ACCADEMIA di FORMAZIONE

SIMTI

Emoglobinopatie:
supporto trasfusionale e nuovi approcci terapeutici

Il trapianto emopoietico nelle emoglobinopatie

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Il sottoscritto, in qualità di Relatore
dichiara che

oppure

negli ultimi due anni ha avuto i seguenti rapporti anche di finanziamento con i soggetti portatori di interessi commerciali in campo sanitario:
- Vertex,
-BMS
-Vifor
-Menarini
-GILEAD
-Novartis

The first experiences: 50 years ago

TDT	ED Thomas et al. The Lancet 1982: 31: 227-9
TDT	Lucarelli G. et al. Exp Hematol 1984; 12: 676-81
SCD	Johnson FL et al. Bone marrow transplantation in a patient with sickle-cell anemia. *N Engl J Med 1984;311:780-3.*
SCD	Milpied NHJ et al. . Bone marrow transplantation for sickle-cell anaemia. *Lancet (letter) 1988;2:328-9.4.*
SCD	*Vermylen C et al. Bone marrow transplantation in five children with sickle cell anaemia. Lancet 1988;1:1427-8.*

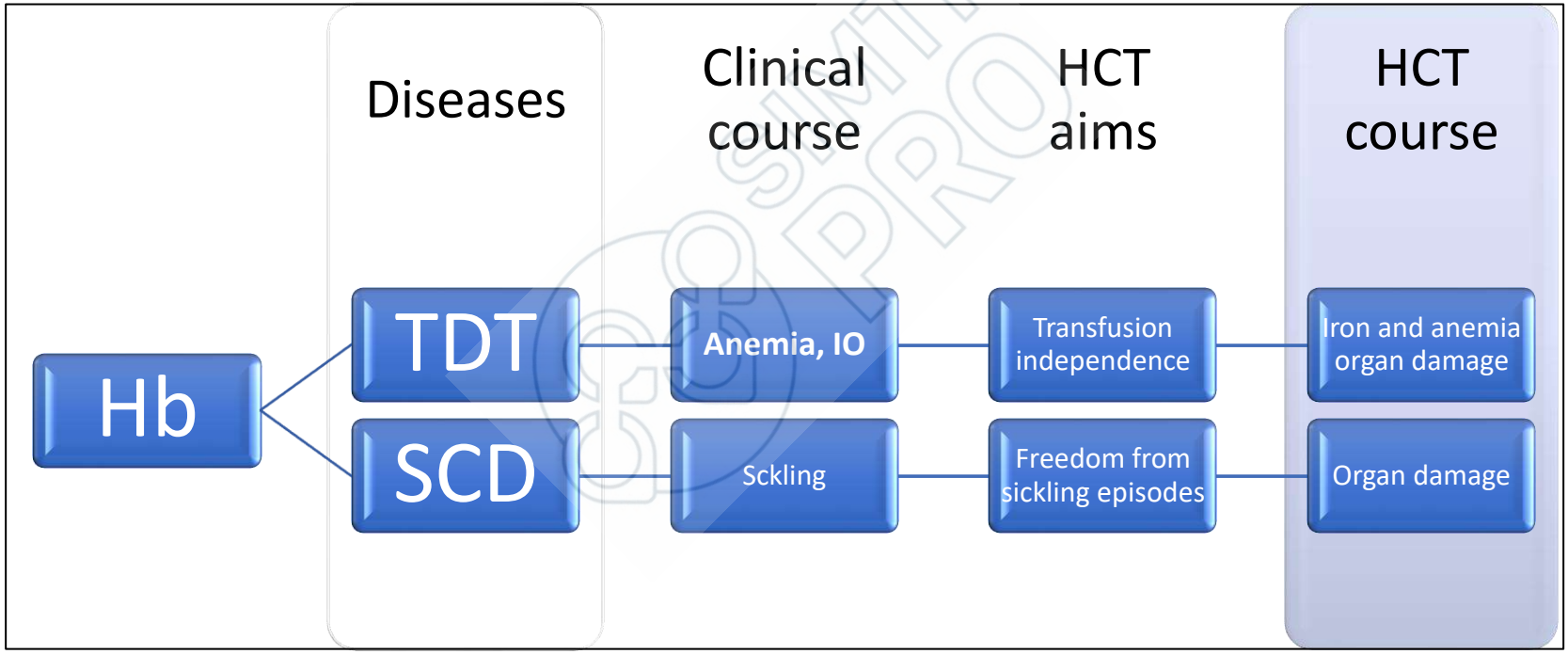
Definition

- **Transfusion dependent thalassemia (TDT)** is an inherited blood disorder caused when the body doesn't make enough hemoglobin. Patients require long life regular PRBCs transfusion
  - Severe anemia can damage organs and lead to death.
  - Iron overload can damage organs and lead to death

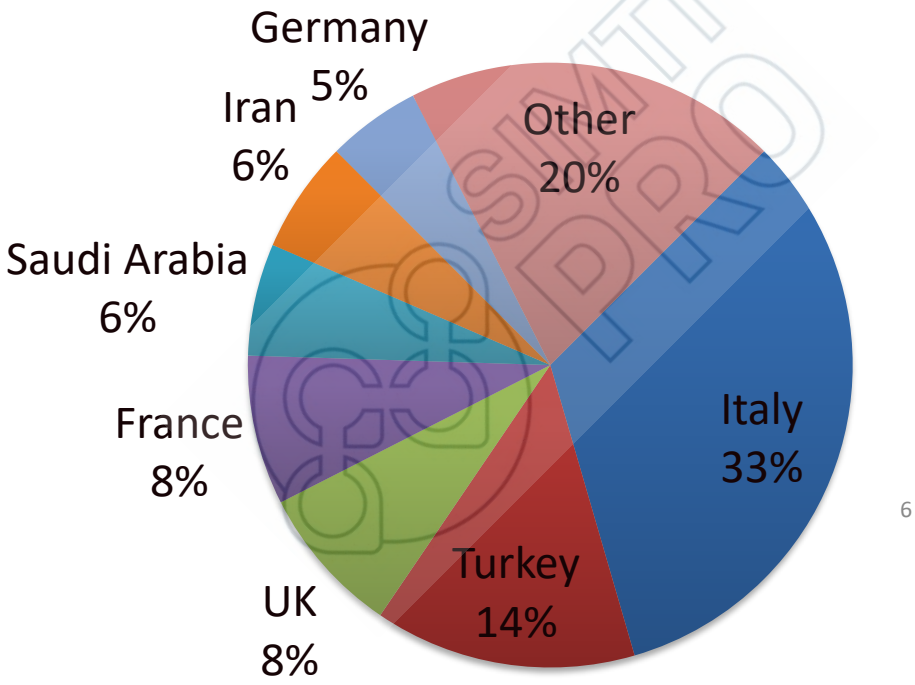
- **Sickle cell disease (SCD)** is a group of inherited red blood cell disorders. In SCD, the hemoglobin is abnormal, which causes the red blood cells to become hard and sticky "sickle." When the sickle cells travel through small blood vessels, they get stuck and clog the blood flow. This can cause
  - stroke,
  - pain,
  - infection,
  - acute chest syndrome
  - others complicationsand organ damage

Derived from CDC definition. https://www.cdc.gov. accessed Oct 24, 2023

TDT and SCD are different diseases



EBMT Hemoglobinopathy Registry:7800 Hemoglobinopathy transplanted patients (1980-2020)

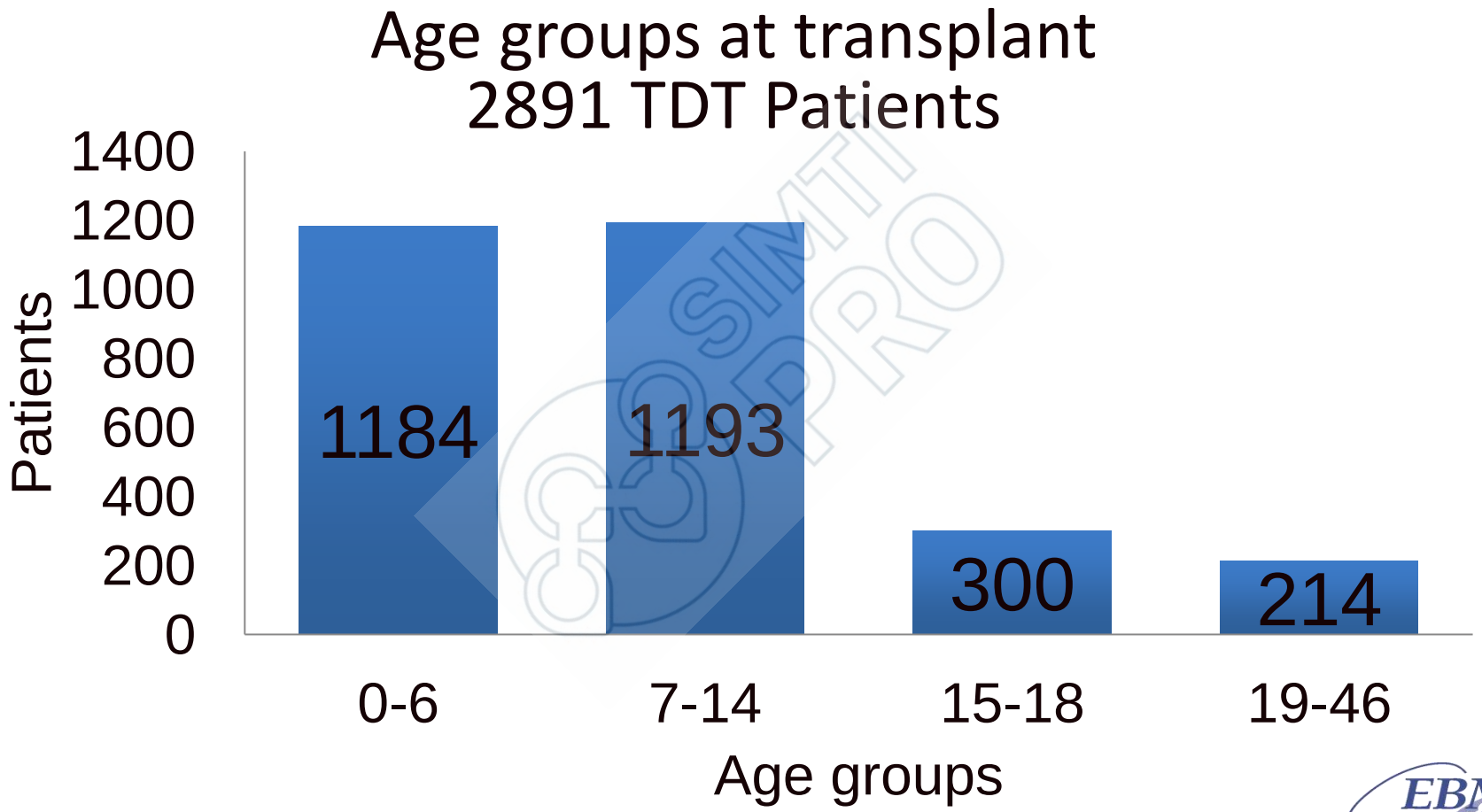


Baronciani D et al Hematopoietic Cell Transplantation in Thalassemia and Sickle Cell Disease:
Report from the European Society for Blood and Bone Marrow Transplantation Hemoglobinopathy Registry: 2000-2017
Blood (2018) 132 (S1): 168.

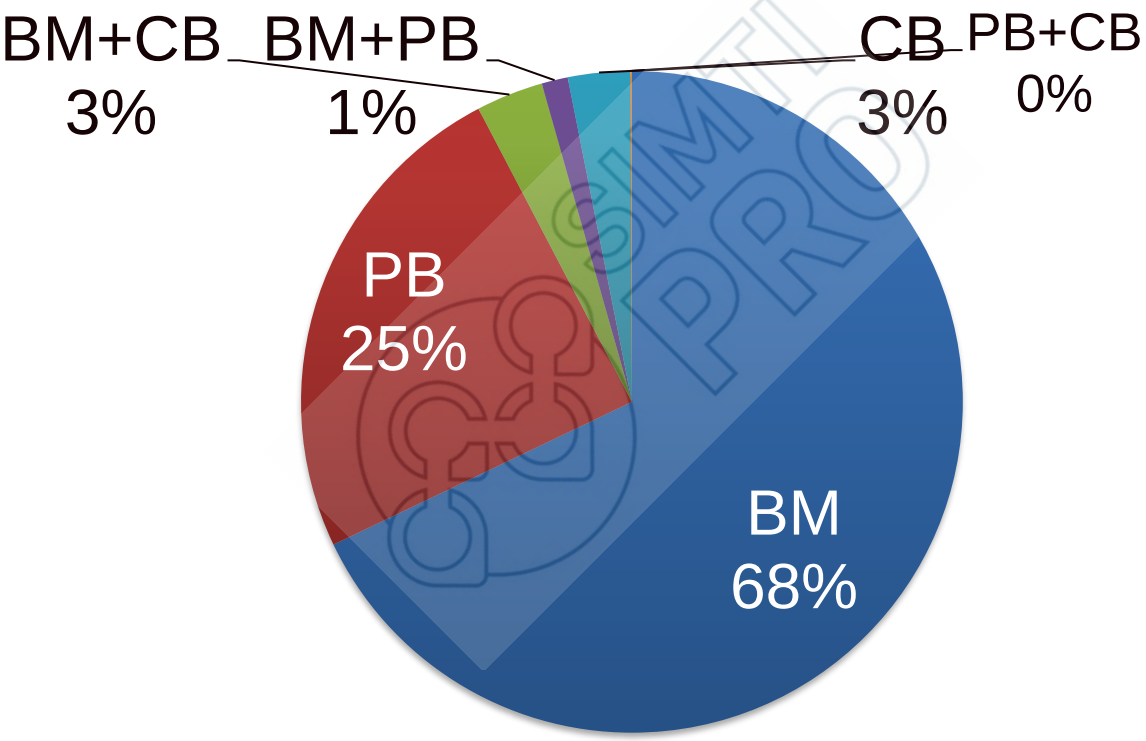
The new EBMT clinical research program in TDT 2000-2018

TDT #	2891
Age at HCT median (years)	7.19 (range 0.48-45.06)
Male/Female/Missing	1538/1334/19
Median Follow up (years)	2.3 (range 2.1-2.4)

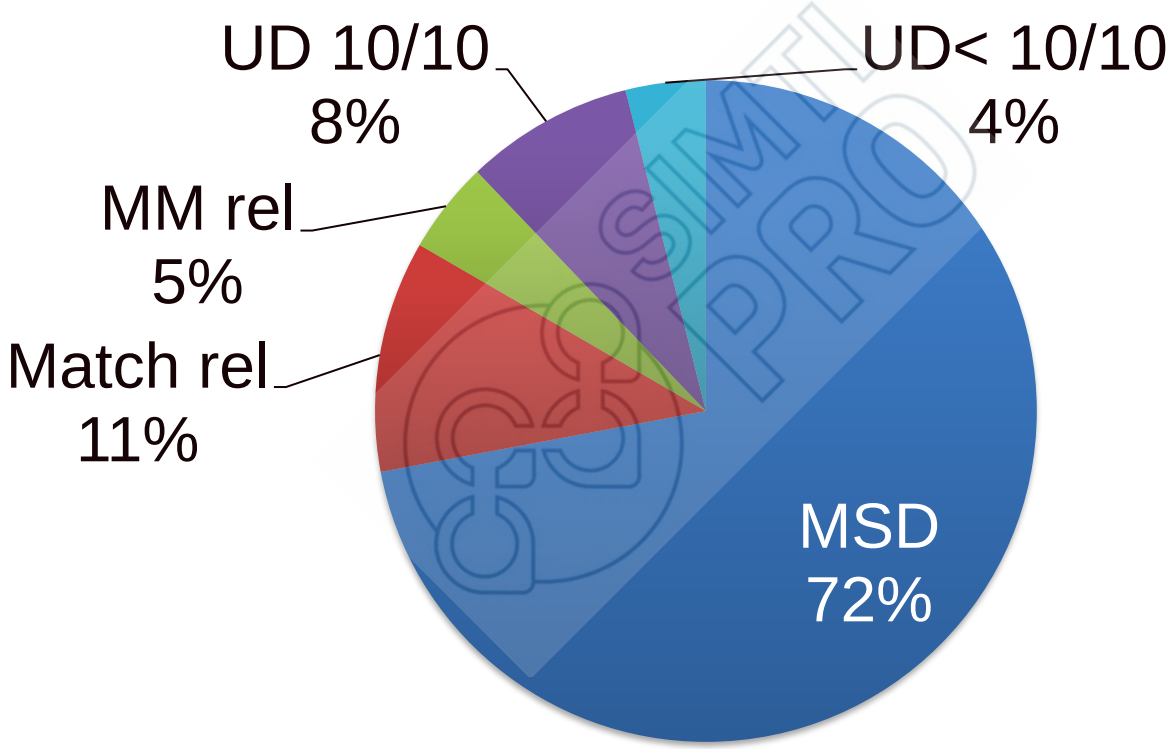
Baronciani D et al Hematopoietic Cell Transplantation in Thalassemia and Sickle Cell Disease:
Report from the European Society for Blood and Bone Marrow Transplantation Hemoglobinopathy Registry: 2000-2017
Blood (2018) 132 (S1): 168.


Age groups at transplant
2891 TDT Patients
Patients
1400
1200
1000
800
600
400
200
0
1184
1193
300
214
0-6
7-14
15-18
19-46
Age groups

Cell Source : 2891 TDT Patients



Donor Types 2891 TDT Patients



Conditioning : 2891 TDT Patients

Conditioning	Patients
MAC	2714 (94.4%)
RIC	175 (6.06%)
Missing	2

Conditioning	Patients (%)
BuCy based	1245 (46.6)
BuCyFlu/Thio based	492 (18.4)
BuFlu/Thio based	379 (14.2)
Other combinations	47 (1.8)
Treo based	508 (19.0)
Missing	220

EBMT 2020 Hemoglobinopathy Registry

2891 TDT Patients: All Patients Outcome (Probability-95% IC)

	OS	TFS	Rejection	NRM
24 mo	90.8% (89.5-91.8)	81.5% (79.7-83.3)	9.6% (7.0-9.6)	9.1% (7.3-9.4)

	Ac GVHD 2-4	Ac GVHD 3-4	Cr GVHD	Cr GVHD EX
24 mo	16.8% (15.4-18.2)	7.6% (6.6-8.6)	15.4% (13.8-17.1)	5.6% (4.6-6.8)

*Baronciani D et al*Hematopoietic Cell Transplantation in Thalassemia and Sickle Cell Disease:
Report from the European Society for Blood and Bone Marrow Transplantation Hemoglobinopathy Registry: 2000-2017
Blood (2018) 132 (S1): 168.

EBMT 2020 Hemoglobinopathy Registry
2891 TDT Patients: Donor and Outcome

Donor	MSD	Match Related	MM Related	UD 10/10	UD<10/10
OS	91.8 %	88.3 %	85.3%	93.2%	81.4%
EFS	83 %	79.5 %	62.4%	85.7%	68 %
Rejection	8.8%	8.8%	22.9%	7.5%	13.4%
NRM	8.1%	11.6%	14.6%	6.7%	18.5%
Ac GVHD >2	6.6%	9,3%	3,1%	12,7%	14.2%
Cr GVHD	13.1%	15.9%	9.3%	15%	17.8%

*Baronciani D et al*Hematopoietic Cell Transplantation in Thalassemia and Sickle Cell Disease:
Report from the European Society for Blood and Bone Marrow Transplantation Hemoglobinopathy Registry: 2000-2017
Blood (2018) 132 (S1): 168.

EBMT Hemoglobinopathy Registry: Age and outcome : 2000-2017

		Age<14years	Age>14years	
TDT	OS	91% (90-93)	83% (79-87)	P<0.001
	EFS	85% (83-86)	77% (72-82)	

*Baronciani D et al*Hematopoietic Cell Transplantation in Thalassemia and Sickle Cell Disease:
Report from the European Society for Blood and Bone Marrow Transplantation Hemoglobinopathy Registry: 2000-2017
Blood (2018) 132 (S1): 168.

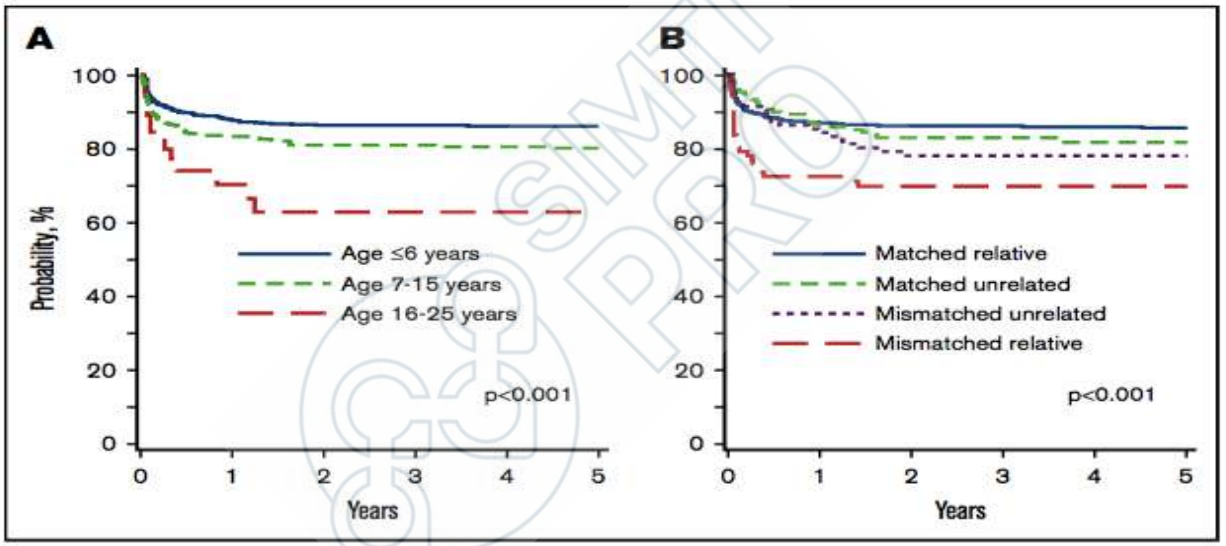
Related and unrelated donor transplantation for TDT :
results of an international survey .
#1110 patients aged <25 years

	HLA matched related	HLA MM related	HLA matched unrelated	HLA MM unrelated
# Patients	677	78	252	103
OS	89%	73%	87%	83%
EFS	86%	70%	82%	78%

-OS and EFS (5 years) were higher for patients<=6 yo
-HLA matched unrelated donor is a suitable alternative if an HLA mached relative is not available

Li C. et al. Blood Advances 2019; 3: 2562-2570

Related and unrelated donor transplantation for B-thalassemia major: results of an international survey



EFS by Age and Donor

Li C. et al. Blood Advances 2019; 3: 2562-2570

Matched family versus alternative donor hematopoietic stem cell transplantation for patients with Thalassemia major.

Experience from a tertiary referral center in South India .

Patients	# 264 (median age 6 years)
Donor	MRD 76%, MUD 22%
Cells source	PB 61%, BM 38%, CB 3%
Thalassemia Free Survival	**MSD 96%, MFD 94%, MUD 84%**
5 years Overall Survival	Age < 7 years = 95% Age > 7 years = 90%

Swaminathan VV. et al. Biol Blood Marrow Transplantation 2020

Multicentric Long Term Results of the NF-08-TM Protocol in Stem Cell Transplant for Patient with TDT.

Multicenter validation of the NF-80 protocol -Blood 2012; 120:3875-81

Patients #	486 (median age 6 years; range 2-23)
Donor	MSD 193, UD 212, PD 35, CB 46
Protocol NF-08-TM	Cyclophosphamide, Busulfan, Thiotepa, Fludarabine
Cells source	PBSC (MNC $8x10^8$/kg)
5 years outcome	
Overall	OS 94.7%, TFS 93.3%, Rejection 2.8%, TRM 5.3%
Matched sibling donor	**OS and TFS 97.4%,**
Unrelated donor	OS 92%, TFS 88.9%
Parental Donor	OS and TFS 94.3%,
Cord Blood (Sibling)	OS 97.8%, TFS 95.3%

Yelin He, et al . A J Hem. August 2020

HCT in adult patients

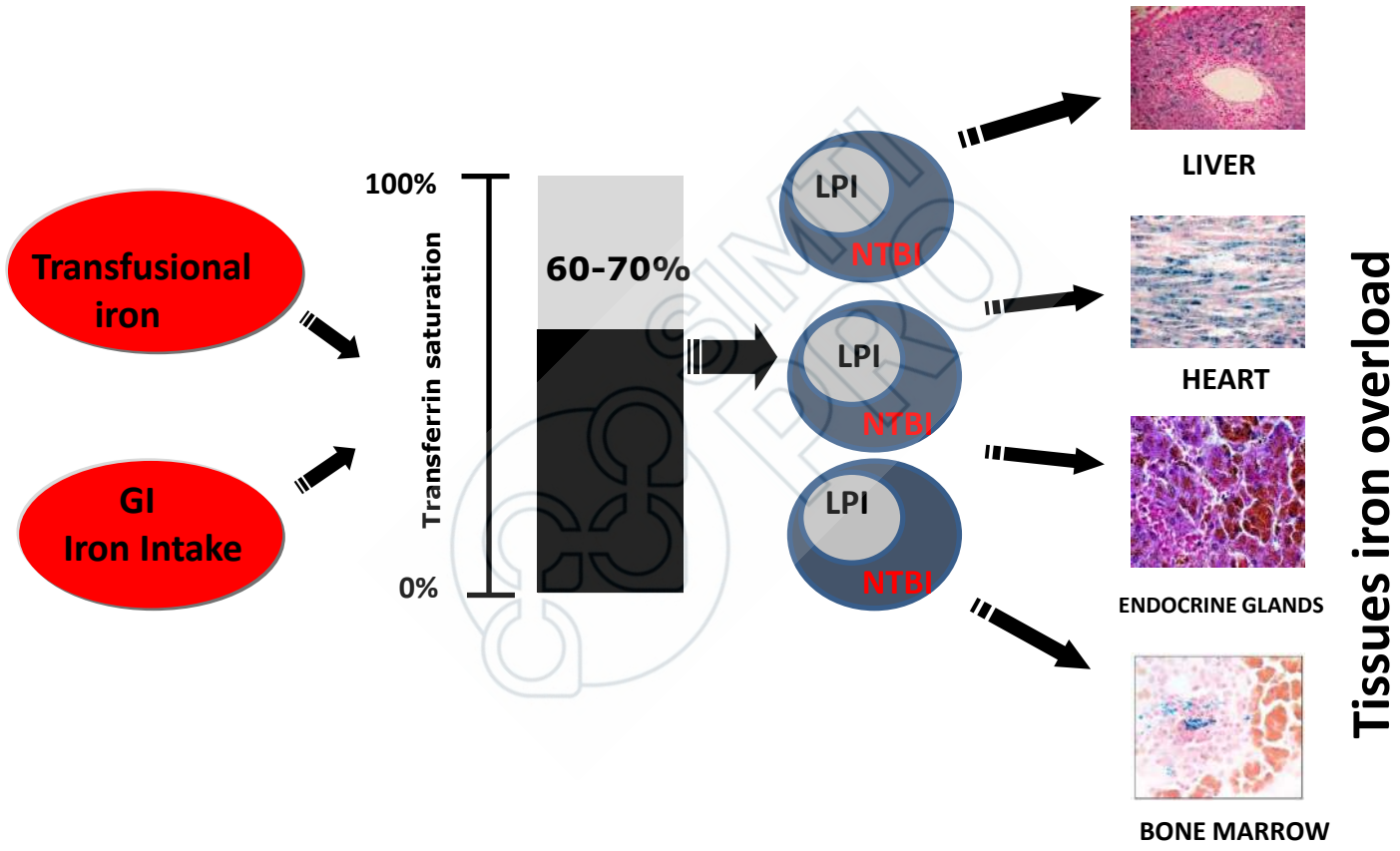
Experience of HCT in adult patients remains very limited, with very few centers performing HSCT in patients over the age of 18 years, and with TRM being persistently around 20%. (Baronciani et al. BMT 2016)

As medical therapy of TDT has improved substantially over the last years, and, therefore, nowadays adult patients are in a much better condition compared to those who underwent HSCT in the past, outcome after HSCT should also improve.

- HSCT in adults who have been well-chelated since infancy should be offered within controlled trials.

- Assessment of clinical condition and adequate transfusions/chelation regimen are the major issues to be evaluated before deciding to perform HSCT.

Haematologica. 2014 May;99(5):811-20.



Annals New York Academy of Sciences 2016

Fe Toxicity tissue =

ΣTissue Iron concentration x Genetics x Environmental Factors x ΔTime

Σ Tissue Iron Concentration	Tissue toxicity sums (Σ) ROS generation
Genetics	The marrow pathology Differences in iron transport Antioxidant defense mechanisms
Environmental Factors	Nutritional status Blood transfusions Drugs that may modulate iron toxicity Co morbidities (Viral infections, ecc) Administration of chelating agents
Time	**Duration of exposition**


Free Radical Biology and Medicine

Review Article

Physiology and pathophysiology of iron in hemoglobin-associated diseases

Thomas D. Coates

Coates TD. Free Radical Biology and Medicine 2014; 72:23-40

Fe Toxicity tissue =

ΣTissue Iron concentration x Genetics x Environmental Factors x ΔTime

DOI 10.1002/ajh.24674

EDITORIAL

WILEY AJH

Transplantation in thalassemia: Revisiting the Pesaro risk factors 25 years later

Pesaro Risk factor	Today interpretation
Not regular long life chelation	Not consistent and sufficient suppression of tissue reactive iron species (NTBI/LPI) over time
Liver fibrosis	Marker of toxic iron exposure and environmental factors (i.e. viral infection) in the liver
Hepatomegaly	Reflects the extend of iron deposition and the time average exposure to transferrin bound iron and toxic reactive iron as loading of the liver significantly increases when NTBI/LPI enters through ion channels and transporters in addition to the regulated entry through transferrin receptor-1 and -2 mediated mechanism mainly operating in the liver
Not only the magnitude of iron overload is important but the duration of exposition to toxic iron is important.	

Am J Hematol. 2017 May;92(5):411-413.

Hematopoietic Stem Cell Transplantation in Thalassemia

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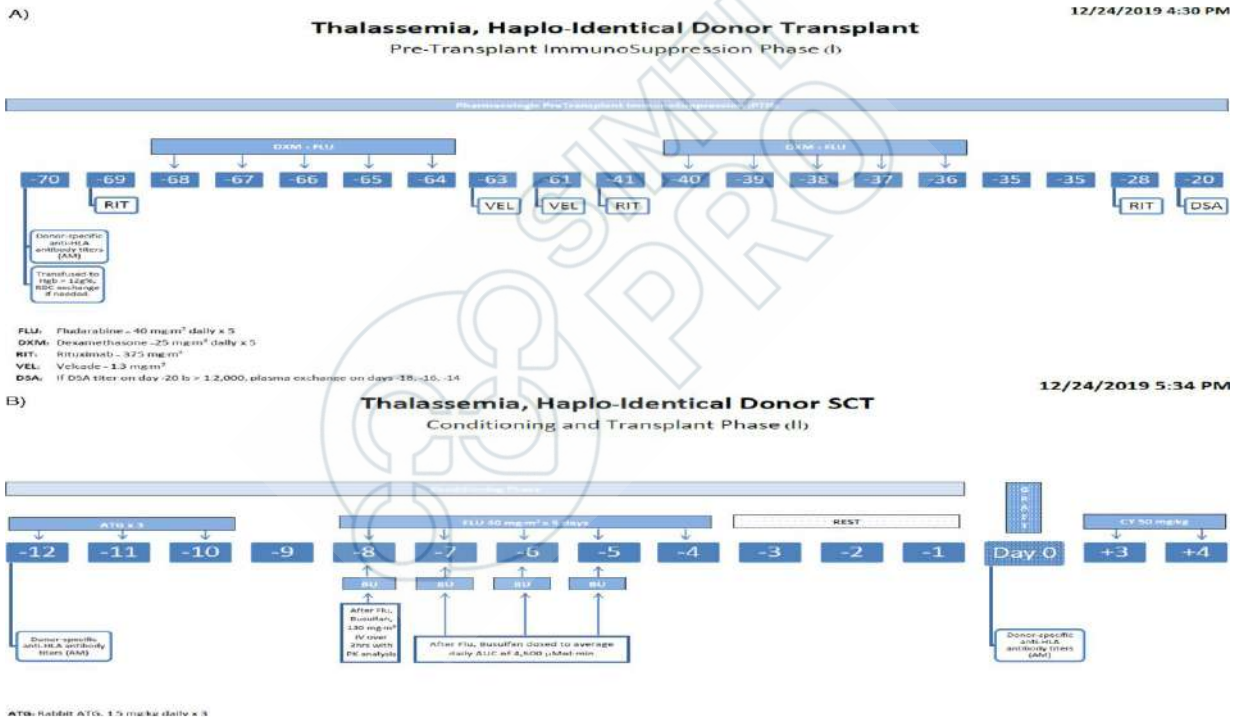
Almost 30 years have passed since the first successful hematopoietic stem cell transplantation in thalassemia and that first patient is now a healthy young adult with a completely normal life. Since that time, more than 3000 such transplants have been performed worldwide. This review provides a brief history of hematopoietic stem cell transplantation in thalassemia and reassesses current clinical results with the objective to provide outcome predictions based on modern transplant technologies. The role of hematopoietic stem cell transplantation in the oral chelation era and implications for possible closure in the approach to future gene therapy will also be discussed.

This demonstrated link between medical therapy and transplantation is a clear demonstration that these two approaches are mutually related. Optimal medical therapy is essential for successful transplant, and the prospective of a potential curative approach is important for optimal medical therapy. Moreover optimization of chelation status leading to transplant (much more feasible today because of recent advances in chelation) could at least partially reverse the demonstrated deleterious effects of iron overload.

Hematopoietic Stem Cell Transplantation for Severe Thalassemia Patients from Haploidentical Donors Using a Novel Conditioning Regimen.

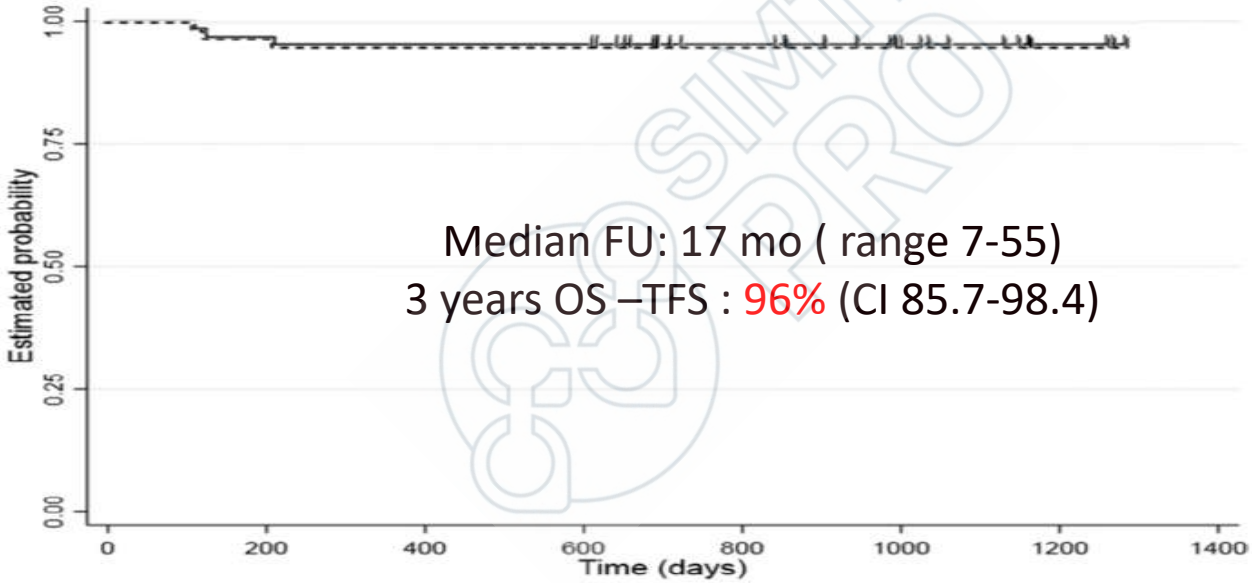
U. Anurathapan et al. Biol Blood Marrow Transplant. 2020 Jun;26(6):1106-1112



HAPLO HCT Using a Novel Conditioning Regimen.

Patients # 83 (median age 12 years, range 1-28)

CD34 dose: $10.4x10^6$/Kg (range 4-19)



Median FU: 17 mo (range 7-55)

3 years OS –TFS : 96% (CI 85.7-98.4)

U. Anurathapan et al. Biol Blood Marrow Transplant. 2020 Jun;26(6):1106-1112.

Sickle Cell Disease

SCD : INDICATIONS FOR HCT EVALUATION

Vaso-occlusive complications of SCD that are not well controlled with medical therapy (hydroxyurea or chronic transfusions).

These may include frequent pain episodes, acute chest syndrome, stroke, or silent cerebral ischemia.

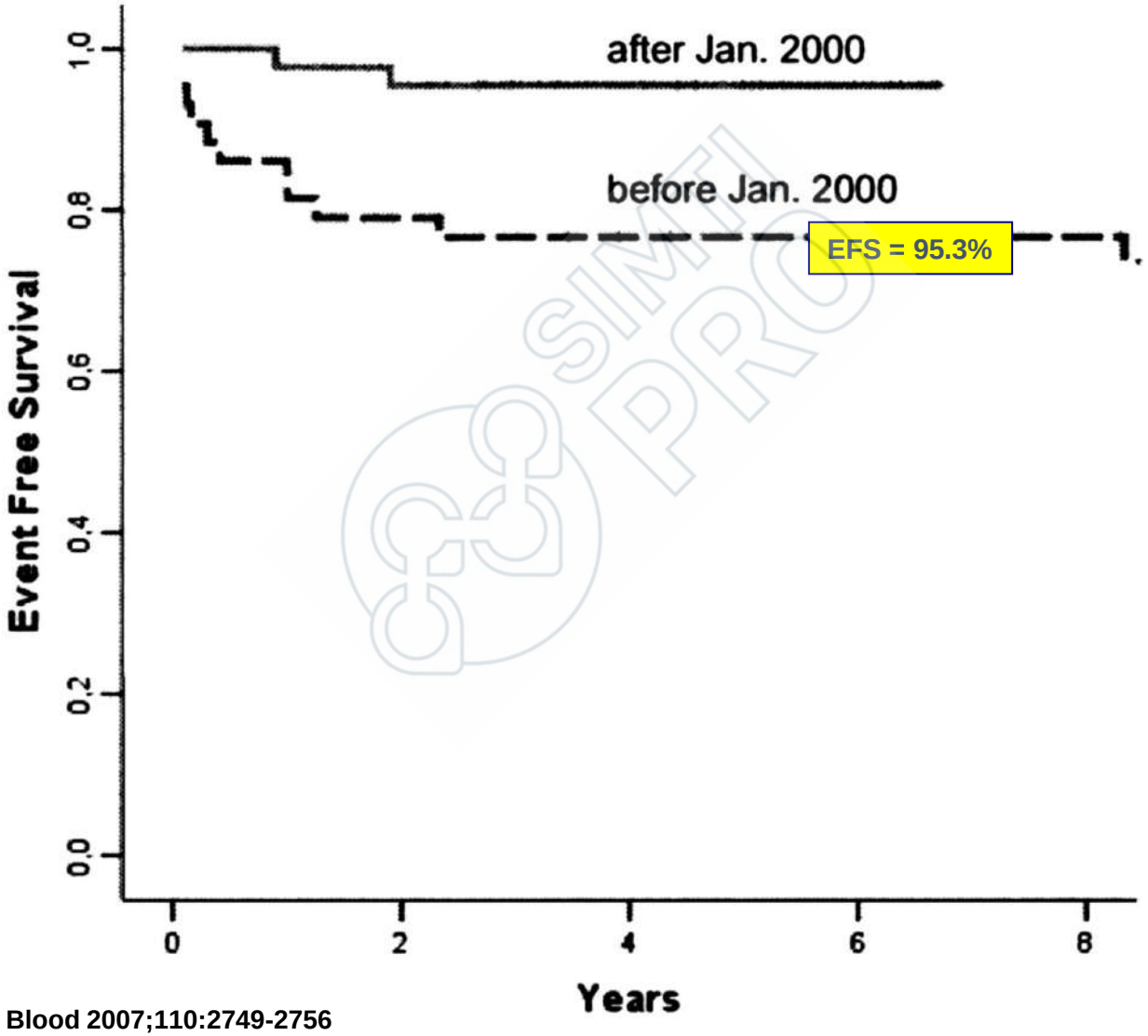
Indication for allogeneic HSCT suggested by Walters et al.

Stroke or central nervous system event lasting longer than 24 h, acute chest syndrome with recurrent hospitalizations or previous exchange transfusions
Recurrent vaso-occlusive pain (more than 2 episodes per year over several years) or recurrent priapism
Impaired neuropsychological function with abnormal cerebral MRI scan
Stage I or II sickle lung disease
Sickle nephropathy (moderate or severe proteinuria or a glomerular filtration rate 30 to 50% of the predicted normal value)
Bilateral proliferative retinopathy with major visual impairment in at least one eye
Osteonecrosis of multiple joints
Red-cell alloimmunization during long-term transfusion therapy

Angelucci et al. Haematologica 2014;99:811-820

Sickle Cell Disease

Comparison of Kaplan-Meier estimates of EFS in patients receiving transplants before (n = 43) and after January 2000 (n = 44): respectively 76.7% and 95.3% at 5 years (P = 0.26).

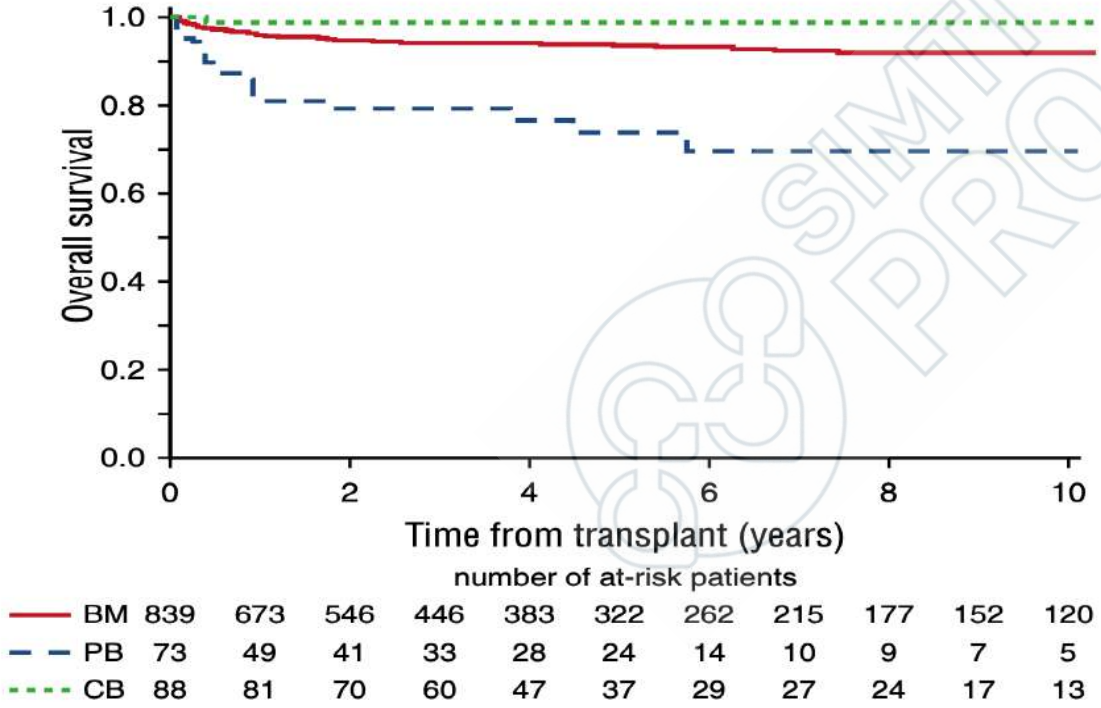


blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

Bernaudin F et al. Blood 2007;110:2749-2756

Sickle cell disease: an international survey of results of **HLA-identical sibling HCT.**
1000 SCD Pts (EBMT,Eurocord,Cibmtr)

B



- HLA-identical sibling transplantation for SCD offers excellent long-term survival.
- Mortality risk is higher for older patients; event-free survival has improved in patients transplanted after 2006.

Blood. 2017;129(11):1548.

Sickle Cell Disease

OPTIMAL Age for Transplant

Children versus adults – In a 2017 retrospective series of 1000 individuals with SCD who underwent allogenic HCT, *Blood. 2017;129(11):1548.*

[

AGE	5 y OS
<16 y	95% (95%CI 93-97)
=>16 y	81% (95%CI 74-88)

●**Older children versus younger children** – A 2017 report retrospectively evaluated outcomes in 161 children treated with HCT for SCD in the US who had survived for two years following transplant [Haematologica. 2017;102(11):1823]).

Overall survival 90%
Children transplanted from age 10 to 21 years had an increased mortality (HR 21.2, 95% CI 2.8-160.8)

SCD: alternative donors. Matched unrelated Cord Blood

- Efficacy of related UCB transplantation is similar to HLA-matched sibling BMT

- The first multicenter unrelated UCB transplant trial, the SCD Unrelated Donor Transplant (SCURT) trial, was discontinued early due to a high incidence of graft rejection *[Biol Blood Marrow Transplant. 2012 Aug;18(8):1265-72.]*.
  - **Engraftment 3/8 (38%)**
- Efficacy was improved in a study that added **thiotepa** to the conditioning regimen:
  - overall survival of 100% and SCD-free survival of 78% *[Biol Blood Marrow Transplant. 2017;23(9):1587]*.

- **Ex-vivo expansion of the UCB graft, is ongoing.** One study that used ex-vivo expanded UCB units reported a high rate of GvHD, but 11/13 patients were off immunosuppression at a median of 14 mo posttransplant *[Blood Adv. 2021;5(3):843]*.

The role of unrelated umbilical cord blood (UCB) transplants in patients with SCD remains experimental.

SCD: alternative donors: matched unrelated donor.

- The first pediatric multicenter MUD HSCT trial was published in 2016 and included a high TRM and chronic GvHD *[Blood. 2016;128(21):2561]*.
- A pilot study that used the same conditioning plus abatacept in 7 patients reported *Blood Adv. 2020;4(16):3894*
  - 2-years OS of 100% and
  - SCD-free survival of 93%,
  - low incidence of GvHD
- Results from the bone marrow arm of the SCURT trial are pending [*Biol Blood Marrow Transplant. 2012 Aug;18(8):1265-72]*.
- Additional trials are ongoing,

SCD: alternative donors: matched unrelated donor.

blood®
Prepublished online September 13, 2016;
doi:10.1182/blood-2016-05-715870

A BMT CTN phase II trial of unrelated donor marrow transplantation for children with severe sickle cell disease

Shalini Shenoy, Mary Eapen, Julie A. Panepinto, Brent R. Logan, Juan Wu, Allistair Abraham, Joel Brochstein, Sonali Chaudhury, Kamar Godder, Ann E. Haight, Kimberly A. Kasow, Kathryn Leung, Martin Andreansky, Monica Bhatia, Jignesh Dalal, Hilary Haines, Jennifer Jaroscak, Hillard M. Lazarus, John E. Levine, Lakshmanan Krishnamurti, David Margolis, Gail C. Megason, Lolie C. Yu, Michael A. Pulsipher, Iris Gersten, Nancy DiFronzo, Mary M. Horowitz, Mark C. Walters and Naynesh Kamani

Figure 1A: Event-Free Survival

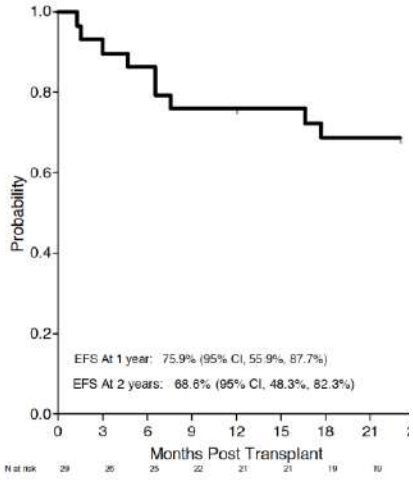


Figure 1B: Two-year Overall Survival

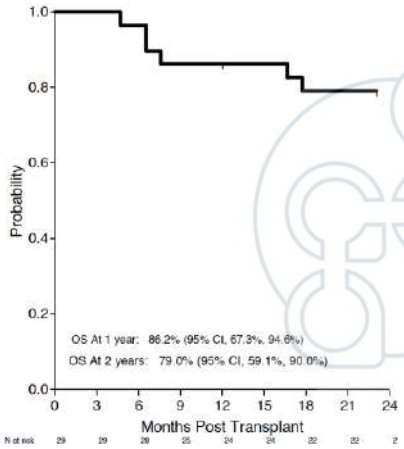


Figure 2A: 100-Day Probability of Acute Grade II-IV Graft-Versus-Host Disea

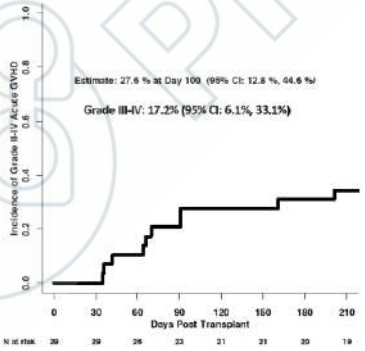
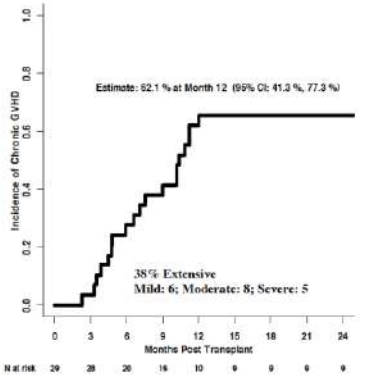


Figure 2B: One-year Probability of Chronic Graft-Versus-Host Disease

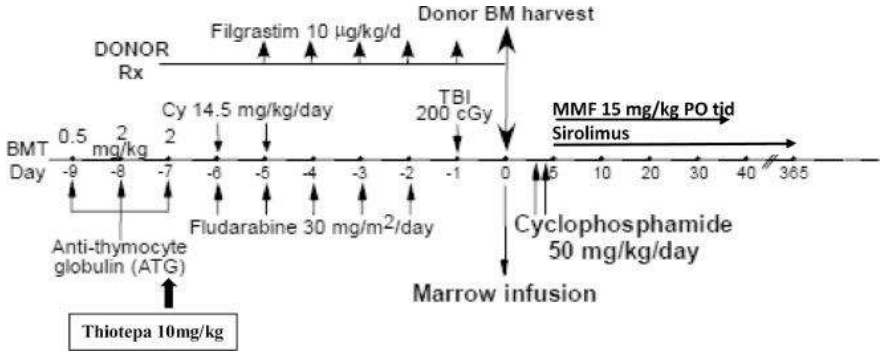


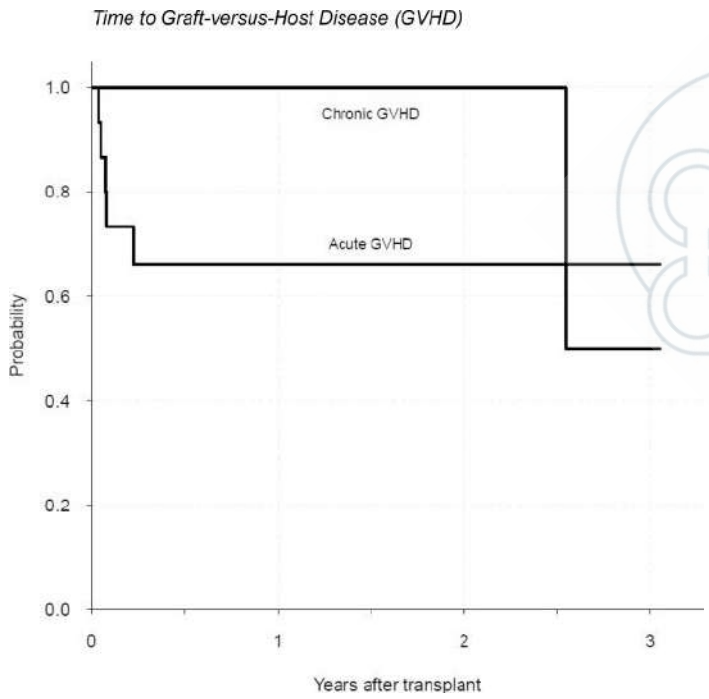
Even if results comparable to those obtained in TM can be expected, there are no firm data on outcome of HSCT from matched unrelated donors for SCD

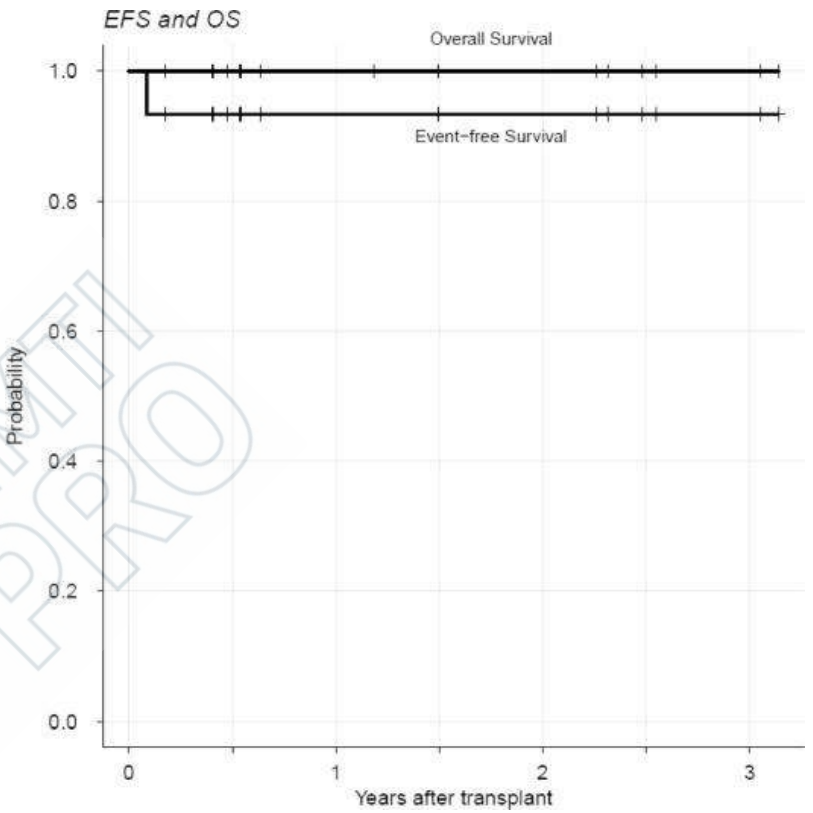
SCD: alternative donors: haplo related donor

- 14 adults (BMT-CTN protocol) with SCD who underwent HSCT with a reduced-intensity conditioning regimen and PT-PCY. [Blood. 2012;120(22):4285].
  - By one year, **50% graft failure**., No GVHD. Additional studies using this approach are underway,

- Haploidentical regimens for SCD using the PT-CY have been used but additional myelosuppression and immunosuppression are required to overcome the engraftment barrier and maintain graft survival *Blood Adv. 2017;1(11):652.*
  - **Pilot data from a large trial that included thiotepa in the conditioning regimen were encouraging [**Biol Blood Marrow Transplant. 2019;25(6):1197].
  - Small series reported that increasing the dose of TBI and using PBSC reduced graft failure [*Lancet Haematol. 2019;6(4):e183.; Biol Blood Marrow Transplant. 2018;24(8):1759*
- Ex-vivo T- and B-cell depletion of PBSC (CD3/CD19- or T-cell receptor αβ/CD19 depleted cells)
  - 25 patients: At a median follow-up of 22 months: **88% SCD free survival with no severe GvHD** *[Hematol Oncol Stem Cell Ther. 2020;13(2):98]*.
- A large number of trials evaluating haploidentical transplant for patients with SCD are planned or ongoing.







[Biol Blood Marrow Transplant. 2019;25(6):1197].

Probabilities of event-free survival (EFS) and Overall survival (OS) after haploidentical BMT with PTCy plus thiotepa in 15 participants with severe SCD.

Major differences between thalassemia major (TM) and sickle cell disease (SCD) on HSCT perspective.

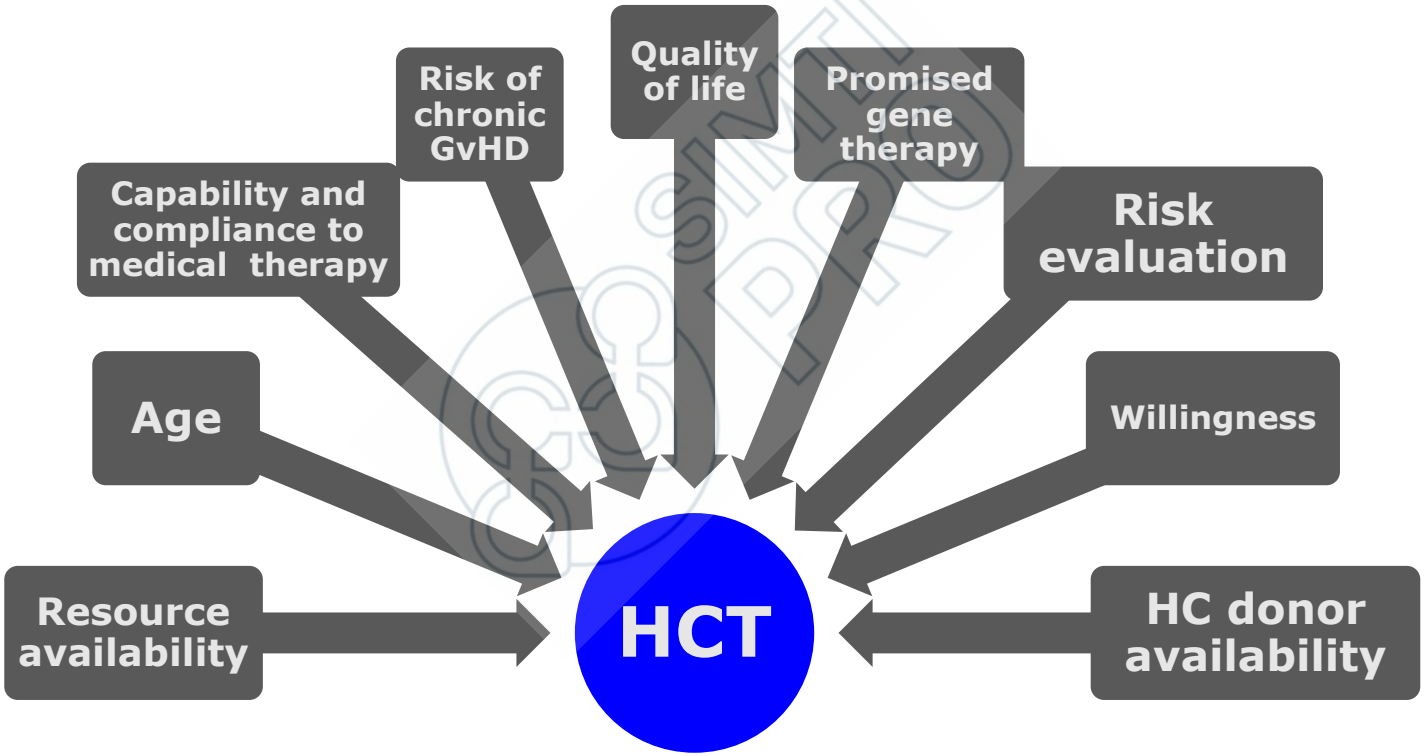
Prognostic criteria for disease severity	Homogenous pattern for TDT	Wide genetic varisability. Inconsistent development of complications
Accepted HSC indication	HLA identical donor (sibling and MUD). As soon as possible	Match sibling donor and complications requiring treatment
HCTs performed	>10000	>1000
Risk factor for HCT outcome	Age and iron related organ dysfunction	Age, history of cerebral events
Alternative effective therapy	Transfusion and chelation	OHU, transfusion and chelation, new drugs
Key issue for HCT outcome	Optimal medical therapy	Cure from chronic inflammatory and prevention of SCD related tissue damage
Conditioning	Full intensity	Non Myeloablative possible
Gene therapy	ongoing	ongoing

Modified from Haematologica 2014;99:811-820

HCT costs

	HCT cost	Expected life year in case of HSCT in infancy.
Matthes-Martin S et al.. Biol Blood Marrow Transplant. 2012.	$: 112,000-150,000	$: 1,900
Diep PP,et al. Bone Marrow Transplant 2018;53:657–660	€: 132,169	///
Broder MS, et al. Am Health Drug Benefits 2017;10: 366–374.	$: 289,283 MAC $: 253,467 RIC	///
Bourgeois W et al. Bone Marrow Transplant 2018 Aug 20	Unrelated HCT €: 280,544 $: 317,994	///

Conclusion 1: Transplantation in Hbpathies: an Individual decision process



Angelucci, E. Hematology 2010;2010:456-462

Conclusioni - 2

- Allogeneic HCT is a well established and worldwide reproduced curative procedure for Hbpathies
- For TDT and SCD: as soon as better
- Remaining medical need:
  - Patients lacking and HLA identical donor
  - adult patients

- Allo HCT is the **bench marking** for any new curative therapy for TDT

MEDICINES CAN CURE DISEASES BUT ONLY DOCTORS CAN CURE PATIENTS.

C. G. Jung

ACCADEMIA di FORMAZIONE

SIMTI

Emoglobinopatie:
supporto trasfusionale e nuovi approcci terapeutici

Thank you for your kind attention

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