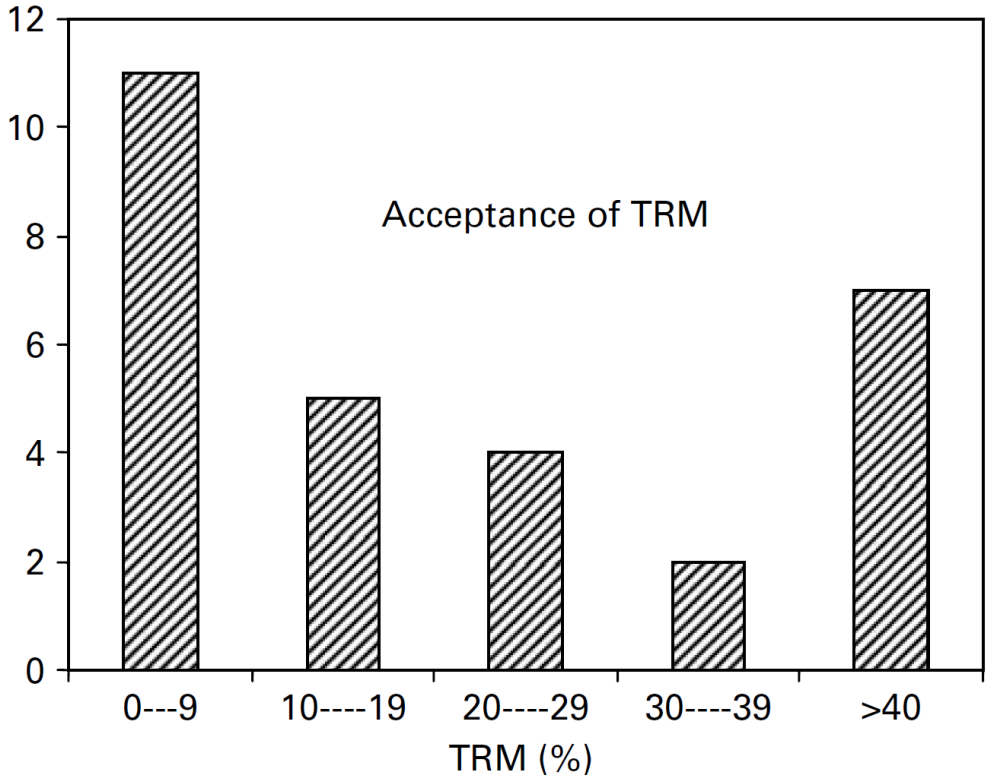


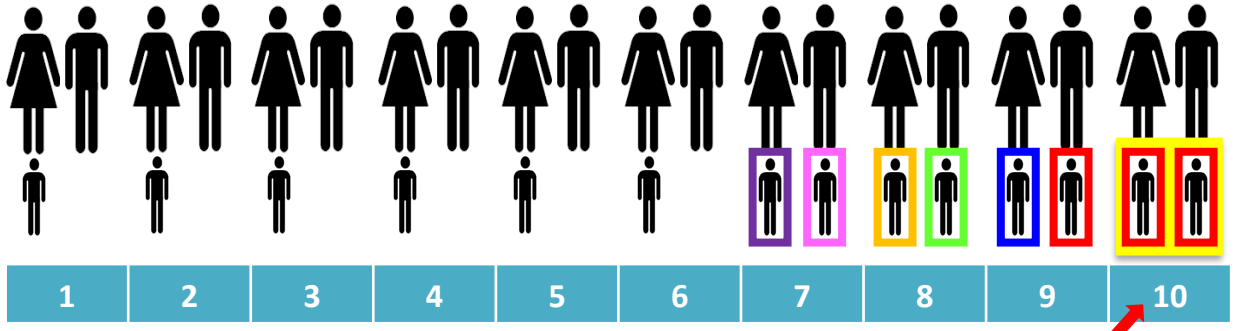
Figure 1 Chart showing the number of patients with SCD who said that a RIC-SCT providing curative option would be acceptable to them at different estimates of TRM. The numbers of patients are shown in the Y-axis and the different ranges of TRM are shown in the X-axis.

The decision: when and why?

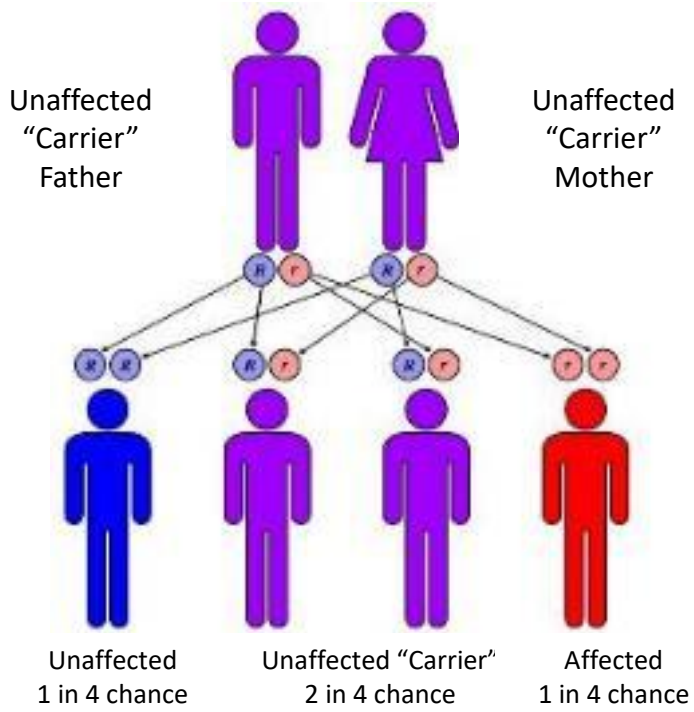
In case of persistence of symptoms related to sickle cell anemia notwithstanding proper treatment with hydroxyurea.

How common is it to have a matched family donor in Italy?

Average number of children per family[1]	ISTAT 2011			
	2011	2012	2013	2014
North	1.46	1.48	1.48	1.48
Centre	1.41	1.38	1.38	1.38
South	1.35	1.35	1.35	1.35
ITALY	***1.42***	***1.41***	***1.41***	***1.42***



- The probability of a sibling being HLA-identical is 25%[2]
- The average number of children per family in Italy is 1.4
- Therefore, only 1 in 10 children with thalassaemia have a healthy and HLA compatible sibling who can be a donor



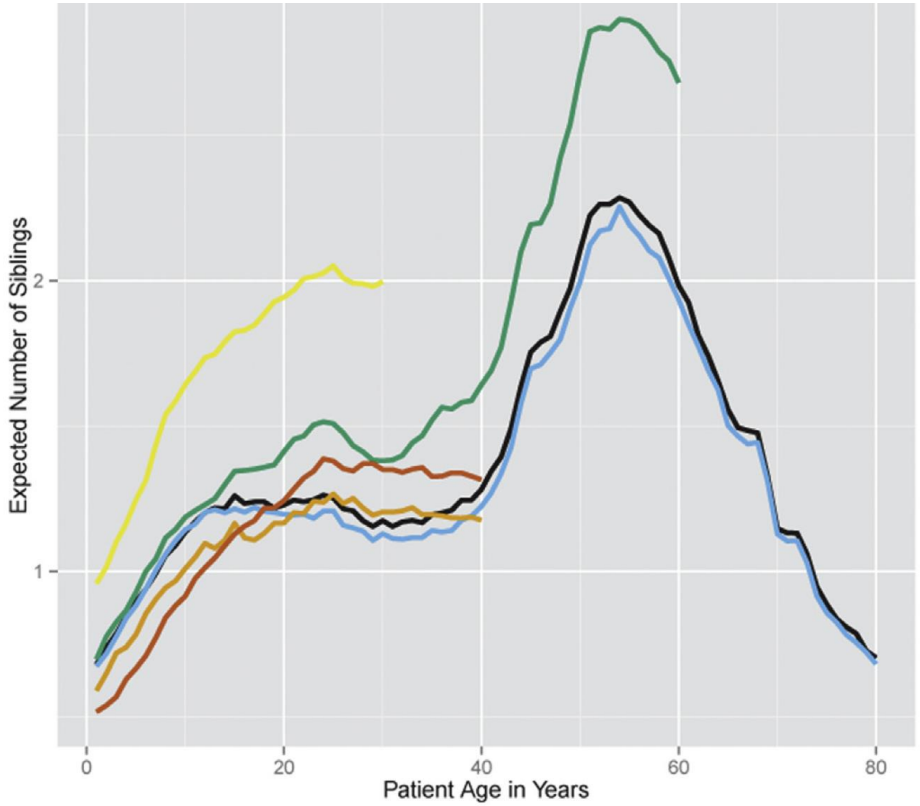
- The probability that a sibling of a child with thalassaemia is unaffected is 75% (25% chance of having thalassemia)[3]
- The probability that a sibling of a child with thalassemia will be healthy or a carrier and HLA compatible is 18.75%
- Only 1 in 13 children with thalassemia have a healthy and HLA-identical sibling

HLA, human leukocyte antigen.

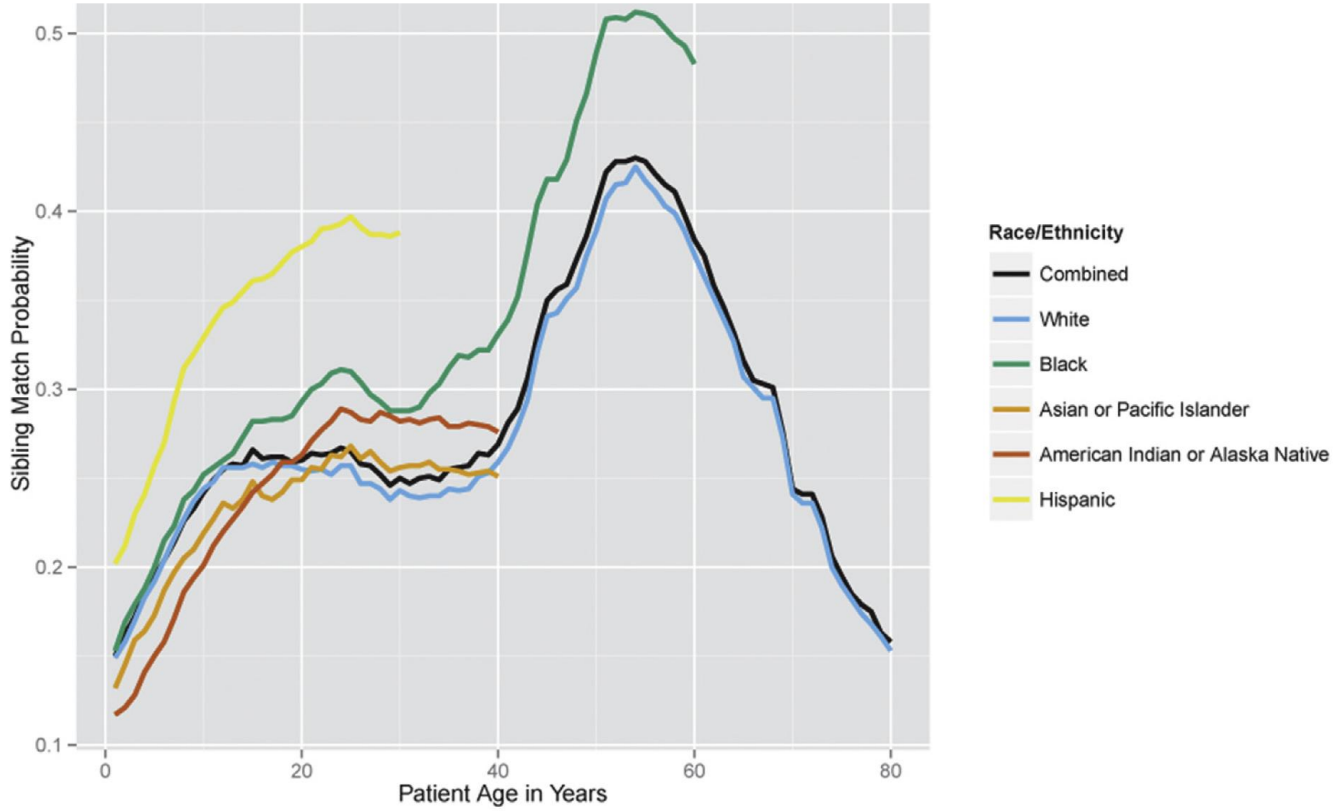
1. ISTAT. Available at: http://dati.istat.it/?lang=en (accessed March 2023); 2. Angelucci E, et al. *Haematologica* 2014;99(5):811–820; 3. Eleftheriou A, et al. 2014, In: Beta (b) thalassaemia, alpha (a) thalassaemia, sickle cell disorders. Thalassaemia International Federation, Cyprus. Information provided based on speaker's clinical experience.

What is the likelihood of having a matched sibling donor?

Expected number of siblings versus patient age by race/ethnicity



Sibling match probability versus patient age by race/ethnicity

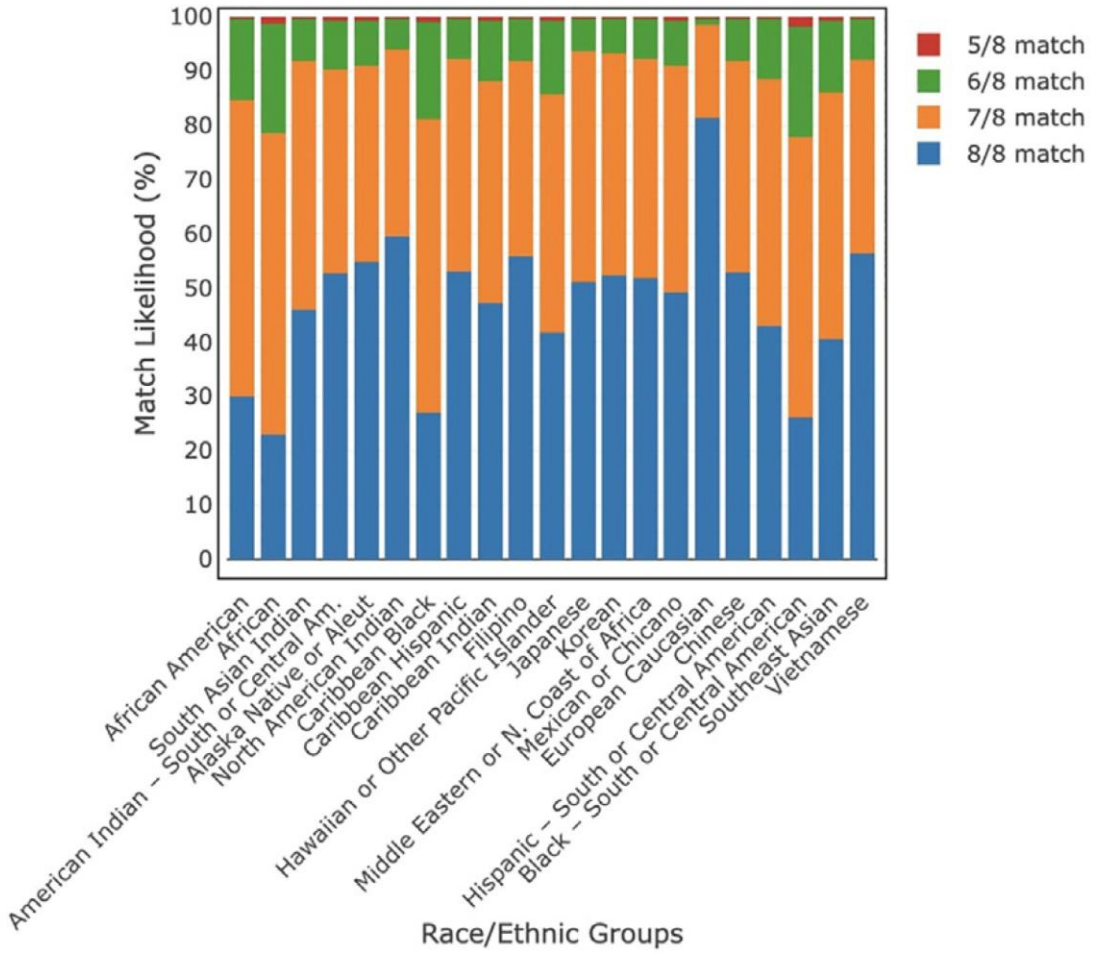


Birth data and statistical modelling was used to assess the probability of having a matched sibling donor among US population cohorts segmented by race/ethnicity and age.

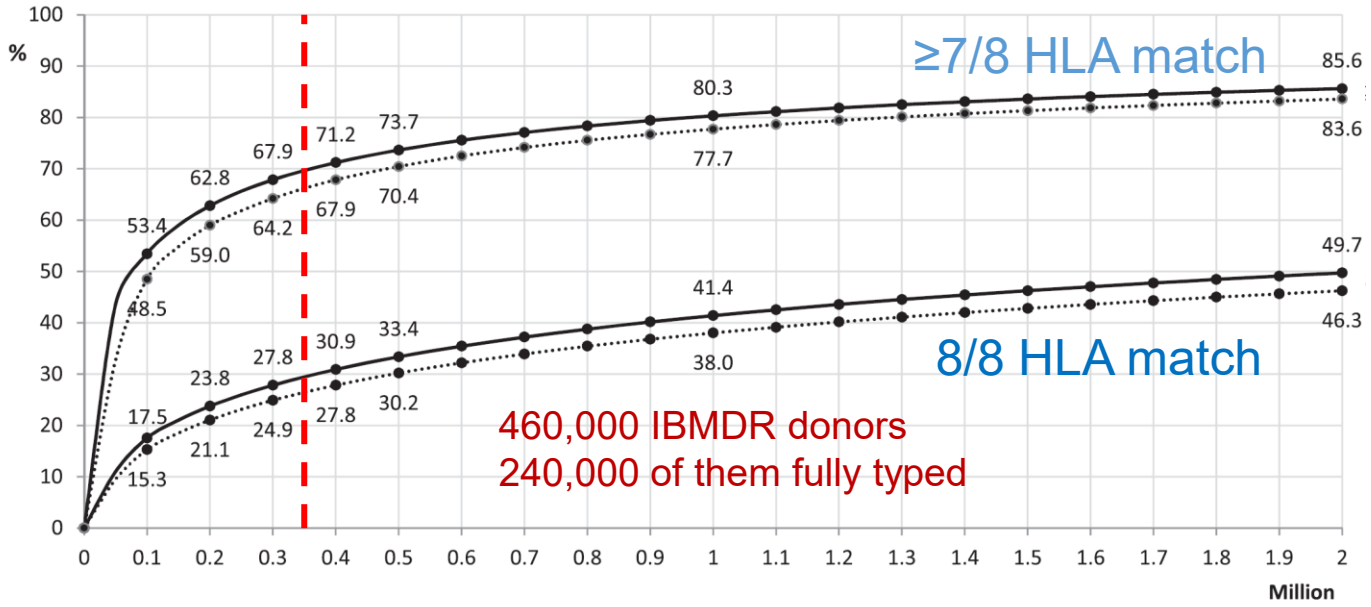
Besse K, et al. *Biol Blood Marrow Transplant.* 2016;22(3):410–417.

What is the likelihood of finding a matched unrelated donor?

Probabilities of finding an unrelated donor in the NMDP[1]



Probabilities of finding a 7/8 or 8/8 matched donor in Italy by registry size[2]

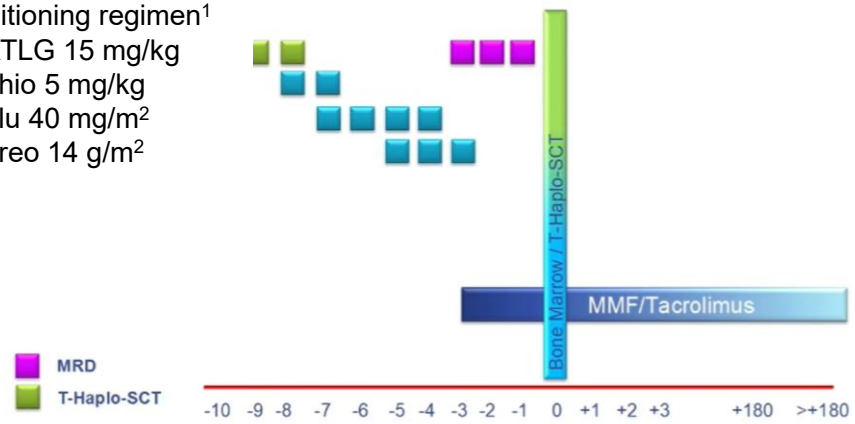


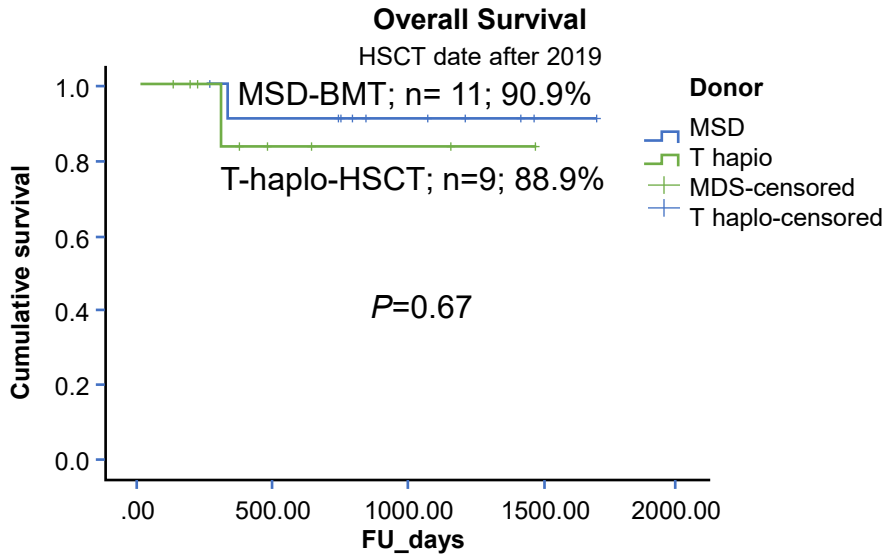
HLA, human leukocyte antigen; IBMDR, Italian Bone Marrow Donor Registry; NMDP, National Marrow Donor Program.

1. Chowdhury AS, et al. *Transpl Cell Ther*. 2023;29:686.e1–686.e8; 2. Sacchi N, et al. *Human Immunol*. 2021;82:758–766.

In vitro T-cell–depleted haplo-HSCT in advanced stage SCD

Conditioning regimen[1]
- ATLG 15 mg/kg
- Thio 5 mg/kg
- Flu 40 mg/m^2
- Treo 14 g/m^2





Outcomes with MSD BMT vs T-haplo-HSCT*[2]

	MSD-BMT (n=20)	T-haplo-HSCT (n=29)
Acute GvHD		
Grade I–II*	10/29 (34%); 8 skin, 2 GIT	4/22 (18%); 2 skin, 2 GIT
Grade III–IV	None	None
Chronic GvHD		
Mild/moderate*	5/29 (17%)	2/22 (9%)
Severe	None	None
OS/DFS	95%/95%	83%/83%
Follow-up, months , median (range)	49 (5–118)	67 (0.5–135)
Engraftment, days, median (range)	29 (17, 41)	17 (11, 35)
Chimerism %, median (range)	94.4% (40.5–100)	97.8% (35.7, 100)
Withdrawal IST, day, median (range)*	170 (104–232)	222 (110–344)
Immune reconstitution (>200 CD3+/µl, day)	62 (24–293)	136 (25–758)
Viral reactivation rate	45%	69%
Antiviral treatment/outcome	No treatment 100% resolved	3% BKV renal failure 14% fatal CMV/HHV6

*Data provided by the speaker. ATLG, anti-T lymphocy globulin; BKV, BK virus; BMT, bone marrow transplantation; CMV, cytomegalovirus; DFS, disease-free survival; Flu, fludarabine; GIT, gastrointestinal tract disease; GvHD, graft versus host disease; HHV6, human herpes virus 6; HSCT, haematopoietic stem cell transplantation; IST, immunosuppressive therapy; MRD, matched related donor; MSD, matched sibling donor; OS, overall survival; SCD, sickle cell disease; T-haplo, T-depleted haploidentical; Thio, thiotepa; Treo, treosulfan.

1. Foell J, et al. *Bone Marrow Transplant* 2019;54(11):1859–1867; 2. Corbacioglu S, et al. 65th Annual American Society of Hematology Meeting. San Diego, California, 6–12 December 2023 (abstract 4915).

T-replete haplo HCT with PTCY[1]

A Phase 2 Multicenter Vanderbilt Global Haploidentical BMT Learning Collaborative to Optimize Curative Therapy for Sickle Cell Disease (SCD)[1]

Context of Research

- Treatment-related mortality associated with myeloablative conditioning regimens represents a major barrier for adults with SCD
- Non-myeloablative conditioning regimens have made haploidentical BMT a promising alternative curative therapy in SCD
- Hypothesis: adding thiotepa (10 mg/kg) to the non-myeloablative related haploidentical BMT with post-transplant cyclophosphamide (PTCy) will improve engraftment in participants to at least 80%

Methods

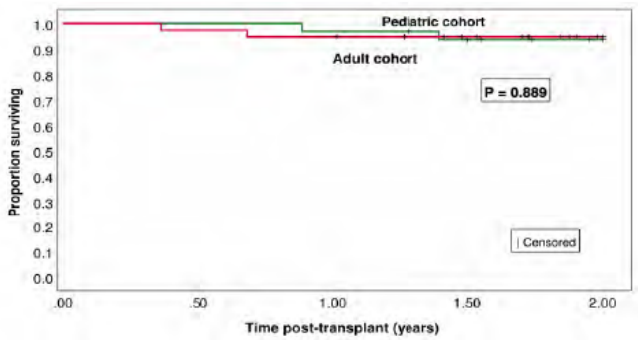
- A phase 2 multicenter trial using non-myeloablative haploidentical BMT to optimize curative therapy for SCD, Global Learning Collaborative (NCT01850108)

Results

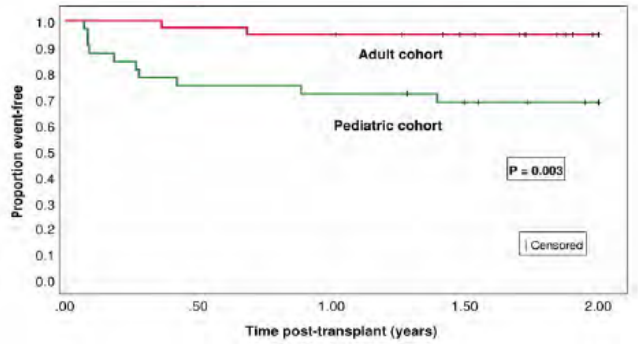
- A total of 32 children and 38 adults were evaluable
- 2 year-overall survival was 94.1%
- 2-year event-free survival was 82.6%

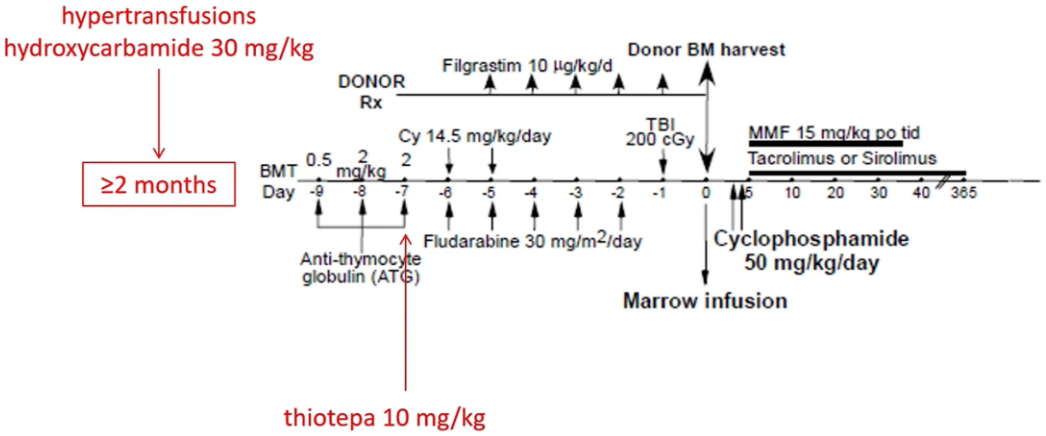
Main Findings

Overall survival



Event-free survival





1-year grade III-IV acute GVHD = 10%
- children 12,5% (4.4-27)
- adults 7.9% (2.3-19.6)

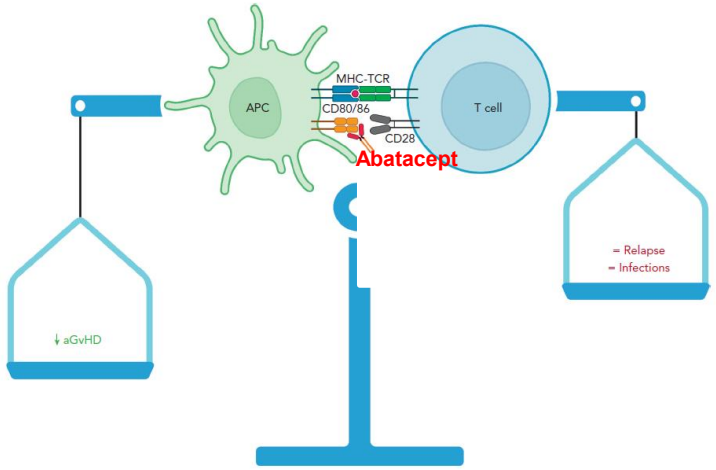
2-year moderate-severe chronic GVHD = 10% (4.6-18.6)
- children: 18.8% (8.2-34.6)
- adults: 2.6% (0.3-11.6)

Graft failure = 11.4% (8/70; 4 primary and 4 secondary)
- All graft failures in children (< 18 years of age)

1. Kassim At et al Blood. 2024 Mar 17:blood.2023023301. doi: 10.1182/blood.2023023301. Online ahead of print.

New strategies for GVHD prophylaxis: **abatacept**

MUD transplants[1,2,3]



Graft-versus-host Disease Prophylaxis With Abatacept Reduces Severe Acute Graft-versus-host Disease in Allogeneic Hematopoietic Stem Cell Transplant for Beta-thalassemia Major With Busulfan, Fludarabine, and Thiotepa

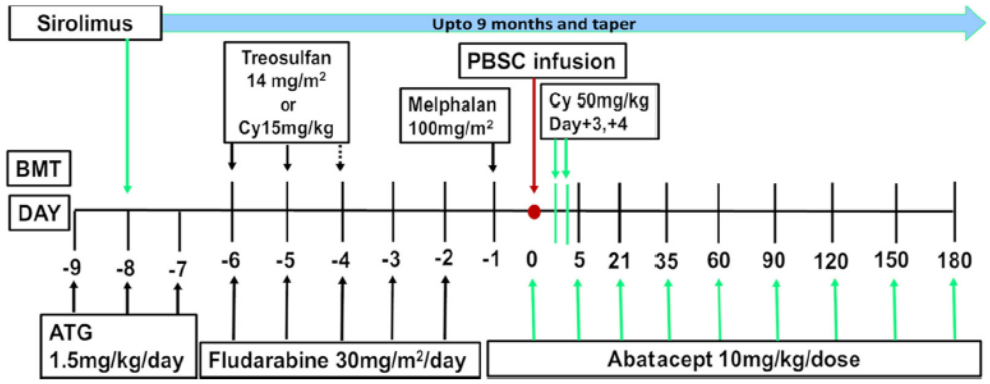
Pooja Khandelwal, MD,[1] Rosa F. Yeh, PharmD,[2] Louie Yu, BS,[2] Adam Lane, PhD,[1,3] Christopher E. Dandoy, MD,[1,3] Javier El-Bietar, MD,[1,3] Stella M. Davies, MBBS,[1,3] and Michael S. Grimley, MD[1,3]

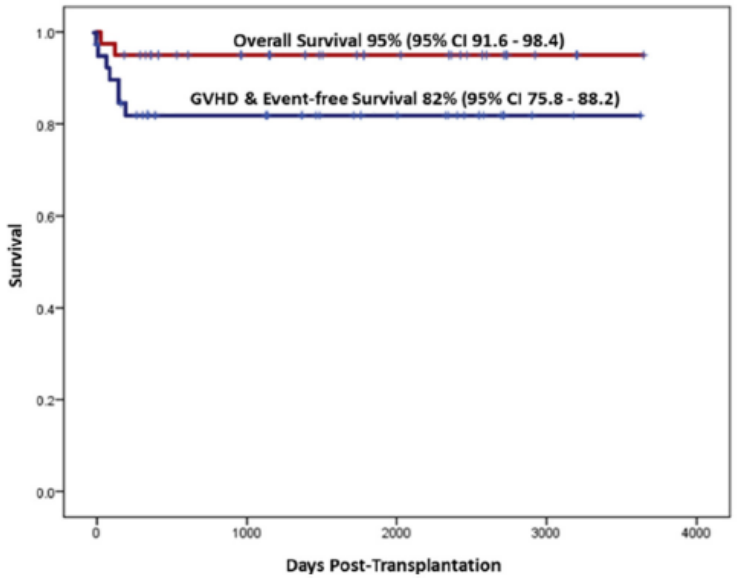
Abatacept is effective as GVHD prophylaxis in unrelated donor stem cell transplantation for children with severe sickle cell disease

Alexander Ngwube,[1] Niketa Shah,[2] Kamar Godder,[3] David Jacobsohn,[4] Monica L. Hulbert,[5] and Shalini Shenoy[5]

[1]Phoenix Children's Hospital, Phoenix, AZ; [2]Pediatric Hematology & Oncology, Yale University, New Haven, CT; [3]Nicklaus Children's Hospital, Miami, FL; [4]Children's National Medical Center, Washington, DC; and [5]Department of Pediatrics, Washington University School of Medicine, St. Louis, MO

Haploidentical transplant[4]

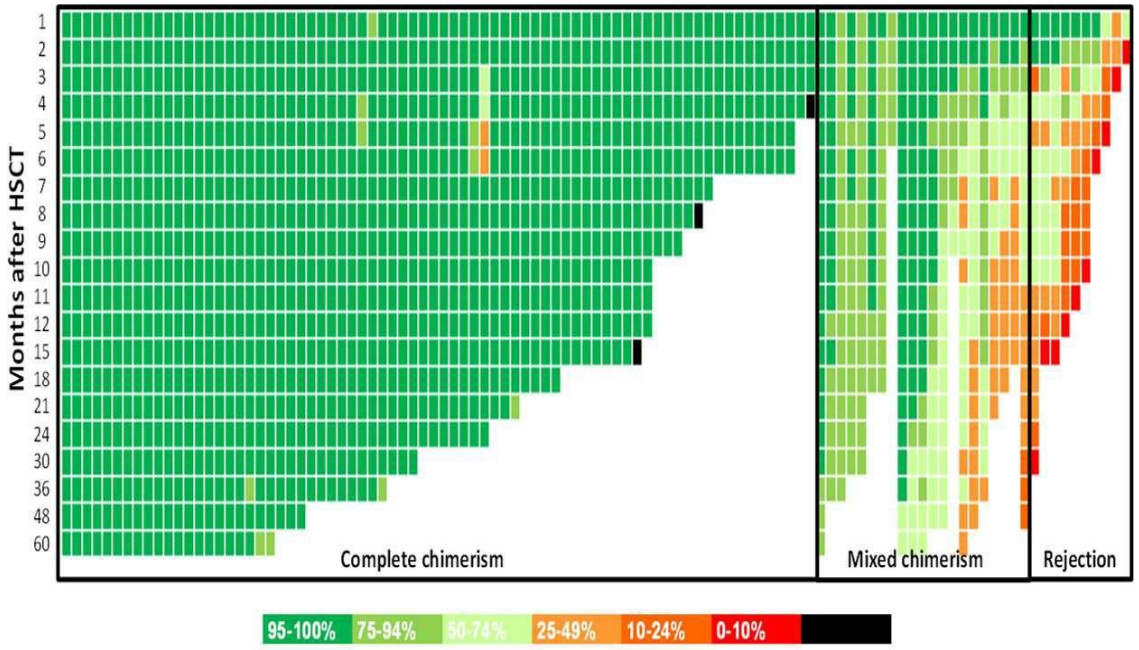




Mixed chimerism is common after HSCT for haemoglobinopathies

Evolution of post-HSCT chimerism[4]

Patients (N=105: β-thalassemia=37; SCD=33, other non-malignant=35)



What do we mean by sufficient engraftment? At least 20–25% donor myeloid chimerism is necessary to achieve disease control in haemoglobinopathies[1–3]

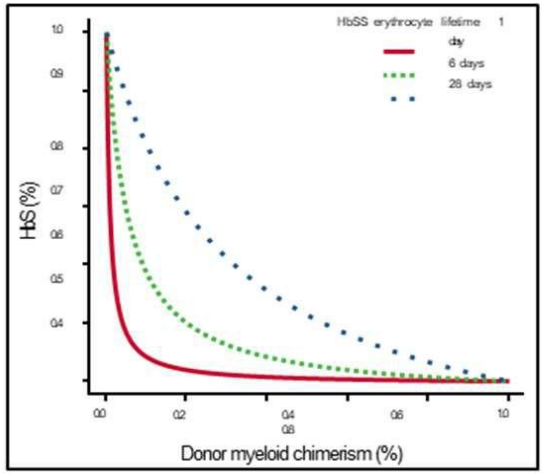
Brief Report

blood

TRANSPLANTATION

At least 20% donor myeloid chimerism is necessary to reverse the sickle phenotype after allogeneic HSCT

Courtney D. Fitzhugh,[1,2] Stefan Cordes,[3] Tiffani Taylor,[2] Wynona Coles,[2] Katherine Roskom,[1] Mary Link,[2] Matthew M. Hsieh,[2] and John F. Tisdale[2]



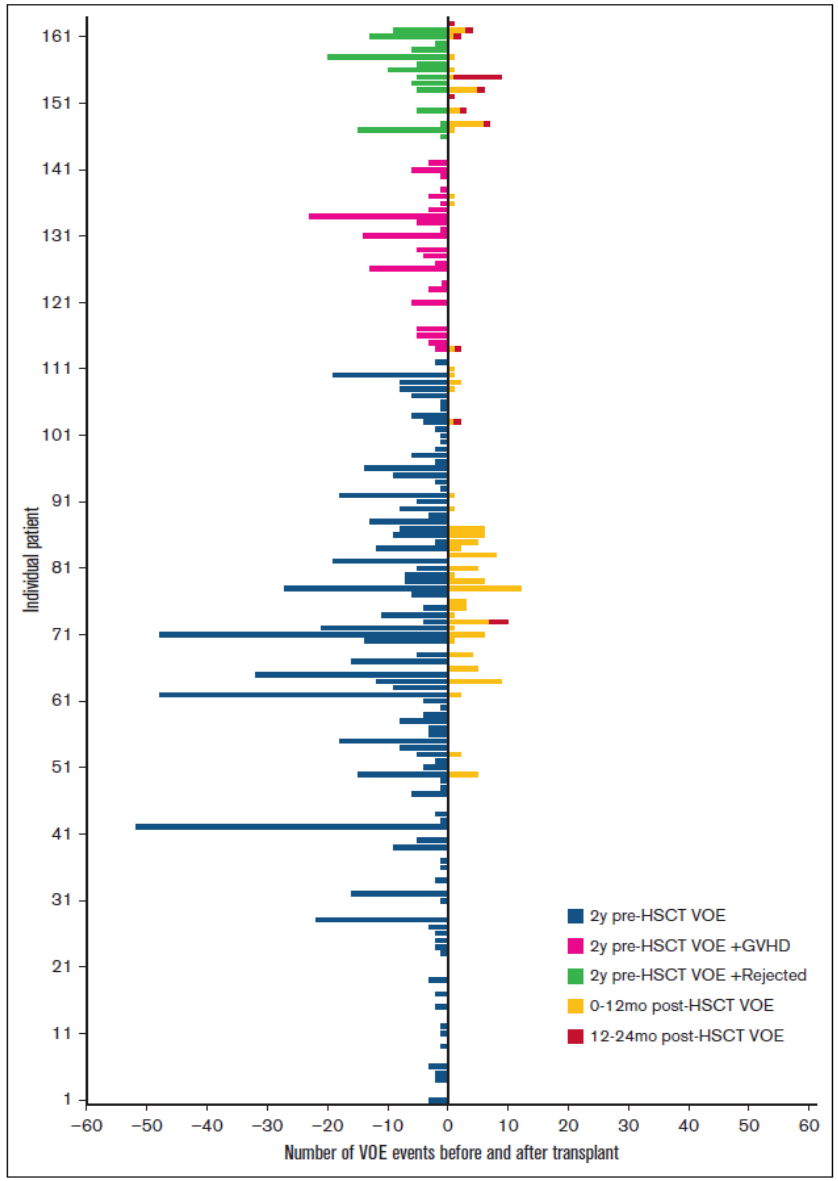
Key Points

- Calculated sickle erythrocyte lifetime was 6.2 days (95% CI, 1.2–29.1)
- Results based on our allogeneic model suggests genetic strategies aimed at correcting **at least 20% of HSCs** are necessary to reverse SCD
- A minority of donor myeloid cells are adequate because of the vast differences in RBC survival between donor and recipient

CI, confidence interval; HbS, sickle haemoglobin; HSCT, haematopoetic stem cell transplantation; RBC, red blood cell; SCD, sickle cell disease.

1. Lisini D, et al. *Haematologica* 2008;93(12):1859–1867; 2. Zimmerman C, et al. *Front Immunol* 2020;11:1791; 3. Fitzhugh CD, et al. *Blood* 2017; 130:1946–1948.
4. Unpublished data provided by speaker; presented at the EBMT Paediatric Diseases Working Party midterm meeting, 8–10 July 2020.

Long-term improvement has been demonstrated after HSCT for SCD



2-year monitoring of VOEs in patients with SCD

Study assessing the **number of VOEs requiring medical attention 2 years before** allogeneic HSCT and up to **2 years** (0–12 months and 12–24 months) **after** allogeneic HSCT in patients with SCD (N=163)[a]

VOEs requiring medical care were **significantly reduced** after allogeneic HSCT for patients with SCD

- Mean VOEs reduced from 5.6 [0–52] to 0.9 [0–12] in the 2 years after HSCT ($p<0.001$)
- In patients who had graft rejection (12%, n=20), VOEs reduced from 6.6 [0–24] to 1.1 [0–6] and 0.8 [0–8] at 0– 12 months and 12–24 months after HSCT, respectively ($p<0.001$)

[a]Between 2005 and 2019.

GVHD, graft versus host disease; HSCT, haematopoietic stem cell transplantation; SCD, sickle cell disease ; VOE, vaso-occlusive event. Leonard A, et al. *Blood Adv*. 2023;7(2):227-234. doi:10.1182/bloodadvances.2022008137

Long-term results of allo-HSCT in SCD

QoL after allo-HSCT in adults[1]

- 31 adult patients, in Saudi Arabia
- Main indication for transplant was VOC
- FACT-G questionnaire
- **Reduction of VOCs, annual number of ER visits**
- **93.5% reported improved QoL**

QoL after allo-HSCT in children[2]

- STELLAR trial interim analysis of children who underwent allo-HSCT in the USA
  - PROMIS-25: n=27
  - PROMIS-29: n=16
- Median time from HSCT was 4.5–7.4 years
- **Long-term HRQoL following HSCT was largely within population norms**
- **Potential psychosocial benefit of HSCT observed**

Organ function[3]

Lungs	**Stable pulmonary function** in children 2–3 years after HSCT
Heart	**TRJV improved** in selected patients with elevated baseline TRJV; LVEF decreased post HSCT
Kidneys	eGFR declined at ≥2 years after HSCT but remained in normal range; presence of proteinuria increased at ≥2 years post HSCT
Spleen	Splenic uptake and phagocytic function **improved** after HSCT in children
Brain	Cerebral haemodynamic **normalise or improve** after HSCT; very low incidence of new SCIs after HSCT, even in high-risk patients
Eyes	Only one study with low prevalence of retinopathy. No evidence-based conclusion possible
Bones	Only incidental cases. No evidence-based conclusion possible
Liver	No evidence-based conclusion possible

Allo-HSCT, allogeneic stem cell transplantation; ASCQ-Me, Adult Sickle Cell Quality of Life Measurement System; BMT, bone marrow transplantation; eGFR, estimated glomerular filtration rate; ER, emergency room; FACT-G, Functional Assessment of Cancer Therapy – General; HRQoL, health-related quality of life; HSCT, haematopoietic stem cell transplantation; LVEF, left ventricular ejection fraction; NRS, numerical rating scale; PRO, patient-reported outcome; QoL, quality of life; SCD, sickle cell disease; SCI, silent cerebral infarct; TRJV, tricuspid regurgitant jet velocity; VOC, vaso-occlusive crisis.

1. Aljaafri BA, et al. *Hematol Oncol Stem Cell Ther*. 2023;17:37–42; 2. Arnold SD, et al. *Am J Hematol*. 2024;99:2037–2040; 3. Dovern E, et al. *Am J Hematol*. 2024;99:1129–1141.