In the name of GOD

MATCH FAMILY

VS

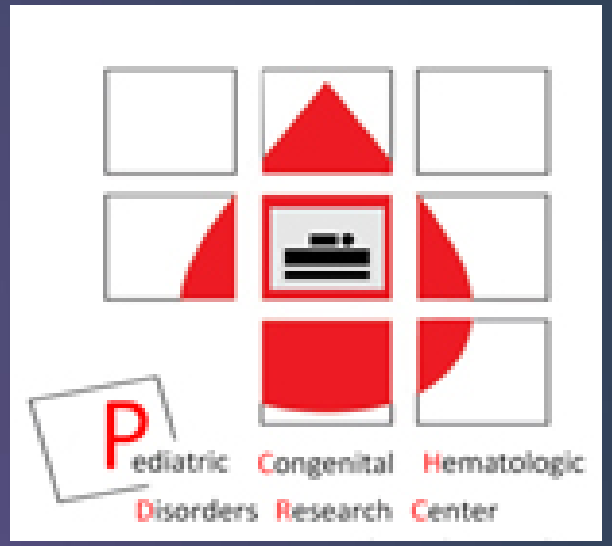
ALTERNATIVE DONOR

HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

IN PATIENTS OF B MAJOR THALASSEMIA

BIBI SHAHIN SHAMSIAN.MD

MOFID CHILDREN HOSPITAL



Hematopoietic cell transplantation and cellular therapy survey of the EBMT: monitoring of activities and trends over 30 year.

Bone Marrow Transplantation (2021) 56:1651–1664. Jakob R. Passweg

- **Annual report of the European Society for Blood and Marrow Transplantation (EBMT)**
- **Changes over 30 years(1990-2019)**
- **2019 ;96% return rate**
- **1990 First survey ; 143 centers , 20 countries 4234 HCT**
- **2019 :700 centers (42 European and 11 collaboraing countries)& 48,512 HCT in 43,581 patients , 51 countries**
- **11 collaborating non-European countries - 2019 EBMT survey: Algeria, Iran, Iraq,** Jordan**…….31 actively transplanting centers , make up 5.3% of the total data**
- 19,798 **(41%) Allogeneic** & 28,714 **(59%) Autologous**
- Main indications were **Myeloid malignancies** 10,764 (25%), **Lymphoid malignancies** 27,895 (64%), & **Nonmalignant disorders 3173 (7%).**

Hematopoietic cell transplantation and cellular therapy survey of the EBMT: monitoring of activities and trends over 30 year. Bone Marrow Transplantation (2021) 56:1651–1664. Jakob R. Passweg

- **Next to the massive expansion of HCT technology most notable developments include Success of :**
  - **Unrelated Donor**
  - **Haplo identical HCT ; any family member with 2 or more (but not more than 5) loci mismatches** within the loci HLA-A, -B, -C, -DRB1, and -DQB1 in GvH and/or HvG direction)

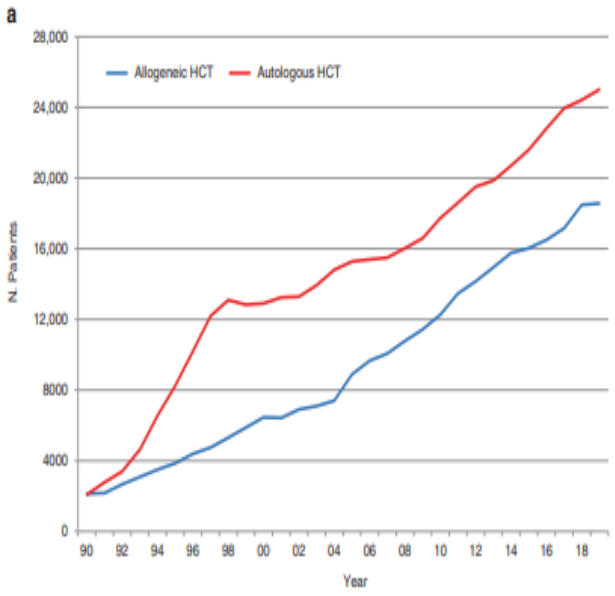
Donor type and stem cell source
Bone Marrow Transplantation (2021) 56:1651–1664. Jakob R. Passweg

- In 2019, the Overall numbers of patients treated with Family donors : stable, but Variation :
- HLA identical sibling and syngeneic twin donors decreased by 6%
- Increase of Unrelated Donors of 1.2%.
- Increases of Haploidentical Donors of 11%
- ***** Increase followed by decrease in the number of cord blood transplants The cord blood HCT rate continued to decrease slowly (1%)

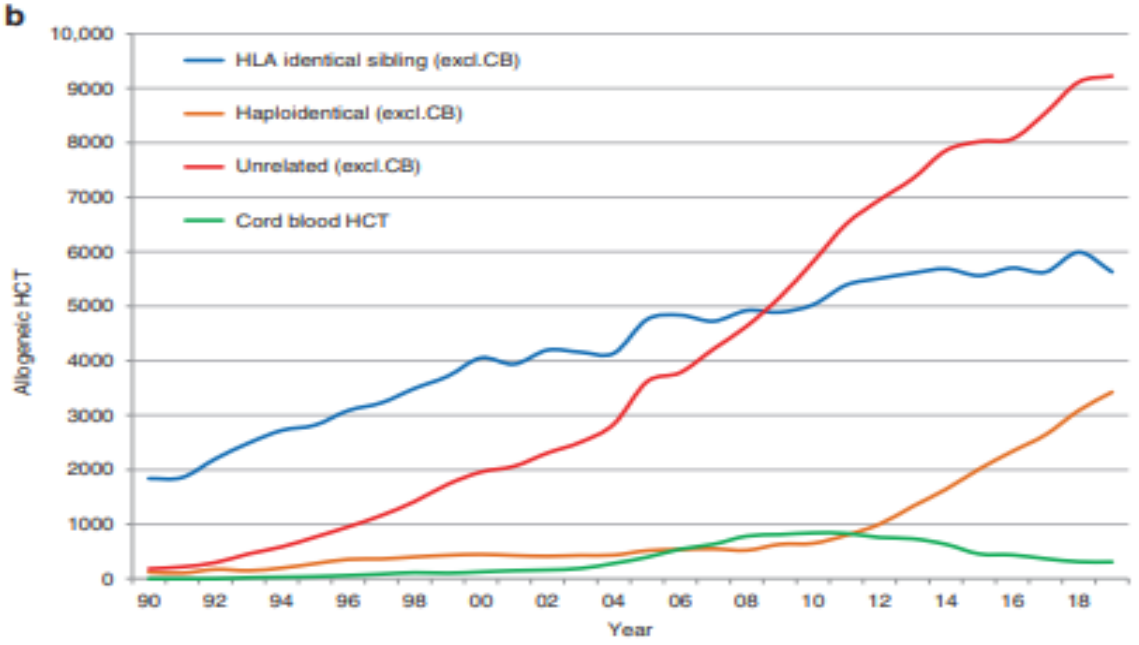
Development of HCT from 1990 to 2019. In the last year,.

10% increase for Haploidentical donors, & 1.9% for unrelated donors. Bone Marrow Transplantation (2021) 56:1651–1664. Jakob R. Passweg

A: Autologous & Allogeneic HCT.



B: **Donor type in Allogeneic HCT**



EBMT Survey Report 2019 in pediatrics.

Bone Marrow Transplantation (2021) 56:1651–1664. Jakob R. Passweg

- In 2019: Pediatric < 18 Y : 5189 HSCT
- 3990 Allogeneic & 1199 Autologous
- Most HCT ;AML 70% ,ALL ,45% , NMD 39% (include PID)
- 1625 Family HSCT ; Haploidentical Relative: 42% ;
- Cord blood stem cells ; 119 patients
- Main indications in Autologous HCT ; Solid tumors, (647 HCT) ; Neuroblastoma (49%)

Thalassemia Syndrome, B Thalassemia

Said Y. Mohamed. Hematol Oncol Stem cell Ther (2017) 10 , 290-298

- **Thalassemia:**
- Patients with severe thalassemia (Thal) commonly have disease-related morbidities, and despite state-of-the-art supportive care with blood component support and chelation therapy, **their survival is shortened compared with the general population.**

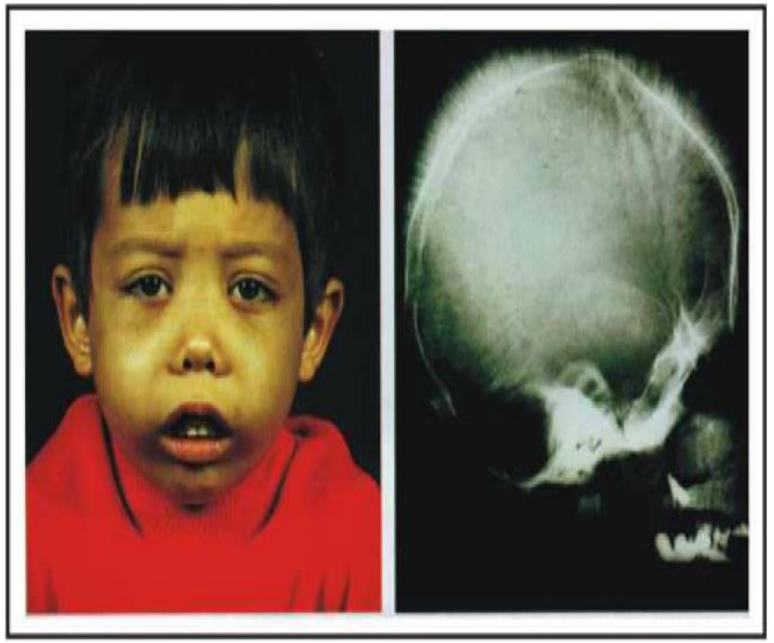
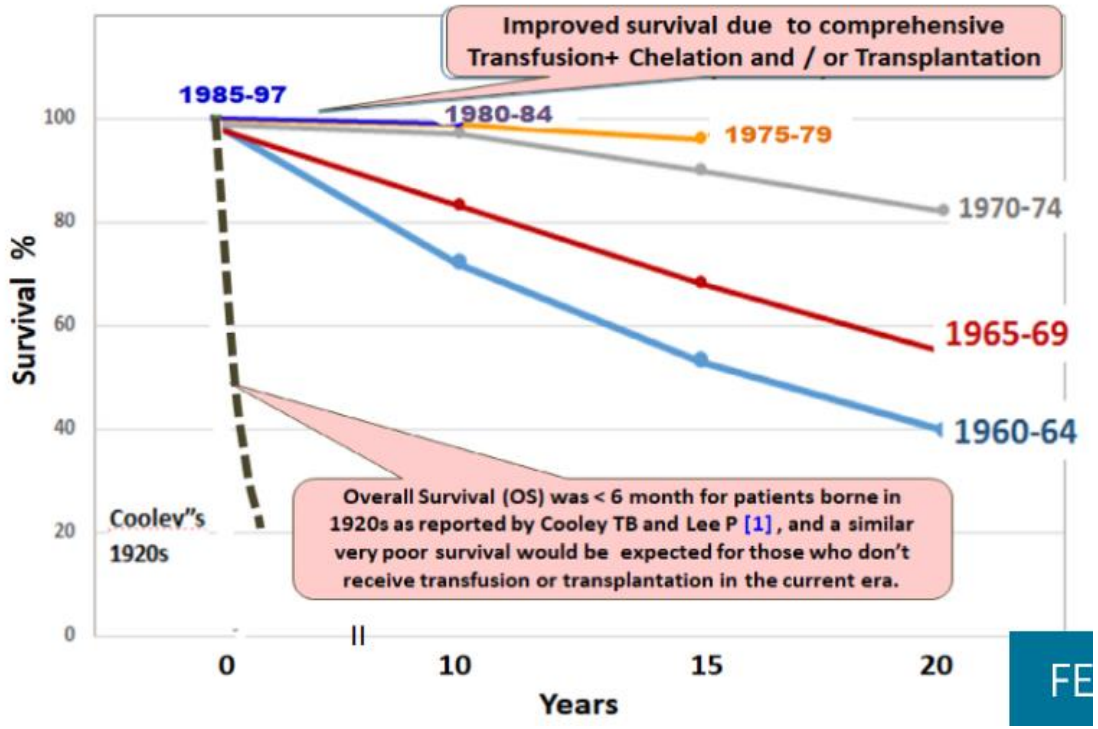


Fig. 2. Beta thalassemia major – bone changes

Comorbidities In TDT in Patients in England, 10 year Retrospective Cohort Analysis(2009-2018). 2020. Minesh jobanputra etal . Br Jhaematol

Said Y. Mohamed. Hematol Oncol Stem cell Ther (2017) 10 , 290-298



- 10 year Mortality rate in TDT patients 6.2% (> 5 times more) versus 1.2% general population
  - Osteoprosis: 40%
  - Endocrine Disordrers :40%
  - Diabetes; 34%
  - Cardiac Disease: 18%

HSCT in Thalassemia

- **Now; Allogeneic HSCT is the only established treatment modality that provides a possibility of cure.**
- **It was first reported by Thomas and associates in 1982**
- **Allo-SCT** is **cost effective compared** with the **conventional transfusion support and chelation therapy** for severe thalassemia patients(transplants are not always available)
- **Approximately 70% of transplants in the last decade used HLA matched sibling donors(MSD)**

British Journal of Haematology, 2018.182, 554–558

HSCT In B major Thalassemia
Olga Mulas. *Journal of Clinical Medicine.2022*

- The success of transplant procedures in patients with beta-thalassemia major (β-thalassemia) goes hand-in-hand with:
- Improvements in disease knowledge
- Better Supportive Care
- Discoveries in Immunogenetics
- Increase in Stem Cell Sources
- &Enhancement of Conditioning Regimen

Case presentation
Thalassemia

B Major Thalassemia

3 Y old girl, Second Child

Diagnosis: B Major Thalassemia (On Blood transfusion and iron Chelation ,Osveral)

Pesaro classification :Class 1

Ferritin :1200

HSCT: MSD ,Brother – 5 Y old ,Full Match, R& D

CMV pos , Both R & Donor BG:O+ pos

Source HSCT: PB

Condition :BU + CPM + Rabbit ATG

GVHD : Cyclos + MTX

Engraft :Day + 15 **Chimerism: 98%**

She is good and is on follow UP

Case presentation Thalassemia

- **A 16 Y old girl** . B MT since 6 mo.
- Blood Transfusion & Iron Chelation (**Desferal – Osveral & L1**)
- Ferritin : 4000-5000,Hepato Splenomegaly
- **Class 3 Pesaro Classification (MRI T2 star & Liver biopsy)**
- **At time of HSCT Ferritin : 3000**
- **Allo HSCT , MSD ,Full match, Sister 12 y, Source: BM**
- **protocol HSCT - 26 Thalassemia**
- **Chimerism : 95%**
- **2.5-3 years later ; Rapid decrease Chimerism & second Graft Rejction & now she is agaian on blood transfusion**

Protocol 26 Thalassemia <17y
BLOOD, 15 AUGUST 2004 VOLUME 104, NUMBER 4

New approach for bone marrow transplantation in patients with class 3 thalassemia aged younger than 17 years

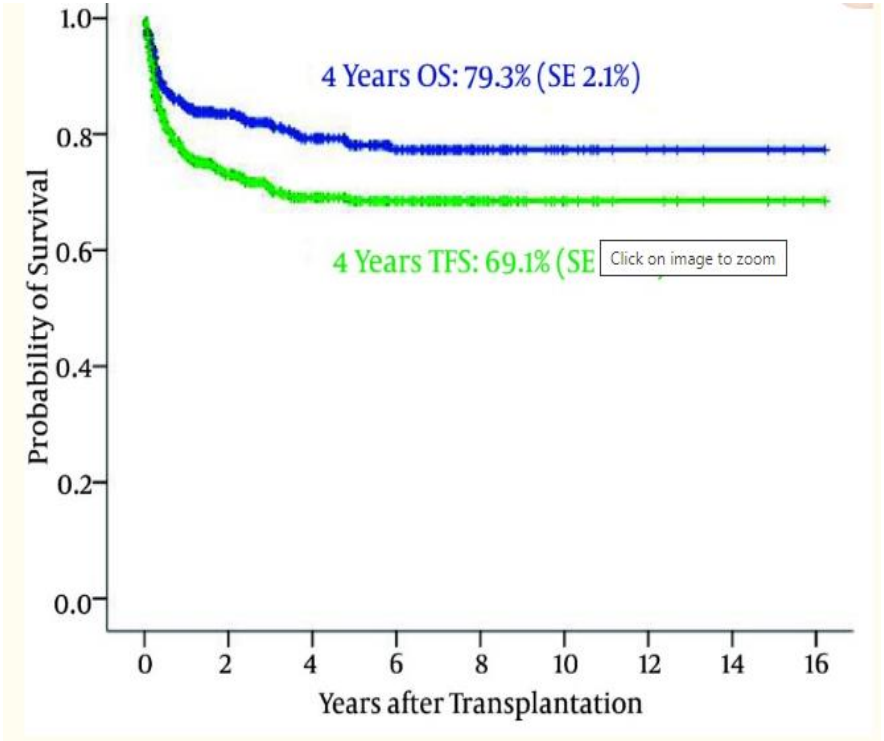
Pietro Sodani, David Gaziev, Paola Polchi, Buket Erer, Claudio Giardini, Emanuele Angelucci, Donatella Baronciani, Marco Andreani, Marisa Manna, Sonia Nesci, Barbarella Lucarelli, Reginald A. Clift, and Guido Lucarelli

When prepared for transplantation with busulfan (BU) 14 mg/kg and cyclophosphamide (CY) 120 to 160 mg/kg, patients with thalassemia in risk class 3, aged younger than 17 years, who receive transplants from HLA-identical donors, had a 30% incidence of transplant rejection with recurrence of thalassemia. This, relatively poor, outcome was ascribed to insufficient immune suppression or to inadequate eradication of the thalassemic marrow, or both. In an attempt to enhance both immune suppression and eradication of the thalassemic clones, hydroxyurea, azathioprine, and fludarabine were added to the BU and CY. This regimen, called protocol 26, was applied to 33 consecutive patients with class 3 thalassemia aged younger than 17 years and was well tolerated with 93% survival. The incidence of recurrent thalassemia after the transplantation decreased from 30% to 8%. (Blood. 2004;104:1201-1203)

We attempted to suppress erythropoiesis by intensive hypertransfusion and chelation. Between day −45 and day −11 before the transplantation, 40 mg/kg deferoxamine was continuously infused through a central venous catheter each 24 hours. Red cells were transfused every 3 days to maintain the hemoglobin level between 140 and 150 g/L (14 and 15 g/dL). During this time interval hydroxyurea 30 mg/kg daily and azathioprine 3 mg/kg daily were administered to eradicate marrow, and growth factors, granulocyte colony-stimulating factor (G-CSF; Neupogen, Filgrastim; Dompè-Biotec, Milan, Italy) and erythropoietin (Globuren; Dompè-Biotec), were given twice weekly to maintain stem cell proliferation in the face of hypertransfusion, thereby facilitating the effect of the hydroxyurea. Fludarabine was administered at a dosage of 20 mg/m^2/d from day −17 through day −13. Starting on day −10, 14 doses of busulfan (BU) 1 mg/kg were administered orally 3 times daily over 4 days (total dose 14 mg/kg over 4 days), followed by intravenous cyclophosphamide (CY) 40 mg/kg daily on each of the next 4 days (total dose 160 mg/kg).

20 Years of Experience on Stem Cell Transplantation in Iran.Ardeshir Ghavamzadeh & etal. 2013

- **1991 -2011; 3237 HSCT**
- **2205 :Allogeneic HSCT**
- **508 P: B-MT** , Sickle cell thalassemia (n=4), Sickle- cell disease (n=2)
- Median age ; 7 y (2-29)
- **4-year OS and DFS (B- MT):79.3% & 69.1%**
- 316 P Acute GVHD Grade I (n= 88)
- Grade II (n= 118) Grade III (n= 82) &
- Grade IV (n= 28)



HSCT B Major Thalassemia. Hematology/Oncology Clinics of North America Volume 32, Issue 2, April 2018, Pages 317-328

- Allogenic HSC transplantation (HSCT) has been proposed as a possible curative option since the **1980s**
- **Since the curative potential of Allogeneic HSCT for TM was first emonstrated, more than 3000 transplant procedures have been reported worldwide.**

Challenges in Thalassemia HSCT

British Journal of Haematology, 2018.182, 554–558.Guido Lucarelli.

- **Active, or even hyperactive immune** system, use of chronic blood transfusions contribute to Alloimmunization against donor-specific HLA antigens.
- Age of HSCT
- Hepatic complications :Sinusoiedal obstructive syndrome(SOS)
- High risk (HR) :**Conditioning Regimen-Related mortality** & **Graft Rejection**, range of 5–30%
- Mixed Chimerism (30%)

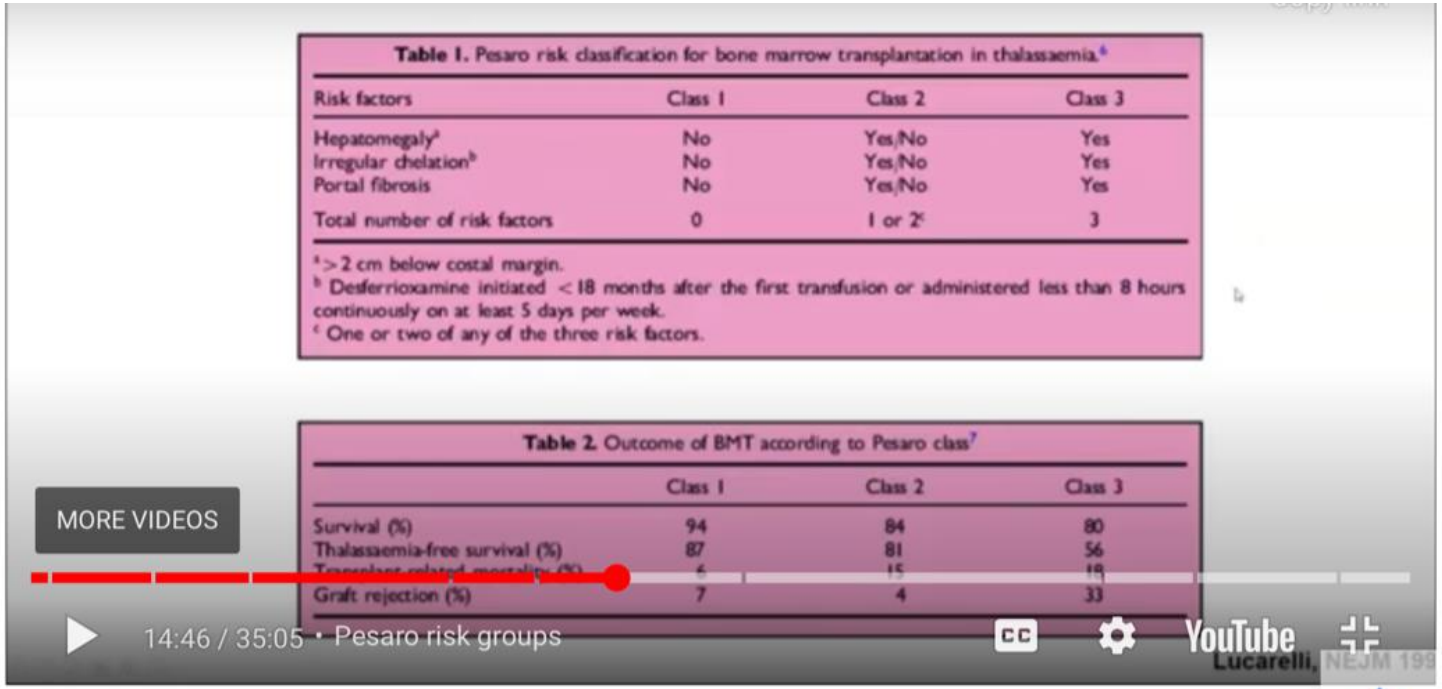
Outcome of HSCT in B Major Thalassemia

- **Outcomes** in β-thalassemia undergoing HSCT are dependent on:
- **Availability of a fully matched HLA donor???? And the problem of finding a suitable sibling donor with well-matchedhuman leukocyte antigens is still a major obstacle patients to curing these patients**
- Use of an appropriate conditioning regimen depending on the **pre-transplant risk assessment**
- Supportive care
- Adequate post-transplant follow-up (such as iron chelation therapy….)

British Journal of Haematology, 2018.182, 554–558

Sun et al. / Biol Blood Marrow Transplant 25 (2019) 15921596

Pesaro classification(1990) : Inadequate chelation, hepatomegaly, portal fibrosis class (I, II, III) survival 90%, 84%, and 78% for class 1, 2, and 3 Adult thalassemia P: higher risk -65% cure rate. Class 3 also contained a group of very high-risk (HR) patients, typically aged ≥ 7 years and with liver size ≥ 5 cm from the costal arch



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This webinar was accredited by the EBAH-CME credits system.

HSCT for Major Thalassemia & Alternative Donors

- Matched related Donor in BM-THALLASEMIA: primary treatment Choice
- **Finding a suitable donor is still a major problem.**
- **A (HLA)- matched donor can be found for only 20–30% of thalassaemia major patients**
- In recent years, there has been an increase in the number of transplants from **Alternative Donors (HLA-matched unrelated donor, unrelated cord blood, HLA-haploidentical relative)**
- **High-resolution HLA typing:** suitable unrelated (Fully HLA-matched donors) for compatibility of HLA class I and class II loci

Review of old articles by alternative donors in Major Thalsassemia

T cell-depleted hla-haploidentical stem cell transplantation in thalassemia young patients young patients. Pietro Sodani. Pediatric Reports 2011; 3(s2):e13. Italy

- **Javid Gaziev etal , 2000:**
  - **Pesaro transplantation group ; HSCT / MT HLA-mismatched Sibling donors , Classical Bu-CY conditioning Regimen:**
  - **OS, EFS , Graft failure & A GVHD :65%, 21%, 55% and 37%, respectively**
- **Sodani et al, 2010:**
  - **Haplo identical HSCT 31 p , 27 mother , 2 father , 2 brother**
  - **Intensive hypertransfusion and chelation**
  - **Adding Hydroxycarbamide & Azathioprine**
  - **GR & TRM :29% and 14%,**
  - **OS and EFS :90% and 61%**

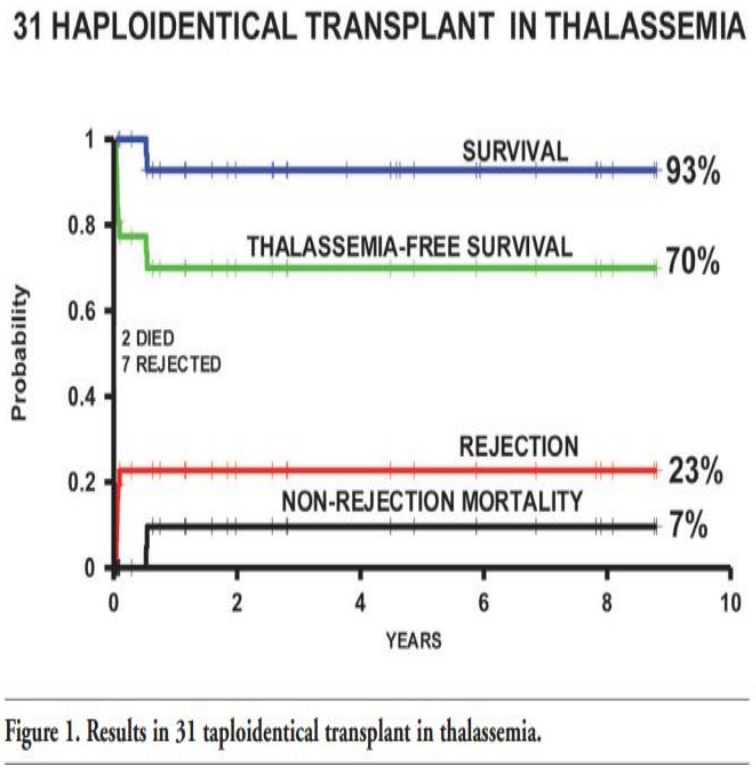


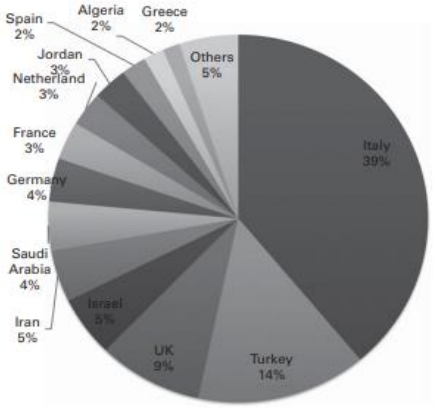
Figure 1. Results in 31 taploidentical transplant in thalassemia.

Conditioning Regimens in Patients with β-Thalassemia Who Underwent HSCT : A Scoping Review. *Journal of Clinical Medicine* Olga Mulas. 2022

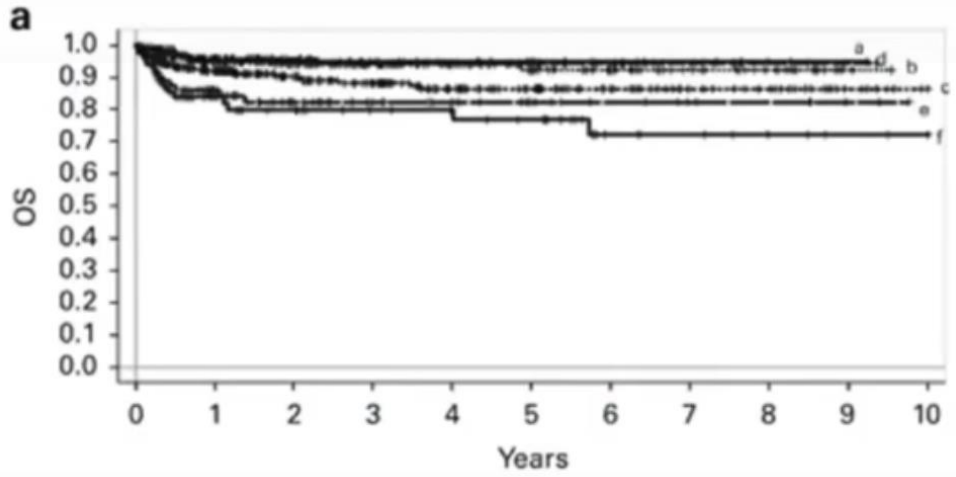
- **Hyper transfusion & Hydroxyurea &/ Azathiperine +** MAC - Busulfan & Cyclophosphamide (Bu/Cy) : Gold standard in BMT
- **& Novel transplant-conditioning Regimens ;**
  - **Addition of FLudarabine (FLU) and/or Thiotepa (TT) to Bu & Cy**
  - **or Treosulfan with FLU and/or TT with favorable outcomes.**
- **Conditoning Regimen :Risk Score, Donor Type, GVHD prophylaxis, Age, Graft Source**

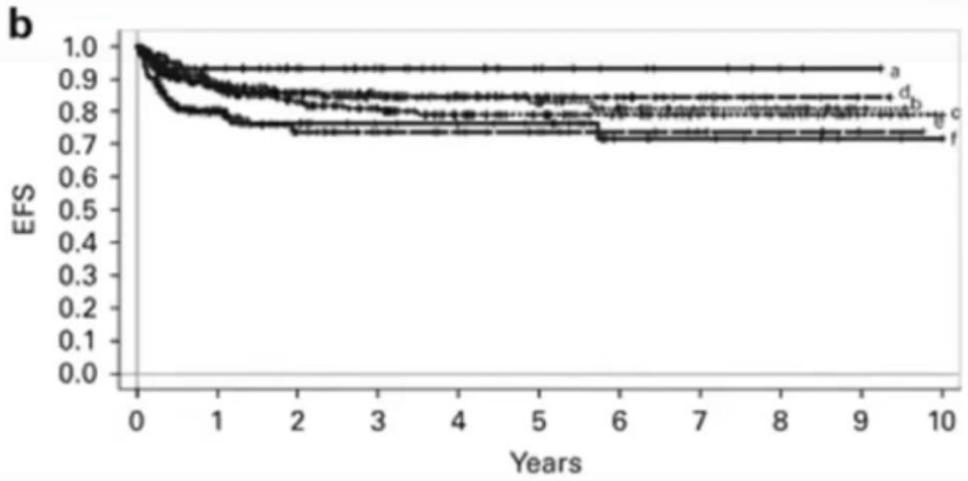
EBMT REPORT : HSCT in thalassemia: a report from the European Society for Blood and Bone Marrow Transplantation Hemoglobinopathy Registry, 2000–2010. D Baronciani. Bone Marrow Transplantation (2016).

- **EBMT REPOT: Retrospective non-interventional study, extracting data from the EBMT hemoglobinopathy prospective registry database.**
- **1493** consecutive patients : BM transplanted **2000 -2010.**
- **In total, 1359 (91%) :patients < 18 years old**
- **1061 HLA identical sibling donor**
- Follow UP post HSCT for 2-year : (OS) and EFS : 88 ± 1% and 81 ± 1%, respectively.
- **HSCT / HLA Ag-identical sibling : best results, with OS and EFS of 91 ± 1% and 83 ± 1%, respectively**
- **The threshold age for optimal HSCT outcomes :14 years, with an OS of 90–96% and an EFS of 83–93%.**



2000 to 2010
1,493 transplants
1,061 sibling BMT





	Patients	A) OS Events	A) OS 2-yrs. OS	B) EFS Events	B) EFS 2-yrs. pEFS
a) < 2 years	66	3	0.95±0.03	4	0.93±0.03
b) 2-<5 years	266	13	0.94±0.02	32	0.86±0.03
c) 5-<10 years	352	33	0.90±0.02	52	0.83±0.02
d) 10-<14 years	197	8	0.96±0.02	24	0.86±0.03
e) 14-<18 years	97	14	0.82±0.04	20	0.74±0.05
f) ≥18 years	82	16	0.80±0.05	18	0.76±0.05

CIBMTR; Related and unrelated donor transplantation for B-MT : Results of an international survey. Chunfu Li .Blood advances. 10 SEP 2019 x VOLUME 3, NUMBER . USA, China, India

- **1110 patients HSCT/ Y 2000 – 2016**
- **Age < 25 HSCT (age <1-25 Y)**
- **HLA-matched related (n = 677; 61%)**, HLA-mismatched related (n= 578; 7%), **HLA-matched unrelated (n = 252; 23%),** & HLA-mismatched unrelated (n = 103; 9%) donors
  - Condition Regimen : MAC
  - **In vivo T-cell depletion with ATG ;was common (75% of transplants).**
- 526 of 1110; (47%), liver biopsy
- **Risk class I (39%), II (8%), and III (54%)**

CIBMTR: Related & unrelated donor HSCT for B-MT: results of an international survey. Related & unrelated donor transplantation for BMT . results of an international survey . Chunfu Li .Blood advances. 10 SEPTEMBER 2019 x VOLUME 3, NUMBER .CIBMTR . USA, China, India

Source

- Bone marrow 321 (%29)
- Peripheral blood 682 (%61)
- Cord blood 107 (%10)

Conditioning Regimen

- BU/Cy/TT/FLU 376 (%34)
- BU/Cy/FLU 259 (%23)
- BU/Cy 249 (%22)
- Treosulfan/TT/FLU 169 (%15)
- BU or Melphalan +- TT 6+ - FLU 57 (%5)

CIBMTR: Related and unrelated donor transplantation for b-thalassemia major: results of an international survey. Related & unrelated donor transplantation for BMT . results of an international survey . Chunfu Li .Blood advances. 10 SEP 2019 x VOLUME 3, NUMBER .CIBMTR . USA, China, India

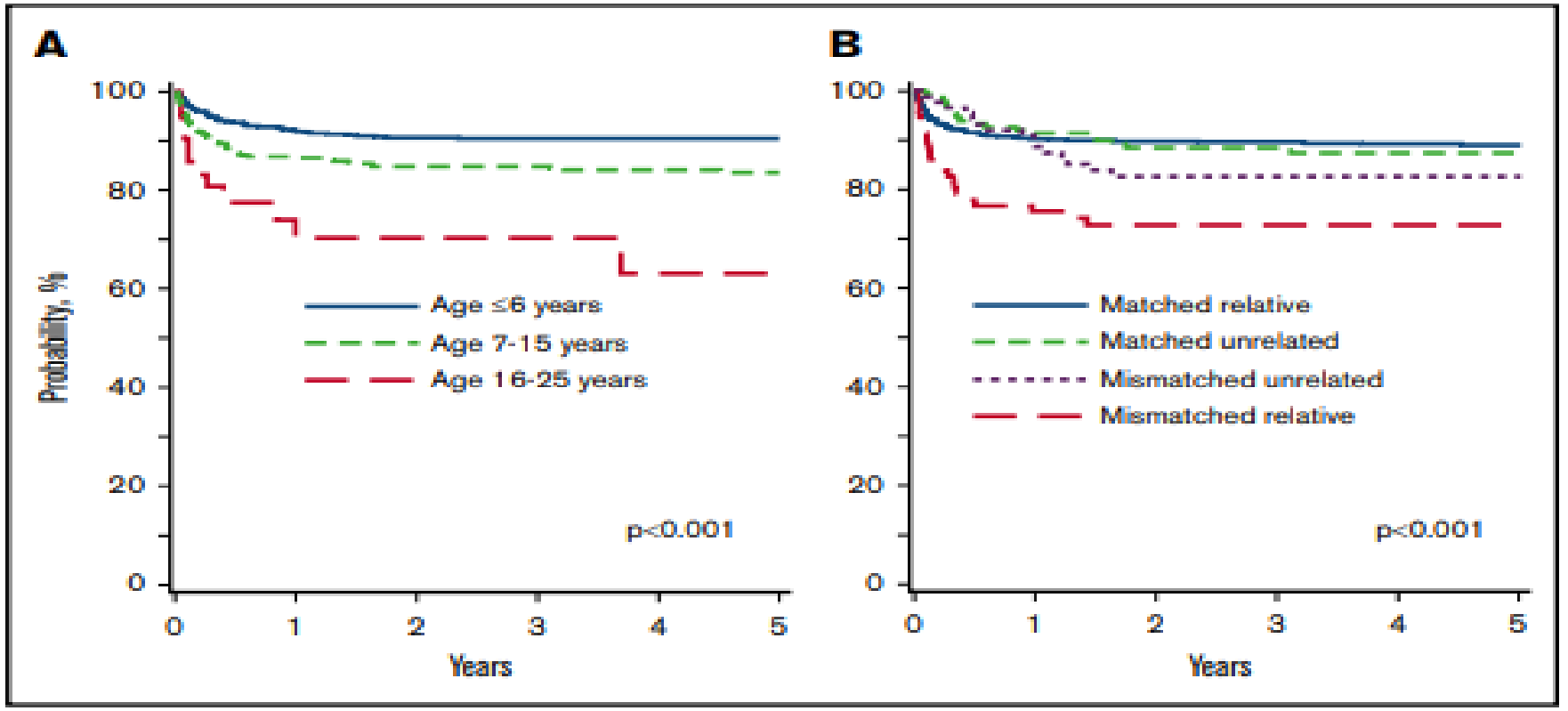
- Median follow-up : 48 mo

- **OS & EFS Highest : patients aged < 6 years & HLA MR & HLAMUR**
- OS & EFS **did not differ** in **HLA MR & HLAMUR , 89% vs 87% and 86% vs 82%, respectively**.
- 5-year OS -P aged <6 Y, 7 - 15 Y , 16 -25 Y(adjusted for **donor type & conditioning regimen) (P , .001).**
  - **OS: 90%, 84%, and 63%** **EFS : 86%(< 6 Y) 80%, and 63%**
  - **Optimal age /HSCT < 6 years**

CIBMTR: Related and unrelated donor transplantation for b-thalassemia major: results of an international survey. Related & unrelated donor transplantation for BMT . results of an international survey . Chunfu Li .Blood advances. 10 SEPTEMBER 2019 x VOLUME 3, NUMBER .CIBMTR . USA, China, India

- primary GF: 56 secondary GF: 43
  - Older age > 15 Y at HSCT
  - HLA-Mismatched Donor HSCT ; Higher risk for GF
- Age & Donor type : with grade III-IV acute GVHD
  - **Conclusion :**
  - **Optimal age < 6 years**
  - **An HLA-matched unrelated donor is a suitable alternative if an HLA-matched relative is not available.**

CIBMTR; Overall survival. A) Overall survival by age at transplantation B)Overall survival by donor type : MRD ,MMRD, MURD,MMURD 89%,73%,87% , 83% .Chunfu Li.Blood advances. 2019 . CIBMTR



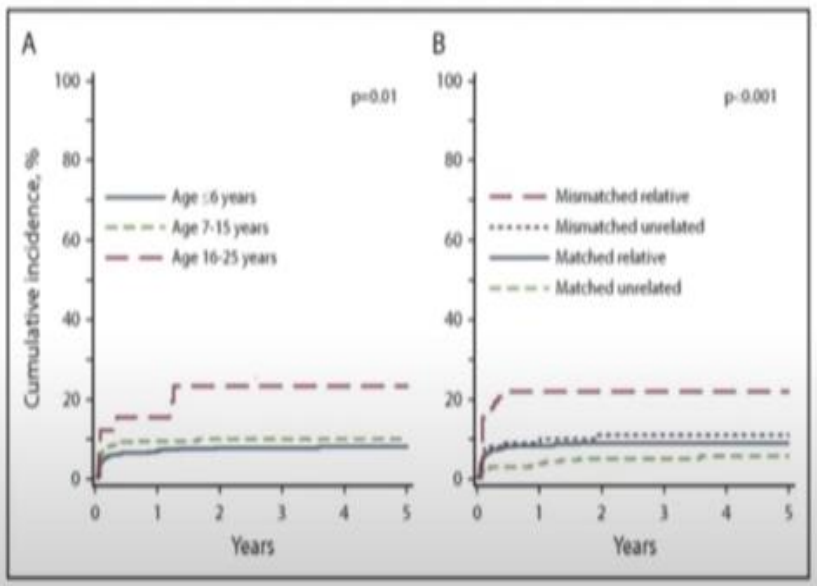
2000 to 2016

1110 patients in US, India and China

61% matched related

event-free survival

graft failure



- it should be offered early (age ≤6 years)
- no difference between HLA-matched related and HLA-matched unrelate donor transplantation
- graft failure rate is different between alternative donors: higher in mismatched donors

L, Blood Advances 2019

23:07 / 35:05 • age determines outcomes in thalassemia

Copy link

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Int J Clin Exp Med 2019;12(11):12912-12919

Original Article

Unrelated-donor, peripheral blood stem cell transplantation in thalassemia major

Jie Meng[1], Xiaoyang Yang[2], Yinghui Zhang[1], Haifeng Lin[1], Dejun Peng[3]

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Abstract: Objective: To investigate the clinical efficacy and complications of unrelated-donor peripheral blood stem cell transplantation (URD-PBSCT) for treating thalassemia major and to evaluate its safety and efficacy. Methods: As study subjects, forty-six children diagnosed with thalassemia major in The Second Affiliated Hospital of Hainan Medical College between October 2014 and November 2016 were selected. Busulfan + Cyclophosphamide + fludarabine + antithymocyte globulin (Bu + Cy + Flu + ATG) was used as a preconditioning approach to perform URD-PBSCT. The hematopoietic stem cell engraftment, adverse reactions, complications, and survival were observed. Results:

Unrelated Donor PB HSCT for Patients with B-MT Based on a Novel Conditioning Regimen. Lan Sun.

Biol Blood Marrow Transplant 25 (2019) . 1592 -1596. Chaina

- **Progress in high-resolution HLA typing technology and supportive care**, outcomes after allogeneic HSCT from an HLA well-matched unrelated donor (UD) now approach those of well-matched sibling donors. UD HSCT is hampered by an increased risk of **GVHD & TRM**
- **48 patients/ BMT , 2 - 11 years . 2014-2018. China.**
- No routin Liver Biposy
- **Donors: Fully matched or/ with no more than 2 Ag mismatches HLA (10/10, 9/10. 8/10)**
- **WZ-14-TM HSCT- protocol: CPM,IV Bu+FLU & ATG**
- **GVHD : Cyclos + MTX & MMF**

Unrelated Donor PB HSCT for Patients with B-MT Based on a Novel Conditioning Regimen. Lan Sun.
Biol Blood Marrow Transplant 25 (2019) . 1592 -1596. Chaina

- **WZ-14-TM conditioning regimen** : Cy (day 10 to day 9),Intravenous Bu (day 8 to day 5),Flu (day 6 to day 2) and Rabbit ATG (day 4 to day 1).
- **Median total CD34+ cell:14.80 x 106 /kg**
- Protocol : More suppression & Mobilized PB /engraft quicker (high number of HSC) , Fast engraftment & less GF
- Overall survivors & TFS ; both 100%.

Unrelated Donor PB HSCT for Patients with b-Thalassemia Major Based on a Novel Conditioning Regimen. Lan Sun. Biol Blood Marrow Transplant 25 (2019) . 1592 -1596. Chaina

- **ACUTE GVHD : 16/48 (33.3%)** **4/48 (8.3%) : chronic GVHD**
  - 6.2%: grade II to III aGVHD The most site : Skin
- **Other Complications:**
- CMV : 19 P (39.6%)
  - Autoimmune hemolytic anemia: 2p :(4.2%)
  - Immune thrombocytopenia 3 (6.3%).
  - 4 p ; PRES 4P : H cystitis
- **Mixed chimerism :6 (12.55%)**

Matched unrelated donor HSCT for thalassemia major using Treosulphan based conditioning protocol for Children:

K. Mullanfiroze et al. / Pediatric Hematology Oncology Journal 2 (2017) 7e1. India

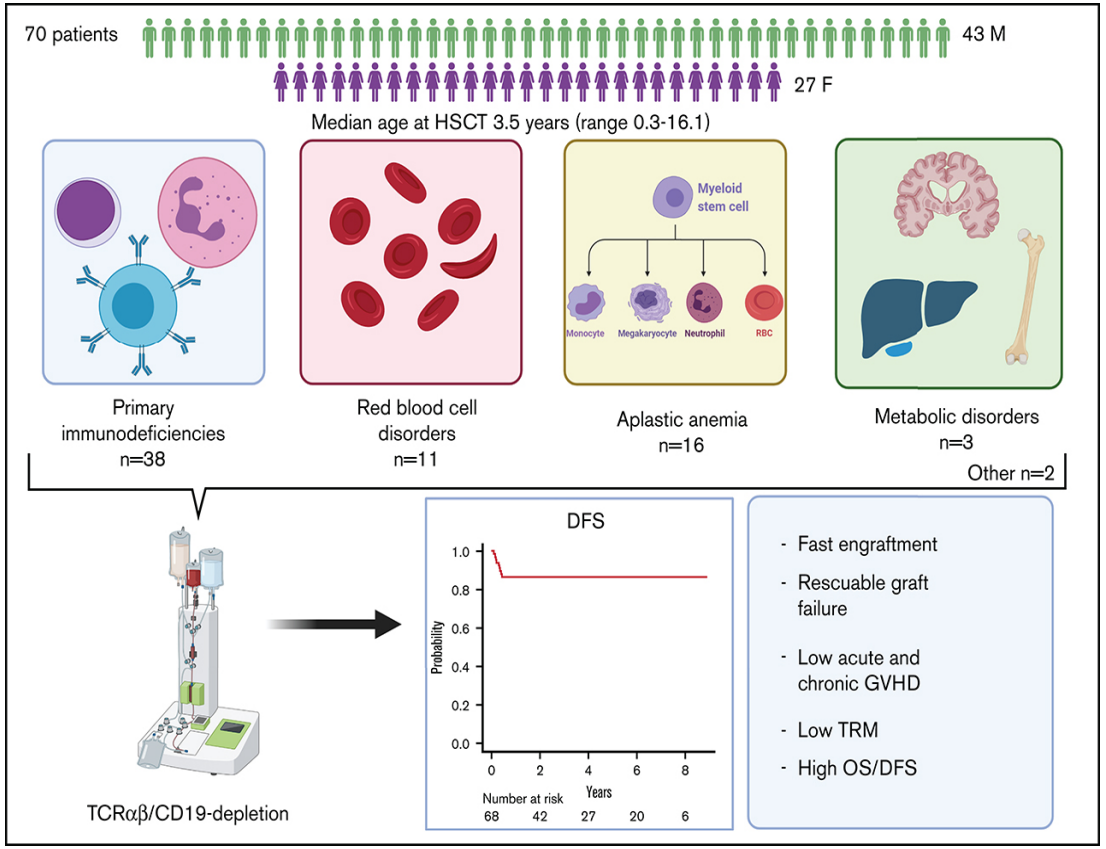
- **MUD HSCT / Treosulfan 2012-2016**
- **25 children** HSCT ; **Matched or minimally mismatched unrelated donors**
- Median age at HSCT ;5 years. **No Liver Biopsy**
- **MAC: Treosulfan ,Thiotepa, Fludarabine, Equine ATG**
- **Survival fully MUR D HSCT ; 95%.**

Haplo-SCT programs in Major thalassemia Wang etal. Transplantation. 2021 . Chaina. Haploidentical HSCT with post-transplant cyclophosphamide for osteopetrosis and other nonmalignant diseases.Ehud Even-O. Bone Marrow Transplantation (2021) 56:434–441.

- In recent decades: HLA-Haploidentical HSCT (T cell depletion)
- Ex vivo (Clini mac s)
- In vivo T cell depletion ; with (CPM post HSCT)
- Haplo HSCT been increasingly performed for Haematological Malignancies (Andreani et al, 2017)

TCRaβ/CD19 depleted HSCT from an HLA-haploidentical relative to treat children with different nonmalignant disorders. Pietro Merli.

Blood Adv (2022) 6 (1): 281–292.Italy

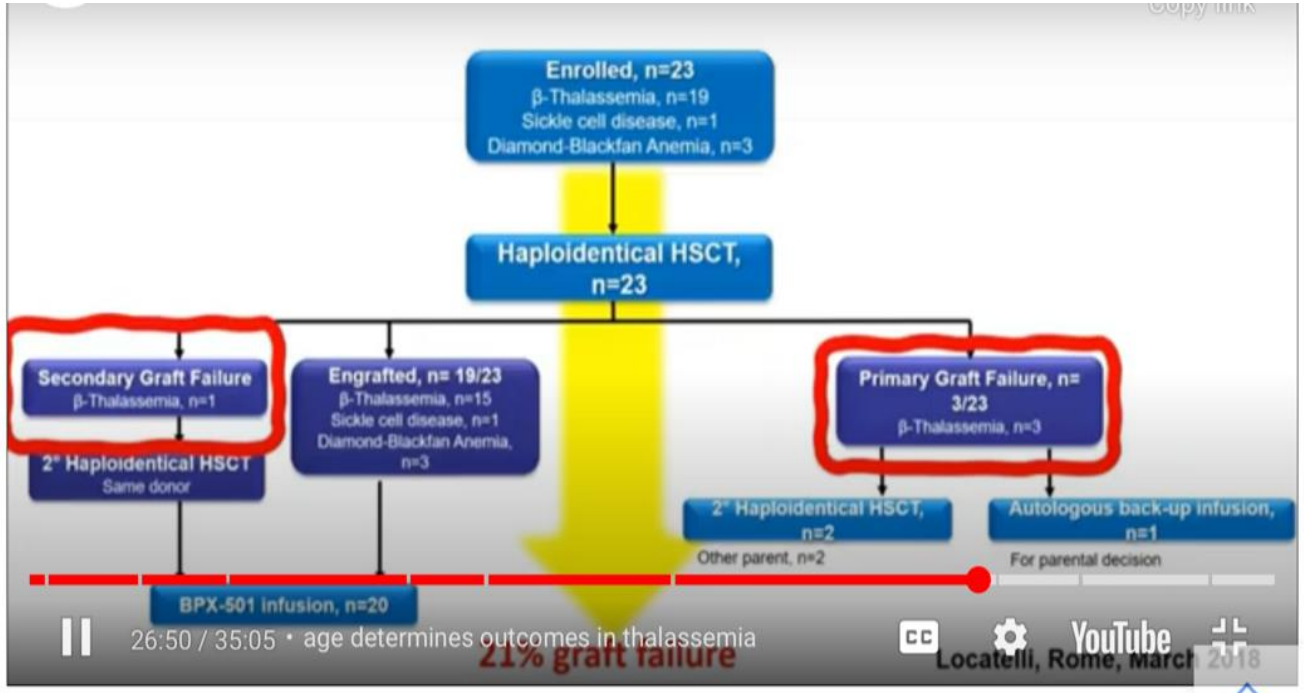


- 2012-2020 70 children < 21 y
- Non malignant disease (PID, AA, Metabolic ,…) , 11-p :Red blood -cell disorders
- Median age ; 3.5 Y
- ATG 12mg/ kg , Rituximab 200/m2
- NO GVHD prophylaxis.
- 51 –p: Engrafted **5 y Mortality: 8.5%**
- **GF 21 P(30%) :(Most in BMT & AA)**
- **A- GVHD : 14.4 % C-GVHD: 1 p**
- **5 Y : OS & EFS: 91% & 86%**

Haploidentical HSCT ; Franco Locatelli: 2018 : Italy

23 p 19 B-MT 1 ; SCD 3 ; DBA

Engrafted ;19/23 15 p/B-MT BMT: PGF: 3p & SGF : 1p



TOP

This webinar was accredited by the EBAH-CME credits system.

Haplo-SCT programs in Major thalassemia Wang etal. Transplantation. 2021 . Chaina

- **Haplo HSCT :The Experience is limited for thalassaemia major.**
- **Outcomes of TM patients that received Haplo SCT vary between different transplant program**

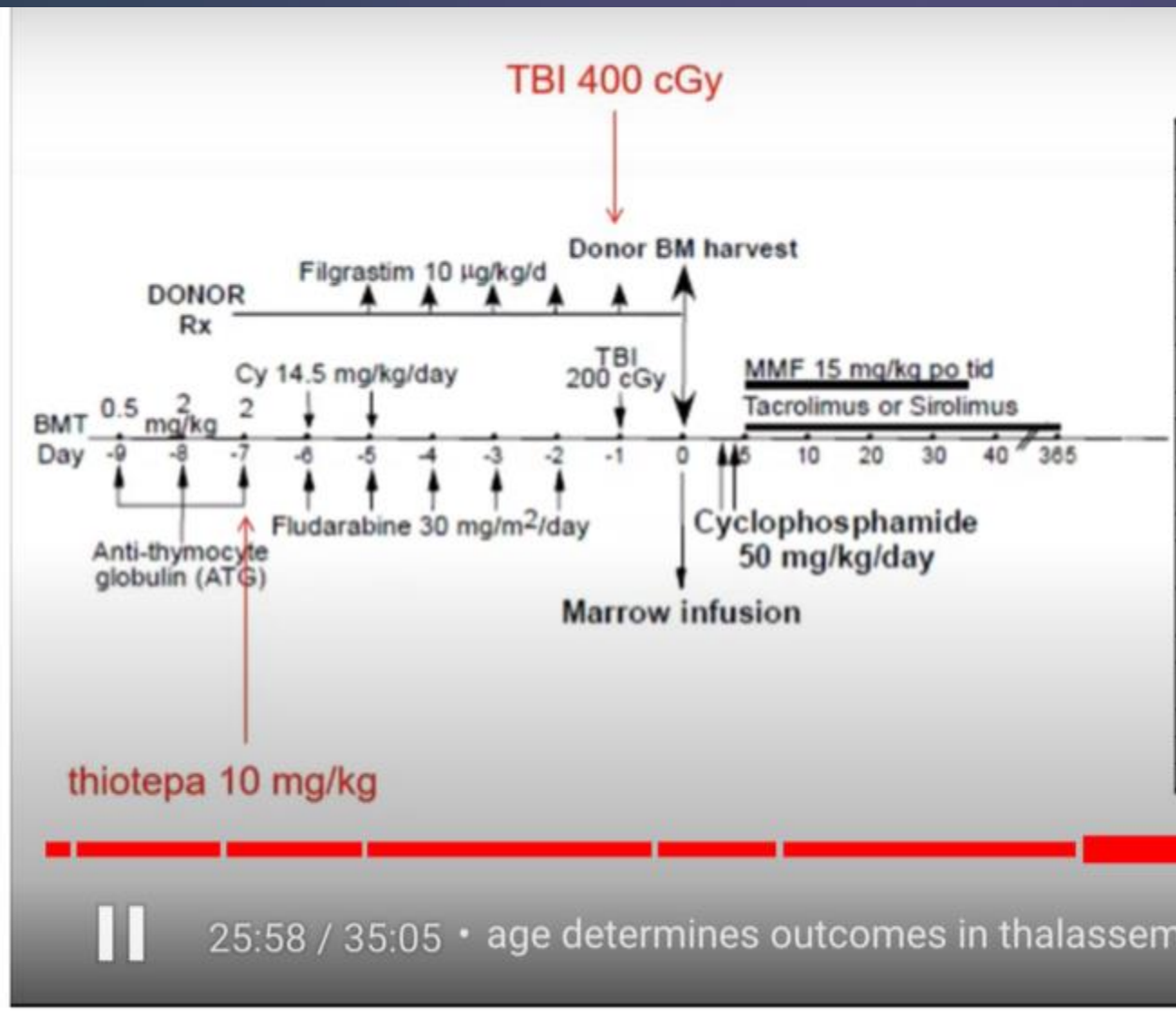
  - **Pre-transplant immunosuppressant (PTIS) therapy (Gaziev et al, 2016; Issaragrisil & Kunacheewa, 2016)**
  - **……**

HSCT for homozygous β-thalassemia & β-thalassemia/hemoglobin E patients from haploidentical donors .U. Anurathapan. Bone Marrow Transplantation (2016) 51, 813–818. Thailand.

- **31 -p Haplo-SCT. P (2-20 Y) Median age : 10 y**
- **2 courses of pre transplant Immunosuppressive (PTIS) ; FLU + Dexamethasone (Dxm).**
- **Conditioning regimen : Rabbit ATG, Flu & IV (Bu)**
- **GVHD prophylaxis ; +3 ,+4 days (post-Cy) & day +5 tacrolimus /or Sirolimus together with a short course of MMF**
- **2 P : primary GF. 5 p mild - moderate, reversible SOS**
- 9 ;acute GvHD grade II. 5 patients ; limited-chronic GvHD.
- **29/31 P; 100% donor chimerism.**
- **Overall & EFS -2 years ; 95% & 94%, .**

Haploidentical HSCT for Th- major based on an FBCA conditioning regimen. British Journal of Haematology, 2018.182, 554–558. China

- **2012 -2017, 8 Children Haploidentical HSCT.(China)**
- Median age ; 5.5 years (range, 3–14)
- **Conditioning regimen - FBCA ; Fludarabine** (25 mg/m2 /day from days 8 to 3), **Bu** (32 mg/kg/ day from days 7 to 4), **CPM** (60 mg/kg infused over 1 h on days 3 and 2) & **Rabbit ATG** (ATG; 25 mg/kg/day infused over 12 h on days -4 to 0
- **GVHD –P :Cyclosporin (CSA) + short-course MTX**
- **CD34+ cell dose : 10.1 x 106 /kg (range, 8.2–27.2 x 106 /kg)**
- **Full donor chimerism (100%) & All independence from blood transfusion**
- **The OS and TFS rates ; both 100%**

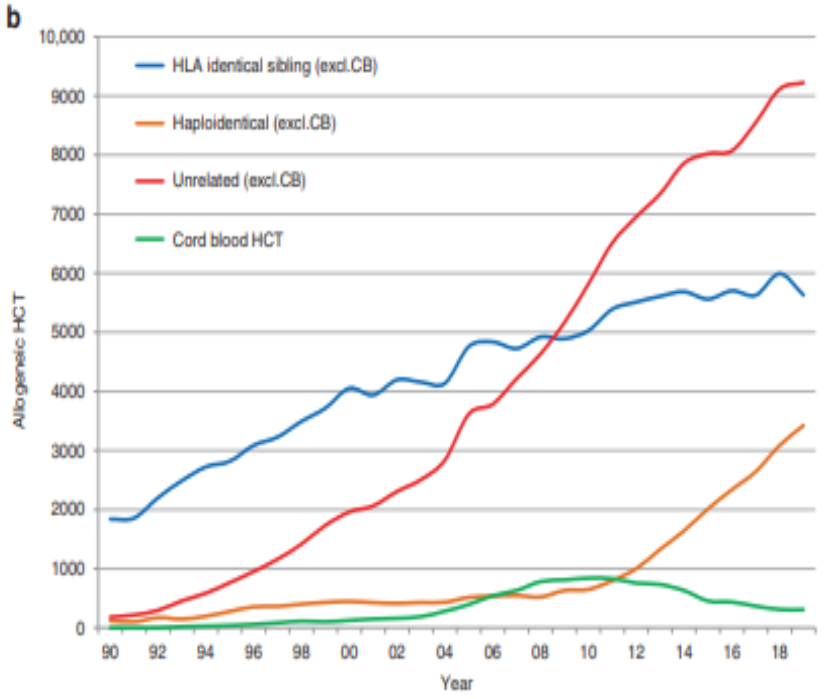


	standard regimen	augmented regimens	
		Regimen A (TBI 400 cGy)	Regimen B (thiotepa 10 mg/kg)
patient number	4 (4 haplo)	9 (6 haplo, 3 MRD)	12 (9 haplo, 2 MRD, 1 MMUD)
preconditioning	3 none, 1 HU	HU	1 none, 5 HU, 6 HU+Aza
median age (years)	9.5 (1.6-16.5)	7 (2.5-16)	12 (10-32)
TNC dose (x 10^8/kg)	11.35 (10.2-11.83)	7.5 (7.3-15)	9.05 (3.13-14.75)
CD34+ dose (x 10^6/kg)	5.31 (3.88-5.57)	7.15 (3.1-18)	4.67 (3.84-7.06)
graft failure	2	0	1
neutrophil engraftment	36 (29-53)	23 (15-29)	18 (12-21)
platelet engraftment	28 (22-41)	24 (21-33)	27.5 (18-45)
WB chimerism at day +28	34.5% (1-100)	100% (85-100)	98% (87-100)
T cell chimerism at day +28	12.5% (0-76)	76% (10-100)	98% (75-100)
follow up (months)	33.5 (9-49)	15 (1-19)	14.5 (3-28)
WB chimerism at last F/U	39.5% (0-100)	97.5% (21-100)	99% (98-100)
T cell chimerism at last F/U	34.5% (0-100)	100% (12-100)	99% (96-100)
death	0	0	2
aGVHD	0	2 grade 2	2 grade 1, 2 grade 2, 1 grade 3
cGVHD	0	0	3 limited
OS	100	100%	83%
TFS	50%	100%	83%

CORD BLOOD IN HSCT

Sandip A. Indian J Hematol Blood Transfus (Jan-Mar 2015) 31(1):9–13. India

- **First successful CBT : Fanconi-anemia ;1988**
- **Advantages ;**
  - Ready availability , No risk to the donor
  - Low rate of viral contamination
  - Low risk of GVHD.
- **Disadvantages :**
  - **Low stem-cell dose**
  - **Lack of stem cells for boost infusions f**



Related umbilical cord blood transplantation in patients with thalassemia and sickle cell disease. Blood. 2003 ; 101: 2137–2143

- **Franco Locatelli :**
- **44 patients ; median age, 5 years; range, 1-20 years**
- **Allogeneic related cord blood ;thalassemia (n = 33)**
- Median TNC :4.0 x 10 7 /kg (1.2-10 x 10 7/kg)
- No patient died
- **36 / 44 children remain: free of disease, median follow-up of 24 months (range, 4-76 mo).**

Unrelated cord blood transplantation for thalassaemia: a single-institution experience of 35 patients T-H Jaing. Bone Marrow Transplantation (2012) 47, 33–39. Taiwan

- 40 P B-MT & B-thalassaemia/Hb E HSCT/ 2003 -2009.
- Median age : 5.5 Y Weight ; 10.7 -36.5
- HLA matching ; 6/6 (n = 8), 5/6 (n = 16), 4/6 (n = 27), or 3/6 (n = 1)
- A double-unit CBT : if no single UCB unit X 2.5 107/kg R TNC
- cell dose / TNC : 2.8–14.7 x 107 /Kg
- Condition : BU iv/po + CY+ ATG GVHD : Cyclospurine + MTX
- 12 donor–recipient : 2-loci HLA mismatches & 10 pairs : mismatch at one locus
- TRM at 2 years : 11.7%
- 5-year OS and TFS ; 88.3 & 73.9%, respectively.
- 30/40 p patients : alive and transfusion-independent

Unrelated Umbilical Cord Blood Transplant for Children with b-Thalassemia Major. Sandip A. Indian J Hematol Blood Transfus (2015) 31(1):9–13. India

- 9 children :Age 1.5 - 7 years weight ; 10.5 - 17 kg.
- **Unrelated UCB HSCT** ,partially HLA-matched
- Conditioning : Oral BU , Cy ,Fludarabine ,ATG - Rabbit
- **TNC -Cell dose : 10.71 x 107 /kg** Range 6.5–17 x 107 /kg TNC
- No mortality
- **5/9 patients engrafted**
- **50–100 % donor chimerism**
- **Major complication :Primary Graft Rejection**

Hematopoietic Stem Cell Transplantation in Thalassemia . Luisa Strocchio, MDa , Franco Locatelli, MD, PhD. Hematol Oncol Clin N Am 32 (2018) 317–328

- **HLA-matched family donors :still the gold standard** for (HSCT) in (TM), with excellent results after either **BM or cord blood HSCT.**

- **Unrelated cord blood transplantation appears to be a suboptimal option in TM patients and is not routinely advisable, unless it is performed in the context of clinical trial**

- High rates of graft failure and delayed hematopoietic recovery mainly due to inadequate cell dose in the graft.[34]

β-Thalassemia intermedia: a comprehensive overview and novel.approaches Chingiz Asadov. International Journal of Hematology (2018) 108:5–21.J Pediatr Hematol Oncol Volume 00, Number 00, ’’ 2018

- (**HSCT) is an accepted treatment option for β-TM, but its use in β-TI is debatable.**
- **Experimental Therapy**
- **Transplant-related mortality (TRM) SHOULD BE CONSIDERED.**
- Only in severe TI
- Consider the quality of life and expected post-transplant survival time
- **HSCT: HLA Match Donors**
- **HscT : Reduced-intensity conditioning(RIC)**
- **Stable mixed chimerism** may be sufficient to correct an intermediate anemia.
- **Gene therapy: may be prefer** ,which is able to eliminate limitations of **conventional HSCT**, **GVHD . (SINCE 2009)**

Mechanistic action of different therapeutic options in thalasssemia intermedia.
J Pediatr Hematol Oncol, '' 2018

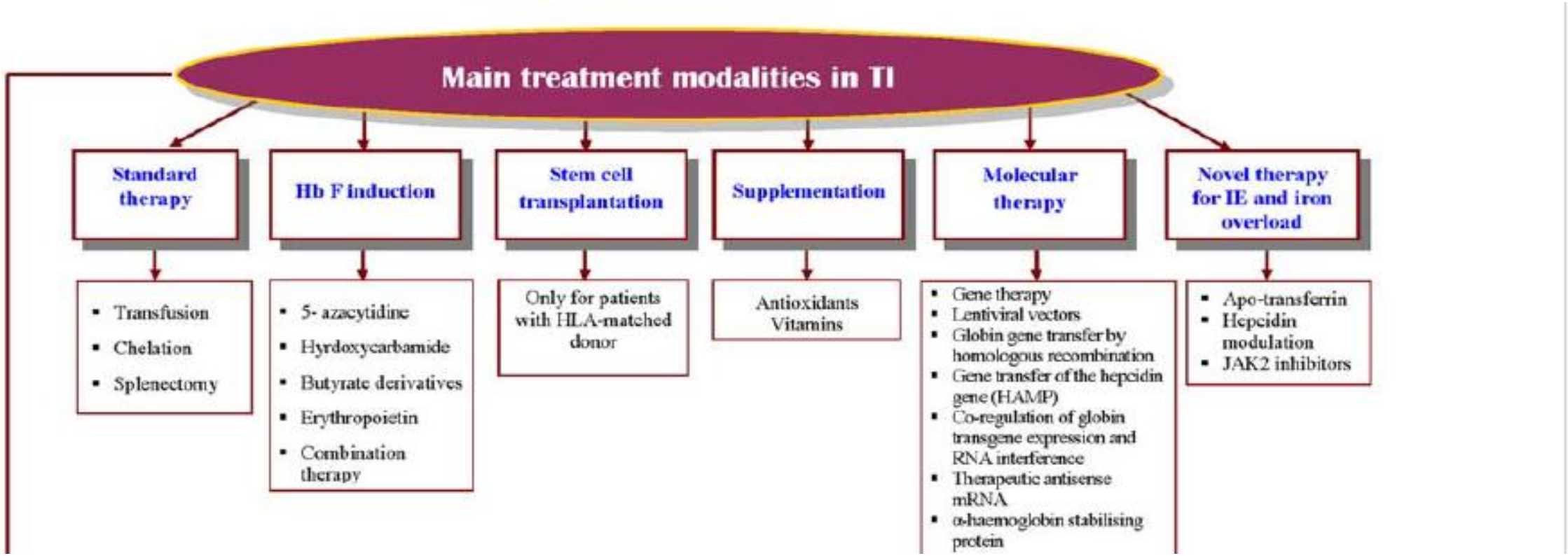
Improve RBCs Survival

- Transfusion
  - Improve anemia
  - Improve hypoxia
  - Decrease BM expansion
  - Decrease hepatosplenomegaly
  - Decrease EMH
- Chelation
  - Decrease iron and free radicles
  - Prevent hemosidrosis complications
- Splenectomy
  - Decrease RBCs destruction
- HbF induction
- Stem cell transplantation
- Molecular and novel therapies

  HbF induction, Stem cell transplantation, Molecular and novel therapies
  - Decrease ineffective erythropiesis
  - Decrease hemolysis

Mangement of Children With β-Thalassemia Intermedia: Overview, Recent Advances, and Treatment Challenges

Amira A. Adly. Pediatr Hematol Oncol Volume ,2018



Conclusion

- M- Related HSCT : primary treatment choice for BTM & other Hemoglobinopathies
- Age is an important issue in BMT - HSCT
- Fully HLA-MURD HSCT in the absence of a M- Family Donor is a realistic curative therapy BMT.

- **Remember: Every patient will now have the option of an Allo-SCT regardless of Donor.**
- Haplo _HSCT program is effective and safe for treating pediatric patients with TM based of specific programs.
- The Experience of Haploidentical HSCT is limited for Thalassaemia Major & More studies are on going .

THANK YOU