HIGHLIGHTS IN EMATOLOGIA

Treviso, Ospedale Ca' Foncello

17-18 Novembre 2017

TALASSEMIA MAJOR: DAL TRAPIANTO ALLOGENICO ALLA TERAPIA GENICA

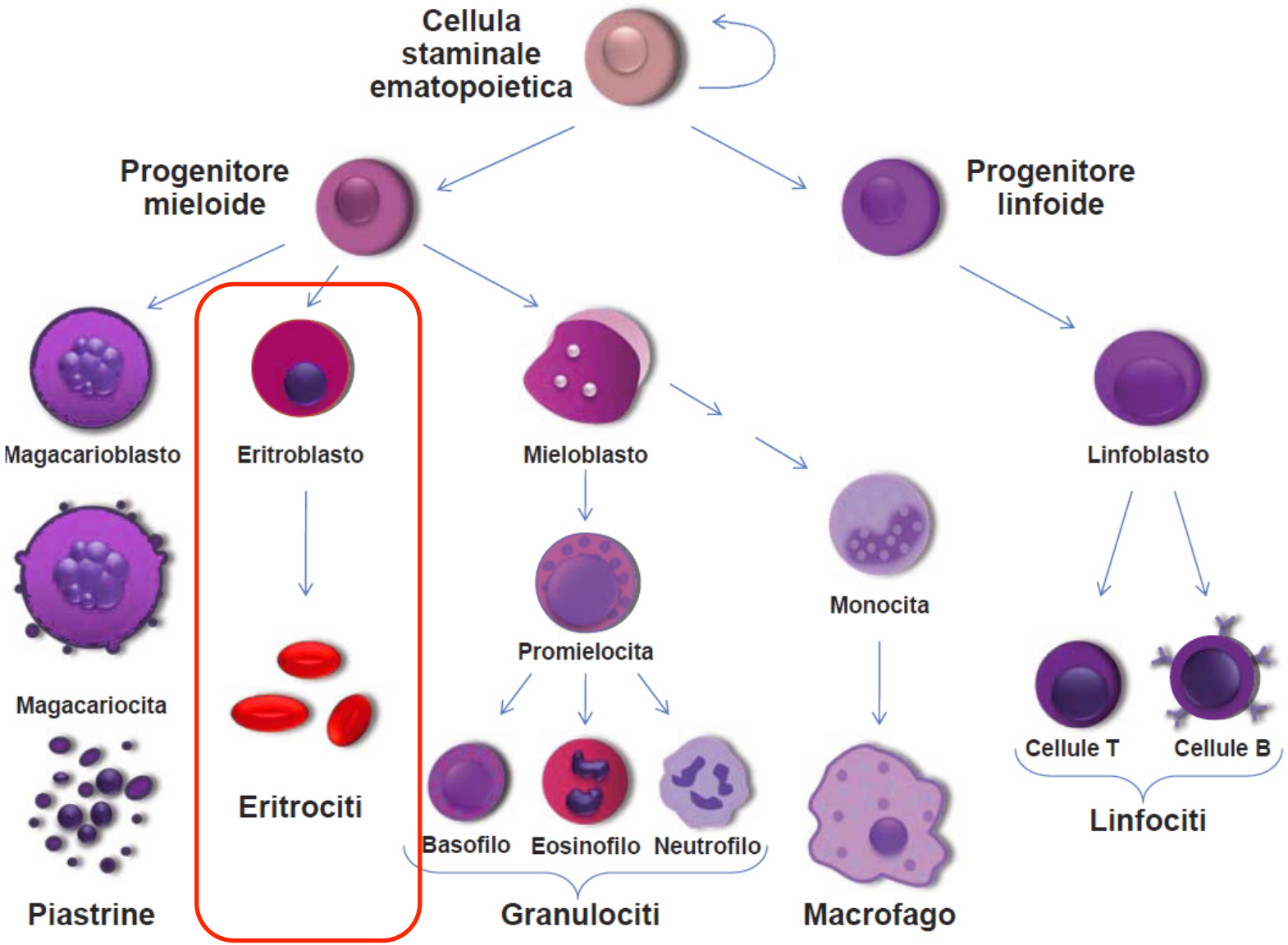
OSPEDALE POLICLINICO SAN MARTINO

Sistema Sanitario Regione Liguria

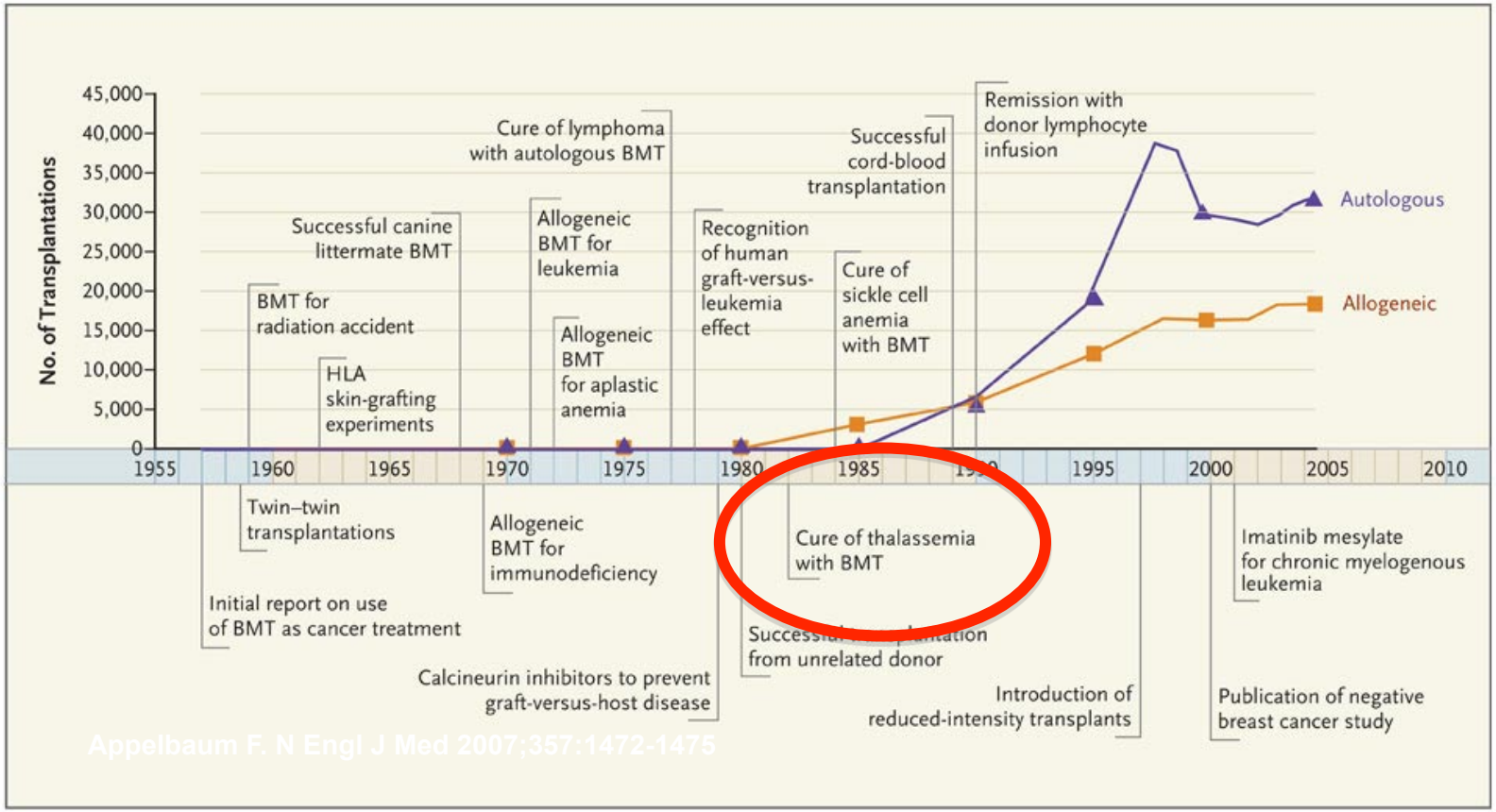
HCT in Thalassemia - Definition

- Cellular replacement therapy
- Replacement of the entire hemopoietic system and not only of the diseased erythropoiesis
- No immunological effect (GvL) is requested

HEMOGLOBINOPATY



Timeline Showing Numbers of Bone Marrow Transplantations and Advances in the Field, 1957-2006



The NEW ENGLAND JOURNAL of MEDICINE

THE LANCET

No 8442 LONDON SATURDAY 15 JUNE 1985 VOL I FOR 1985

ORIGINAL ARTICLES

Sudden cardiac tamponade after chemotherapy for marrow transplantation in thalassaemia

EMANUELE ANGELUCCI EGIDIO MARIOTTI GUIDO LUCARELLI
DONATELLA BARONCIANI PIERO CESARONI
SUZY MARIA TERESA DURAZZI MARIA GALIMBERTI
CLAUDIO GIARDINI PIETRO MURETTO PAOLA POLCHI
ERNESTO SGARBI

Published work suggests that cardiac tamponade occurs only occasionally after bone-marrow transplantation (BMT) but the worrying number of cases encountered in the transplant programme in Pesaro, Italy, has led to an analysis of this complication.

Cardiac tamponade occurred in 8 (2%) of 400 consecutive thalassaemic patients during conditioning for or within a month of BMT. 6 cases were fatal; these represented 9% of all causes of death and 29% of those occurring between start of

been the drugs used for conditioning, acting alone or together with bacteraemia and trauma.

The frequency with which we encountered the syndrome, and the similarity among our patients in clinical picture, and in characteristics of the effusion, indicate that cardiac tamponade occurring in thalassaemic patients after start of chemotherapy as conditioning for BMT is a specific syndrome requiring rapid treatment.

Lancet 1992; **339**: 287–89.

Fate of iron stores in thalassaemia after bone-marrow transplantation

G Lucarelli, E Angelucci, C Giardini, D Baronciani, M Galimberti, P Polchi, M Bartolucci, P Muretto, F Albertini

Lancet 1993; **342**: 1388–91

Reversibility of Cirrhosis in Patients Cured of Thalassemia by Bone Marrow Transplantation

Pietro Muretto, MD; Emanuele Angelucci, MD; and Guido Lucarelli, MD

Ann Intern Med. 2002;136:667-672.

MARROW TRANSPLANTATION IN PATIENTS WITH ADVANCED THALASSEMIA

GUIDO LUCARELLI, M.D., MARIELLA GALIMBERTI, M.D., PAOLA POLCHI, M.D., CLAUDIO GIARDINI, M.D., PATRICIA POLITI, M.D., DONATELLA BARONCIANI, M.D., EMANUELE ANGELUCCI, M.D., FLAVIA MANENTI, M.D., CONSTANTE DELFINI, M.D., GIOVANNI AURELI, M.D., AND PIETRO MURETTO, M.D.

Abstract In a study of the outcome of marrow transplantation in patients with advanced thalassemia, 40 patients with homozygous β-thalassemia who were 8 to 15 years of age (median, 10) received HLA-identical allogeneic marrow after treatment with busulfan and cyclophosphamide. Twenty-eight of the 40 patients were alive and free of disease 260 to 939 days after transplantation, and 2 patients were alive with thalassemia 372 and 1133 days after transplantation. The actuarial probabilities of survival and of disease-free survival at two years were 75 percent and 69 percent, respectively. Ten patients (25 percent) died. Three died of cardiac failure, interstitial pneumonitis, or septicemia within 14 days of transplantation. Three died of infectious complications associated with acute graft-versus-host disease at 46 to 97 days, and two died of infectious complications of chronic graft-versus-host disease at 249 and 290 days. Two patients had transplant rejection and died with marrow aplasia 115 and 192 days after transplantation. One patient had rejection after four months and while the marrow was aplastic underwent a successful second transplantation; the patient was alive without thalassemia 624 days after the first transplantation. The actuarial probability of grade 2 or higher acute graft-versus-host disease in the 32 patients with initial sustained engraftment was 35 percent. Three patients had chronic graft-versus-host disease, which was fatal in two and still active on day 710 in the third.

We conclude that bone marrow transplantation can potentially save patients with advanced thalassemia from an otherwise inexorable progression to death from the complications of blood transfusions. The ultimate outcome in this group of patients must await a longer follow-up. (N Engl J Med 1987; 316:1050-5.)

The New England Journal of Medicine

Volume 322 FEBRUARY 15, 1990 Number 7

BONE MARROW TRANSPLANTATION IN PATIENTS WITH THALASSEMIA

GUIDO LUCARELLI, M.D., MARIA GALIMBERTI, M.D., PAOLA POLCHI, M.D., EMANUELE ANGELUCCI, M.D., DONATELLA BARONCIANI, M.D., CLAUDIO GIARDINI, M.D., PATRIZIA POLITI, M.D., SUZY MARIA TERESA DURAZZI, M.D., PIETRO MURETTO, M.D., AND FEDERICO ALBERTINI, M.A.

840 THE NEW ENGLAND JOURNAL OF MEDICINE Sept. 16, 1993

MARROW TRANSPLANTATION IN PATIENTS WITH THALASSEMIA RESPONSIVE TO IRON CHELATION THERAPY

GUIDO LUCARELLI, M.D., MARIA GALIMBERTI, M.D., PAOLA POLCHI, M.D., EMANUELE ANGELUCCI, M.D., DONATELLA BARONCIANI, M.D., CLAUDIO GIARDINI, M.D., MARCO ANDREANI, PH.D., FABRIZIO AGOSTINELLI, PH.D., FEDERICO ALBERTINI, M.A., AND REGINALD A. CLIFT, F.I.M.L.S.

The New England Journal of Medicine

Images in Clinical Medicine

HEPATIC IRON CONCENTRATION AND TOTAL BODY IRON STORES IN THALASSEMIA MAJOR

EMANUELE ANGELUCCI, M.D., GARY M. BRITTENHAM, M.D., CHRISTINE E. MCLAREN, PH.D., MARTA RIPALTI, PH.D., DONATELLA BARONCIANI, M.D., CLAUDIO GIARDINI, M.D., MARIA GALIMBERTI, M.D., PAOLA POLCHI, M.D., AND GUIDO LUCARELLI, M.D.

(N Engl J Med 2000;343:327-31.)

HCT indication in Hemoglobinopathies

Disease	Indication	Problem	Experience
Thalassemia Major	Transfusion dependency	High success of medical therapy	Large (>4000 HCTs)
SCD	Complication. Low treatment possibility for severe complications	Unpredictability of disease course.	Limited (500 HCTs)

Haematologica 2014; **99**: 811–820.

Bone Marrow Transplantation (2016), 1–6

www.nature.com/bmt

ORIGINAL ARTICLE

Hemopoietic stem cell transplantation in thalassemia: a report from the European Society for Blood and Bone Marrow Transplantation Hemoglobinopathy Registry, 2000–2010

D Baronciani[1], E Angelucci[1], U Potschger[2], J Gaziev[3], A Yesilipek[4], M Zecca[5], MG Orofino[6], C Giardini[7], A Al-Ahmari[8], S Marktel[9], J de la Fuente[10], A Ghavamzadeh[11], AA Hussein[12], C Targhetta[1], F Pilo[1], F Locatelli[13], G Dini[14], P Bader[15] and C Peters[2]

Allogeneic hemopoietic stem cell transplantation (HSCT) is the only method currently available to cure transfusion-dependent thalassemia major that has been widely used worldwide. To verify transplantation distribution, demography, activity, policies and outcomes inside the European Group for Blood and Marrow Transplantation (EBMT), we performed a retrospective non-interventional study, extracting data from the EBMT hemoglobinopathy prospective registry database. We included 1493 consecutive patients with thalassemia major transplanted between 1 January 2000 and 31 December 2010. In total, 1359 (91%) transplants were performed on patients <18 years old, 1061 were from a human leukocyte Ag-identical sibling donor. After a median observation time of 2 years, the 2-year overall survival (OS) and event-free survival (EFS; that is, thalassemia-free survival) were $88 \pm 1\%$ and $81 \pm 1\%$, respectively. Transplantation from a human leukocyte Ag-identical sibling offered the best results, with OS and EFS of $91 \pm 1\%$ and $83 \pm 1\%$, respectively. No significant differences in survival were reported between countries. The threshold age for optimal transplant outcomes was around 14 years, with an OS of 90–96% and an EFS of 83–93% when transplants were performed before this age. Allogeneic HSCT for thalassemia is a curative approach that is employed internationally and produces excellent results.

Bone Marrow Transplantation advance online publication, 11 January 2016; doi:10.1038/bmt.2015.293

HCT for thalassemia.

Data from the EBMT hemoglobinopathy registry.

Bone Marrow Transplantation (2016) **51,** 536–541

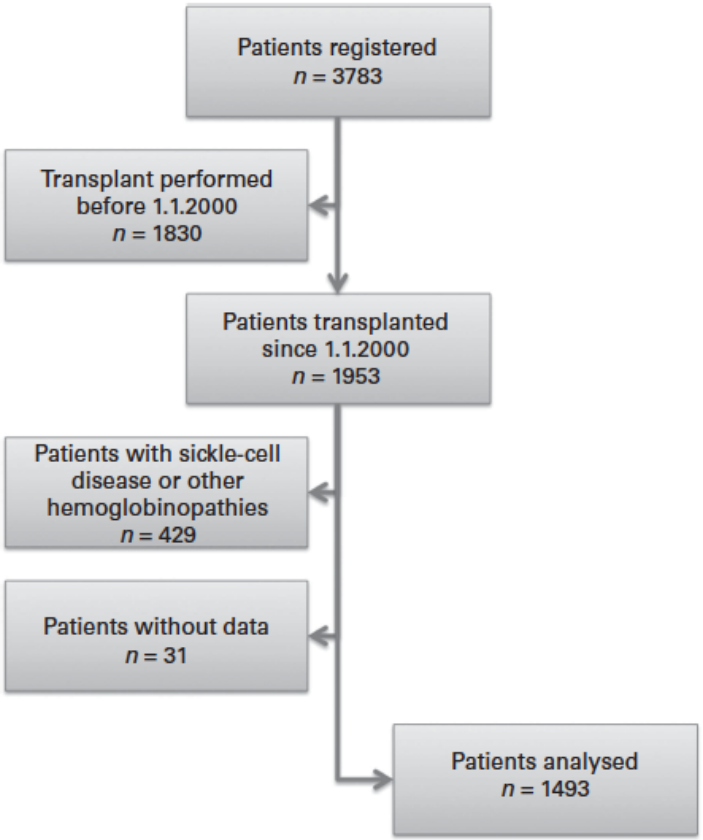


Figure 1. Study flow diagram. Patients registered in the EBMT ProMISe database and included in this report.

HCT Centers: 127

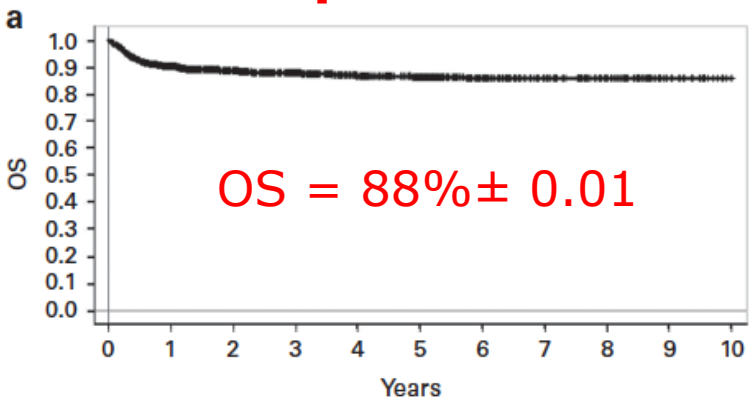
- Europe 990 (66%)
- Asia 472 (32%)
- Africa 26 (2%)
- Oceania 3
- S. America 1

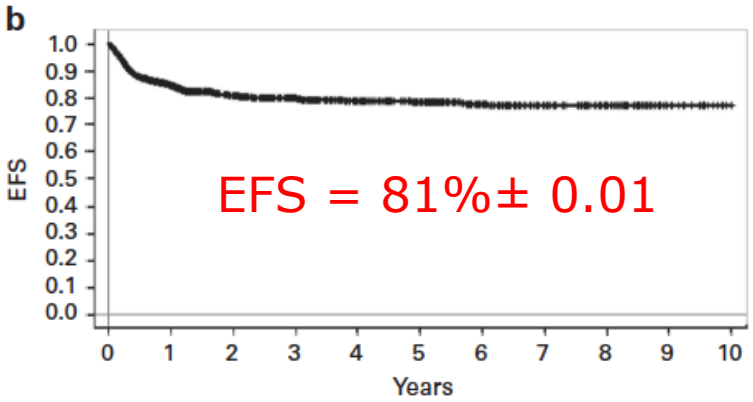
HCT for thalassemia.

Data from the EBMT hemoglobinopathy registry.

1493

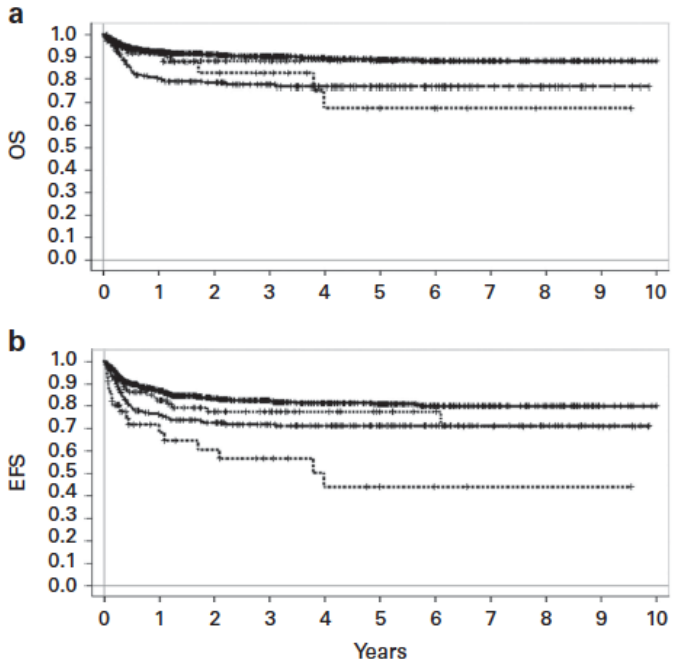
All patients





	Patients	Events	*Probability*
A) Overall survival	1493	154	0.88±0.01
B) EFS	1493	253	0.81±0.01

Figure 3. Survival rates for 1493 transplant recipients in the period 2000–2010. OS (**a**) and EFS (**b**) are shown.



	Patients	A) OS Events	A) OS 2-year OS	B) EFS Events	B) EFS 2-year EFS
a) MSD	1061	88	0.91±0.01	151	0.83±0.01
b) MFD	127	11	0.88±0.04	22	0.78±0.05
c) MMFD	57	8	0.68±0.11	8	0.68±0.11
d) UD	210	43	0.77±0.03	43	0.77±0.03
P-value		<0.001		<0.001	

*donor information missing in 38 cases (2.5%)

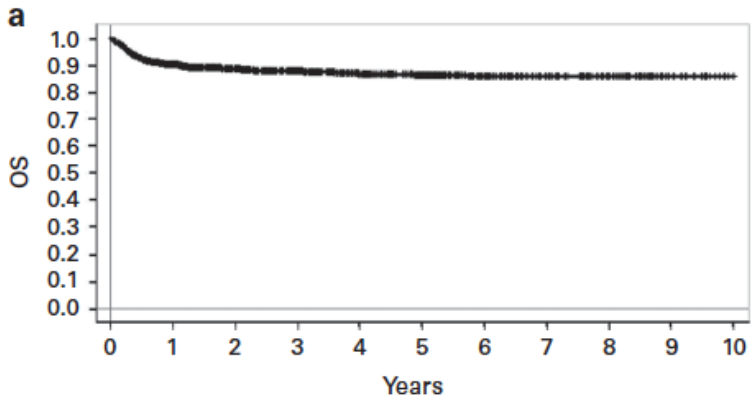
Figure 4. Transplant results by donor. OS (**a**) and EFS (**b**) by donor. MFD, matched family donor other than sibling; MMFD, mismatched family donor; MSD, matched sibling donor; UD, unrelated donor.

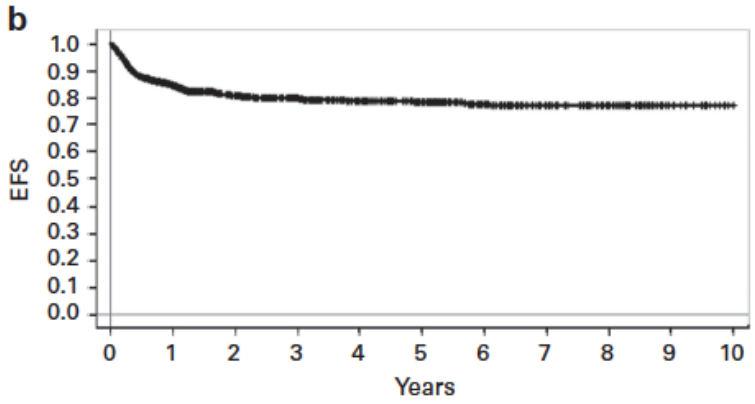
Bone Marrow Transplantation (2016) **51,** 536–541

HCT for thalassemia.

Data from the EBMT hemoglobinopathy registry.

1493





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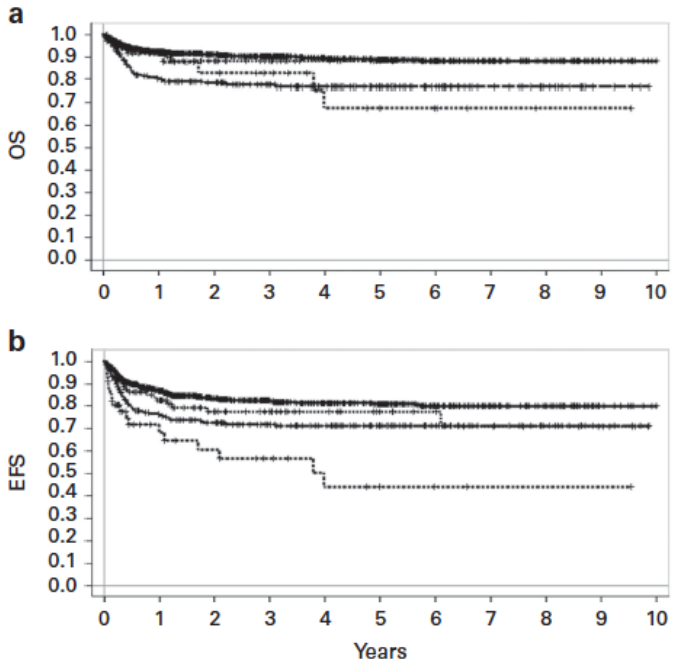
By donor



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Bone Marrow Transplantation (2016) **51,** 536–541

HCT for thalassemia.

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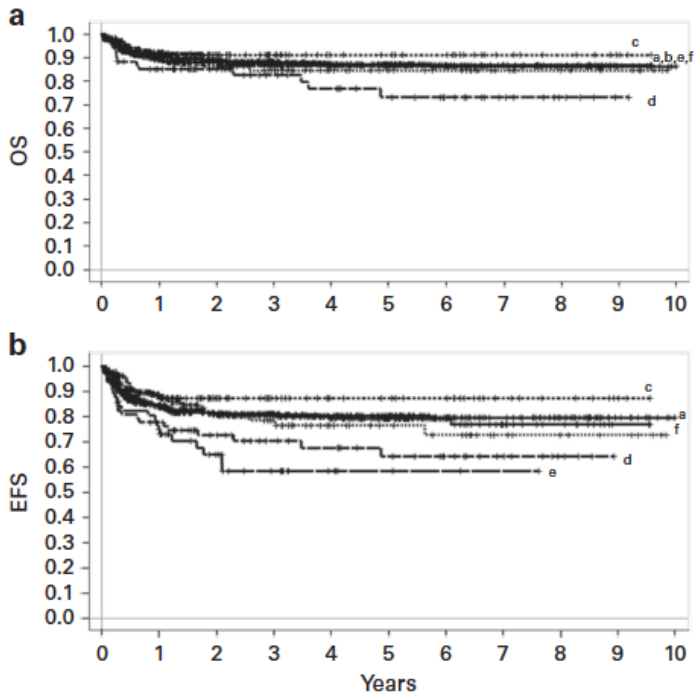
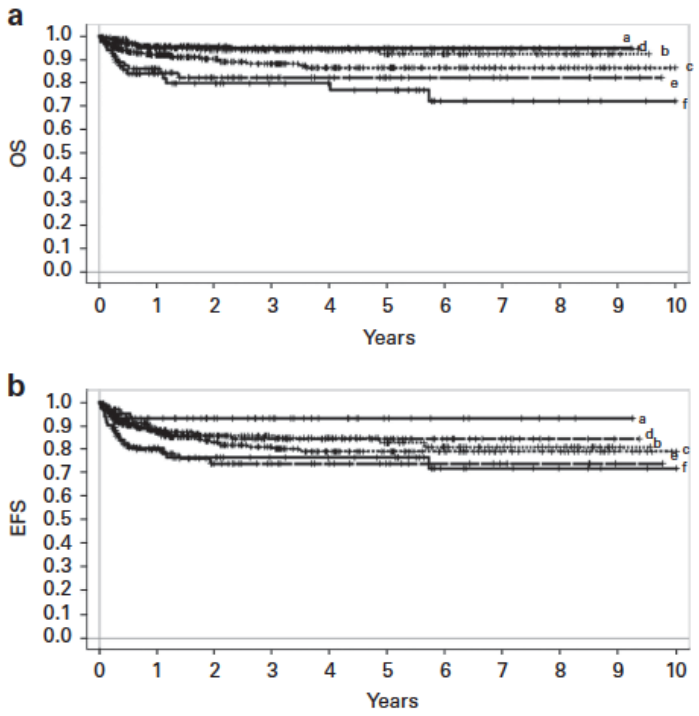
By country



	Patients	A) OS Events	A) OS 2-year OS	B) EFS Events	B) EFS 2-year EFS
a) Italy	581	55	0.89±0.02	90	0.82±0.02
b) Turkey	216	21	0.86±0.03	32	0.80±0.04
c) UK	133	10	0.91±0.03	14	0.87±0.03
d) Iran	68	14	0.85±0.04	21	0.73±0.06
e) Saudi Arabia	64	7	0.89±0.04	21	0.65±0.07
f) Others	431	47	0.88±0.02	75	0.81±0.02
P-value		0.347		<0.001	

Figure 5. Transplant results by country. OS (**a**) and EFS (**b**) are shown. Countries performing < 50 transplants were included in the 'other' category.



	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
P-value (for trend)		<0.001		<0.001	

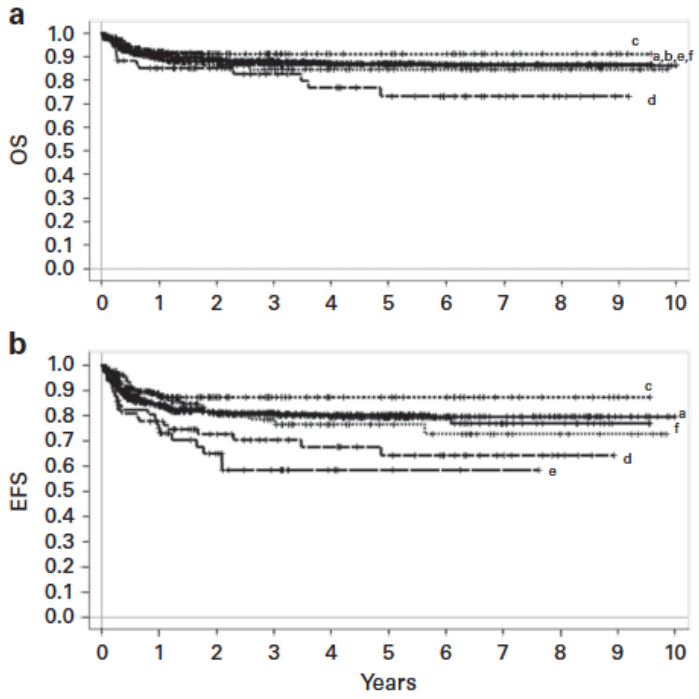
Figure 6. Results by age group among patients who received an HLA-identical sibling donor transplant. OS (**a**) and EFS (**b**) are shown. Age data were missing for one patient.

HCT for thalassemia.

Data from the EBMT hemoglobinopathy registry.

1493

By age



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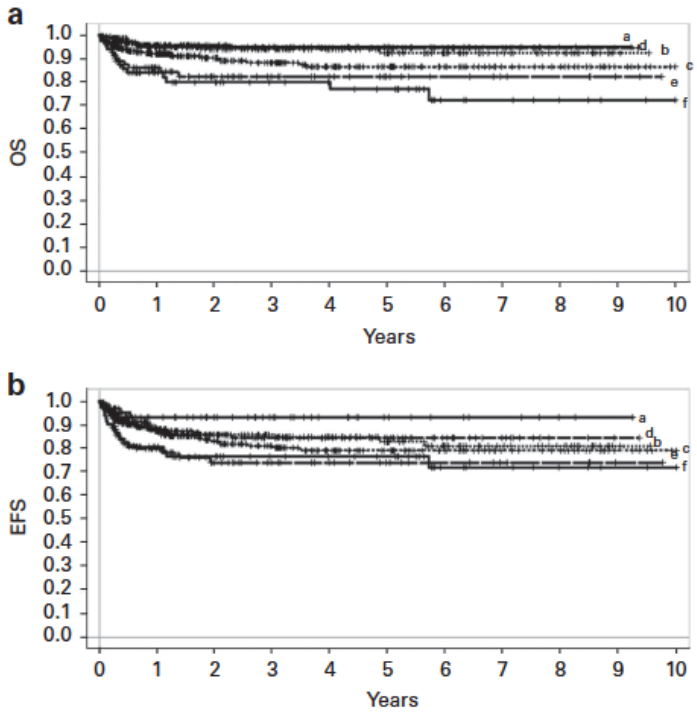

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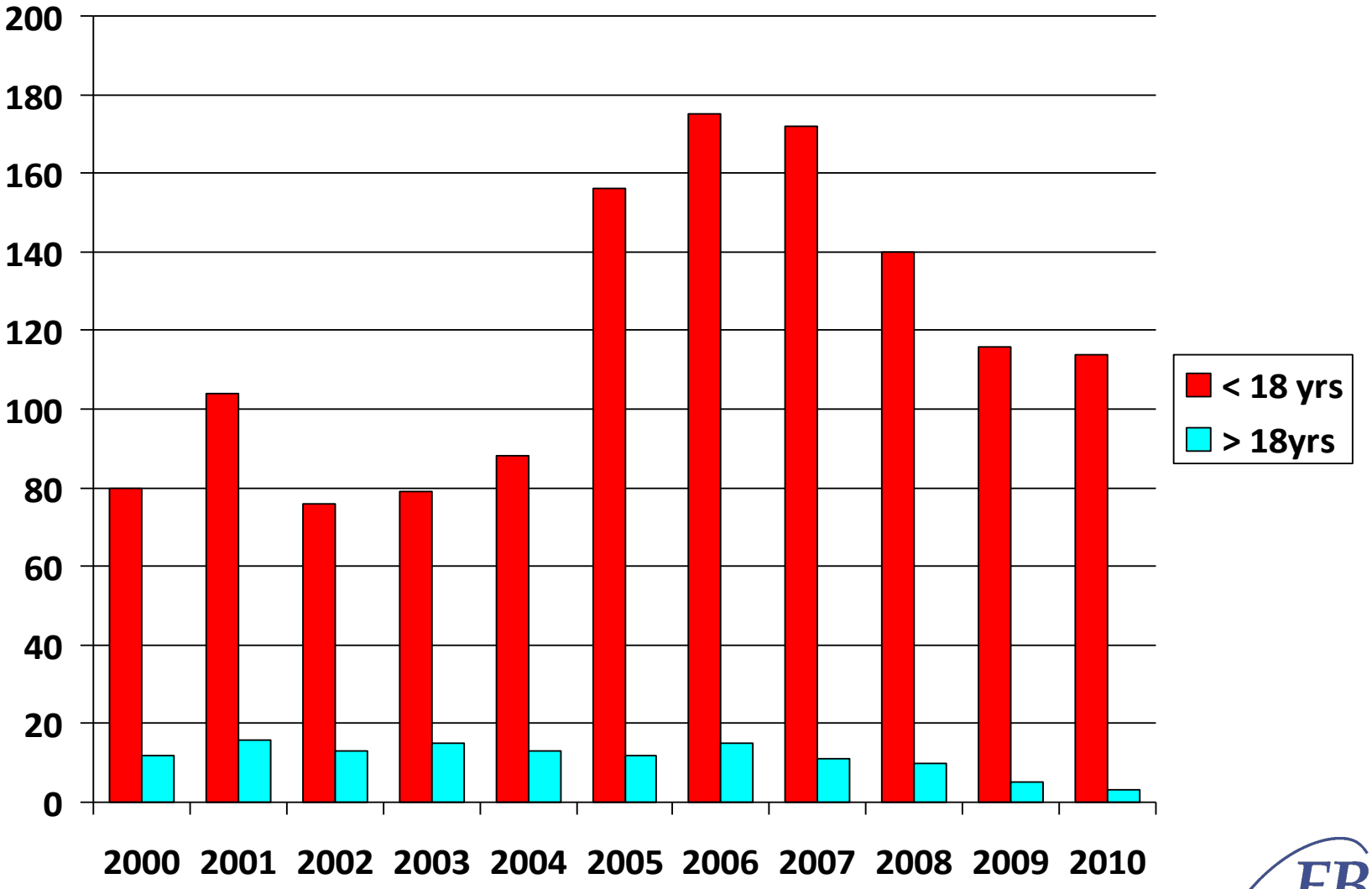
EBMT REGISTRY: HCT and age



Bone Marrow Transplantation (2016) **51,** 536–541

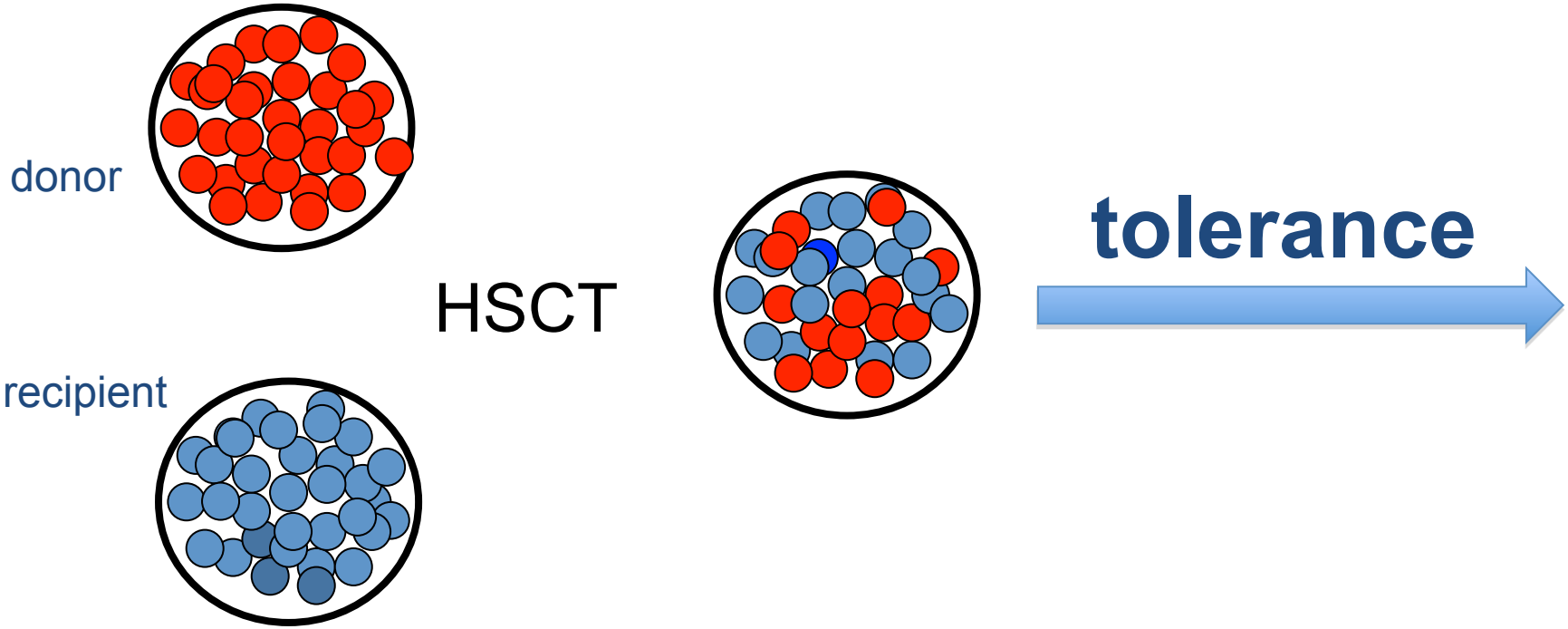
Chronic GvHD

- Chronic GvHD (# 1140 who survived at least 2 years with a functioning graft)
  - Limited 15% ±1
  - Extended 6% ±1
    - HLA id sibling 5% ±1
    - Family match 14% ±5
    - MUD 12%±3

Bone Marrow Transplantation (2016) **51,** 536–541

Mixed chimerism

A permanent co-existence of donor and host hematopoietic cells



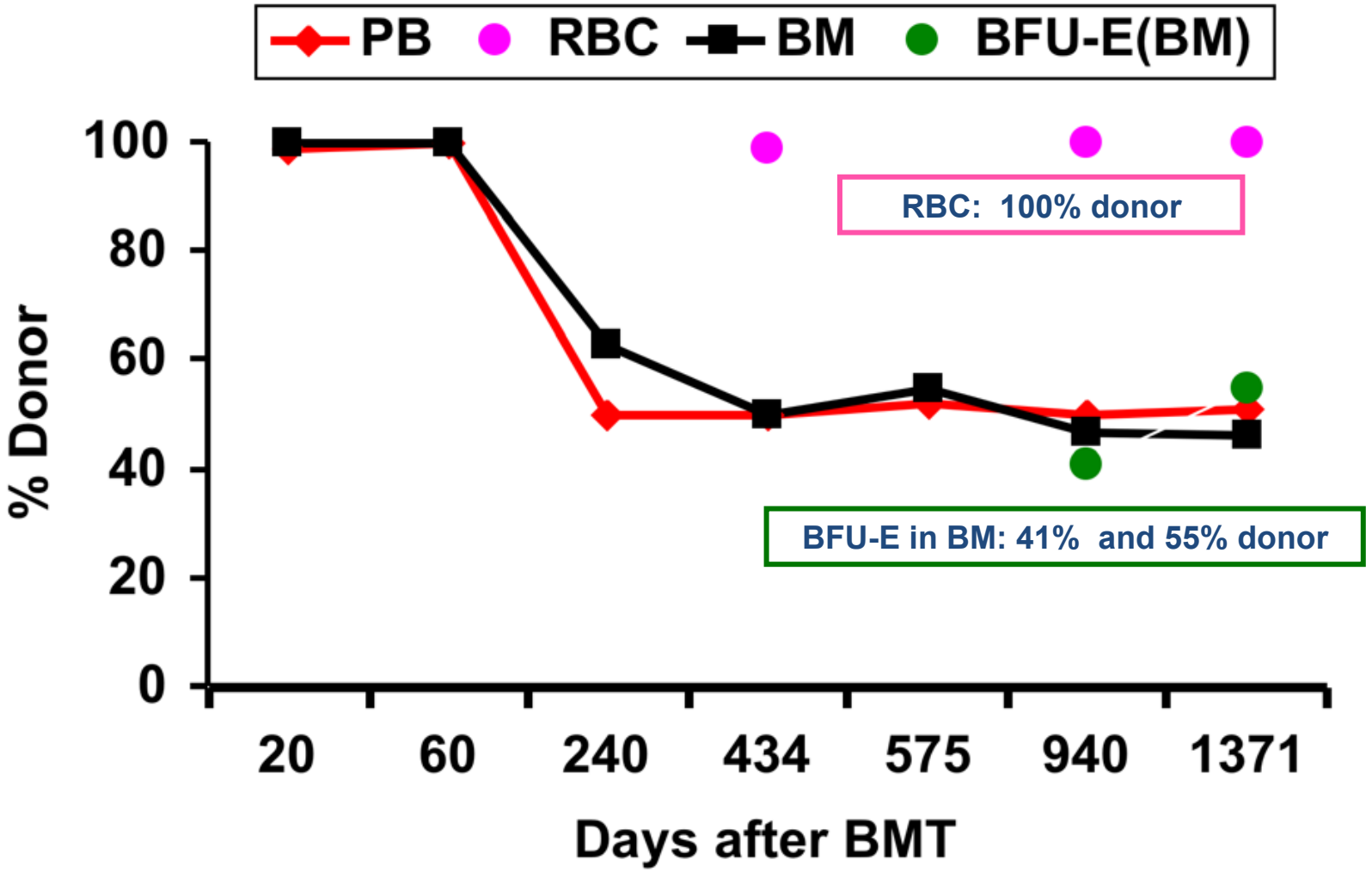
Mixed chimerism

34 (11%) patients over 335 prospectively studied.
Follow up 2-14 years

Donor cells	Hb level	Beta chain
25 – 90%	9.3 – 14 g/dl stable	65 -100%

Bone Marrow Transplant 2000; 25:401.4.

Split erythroid chimerism



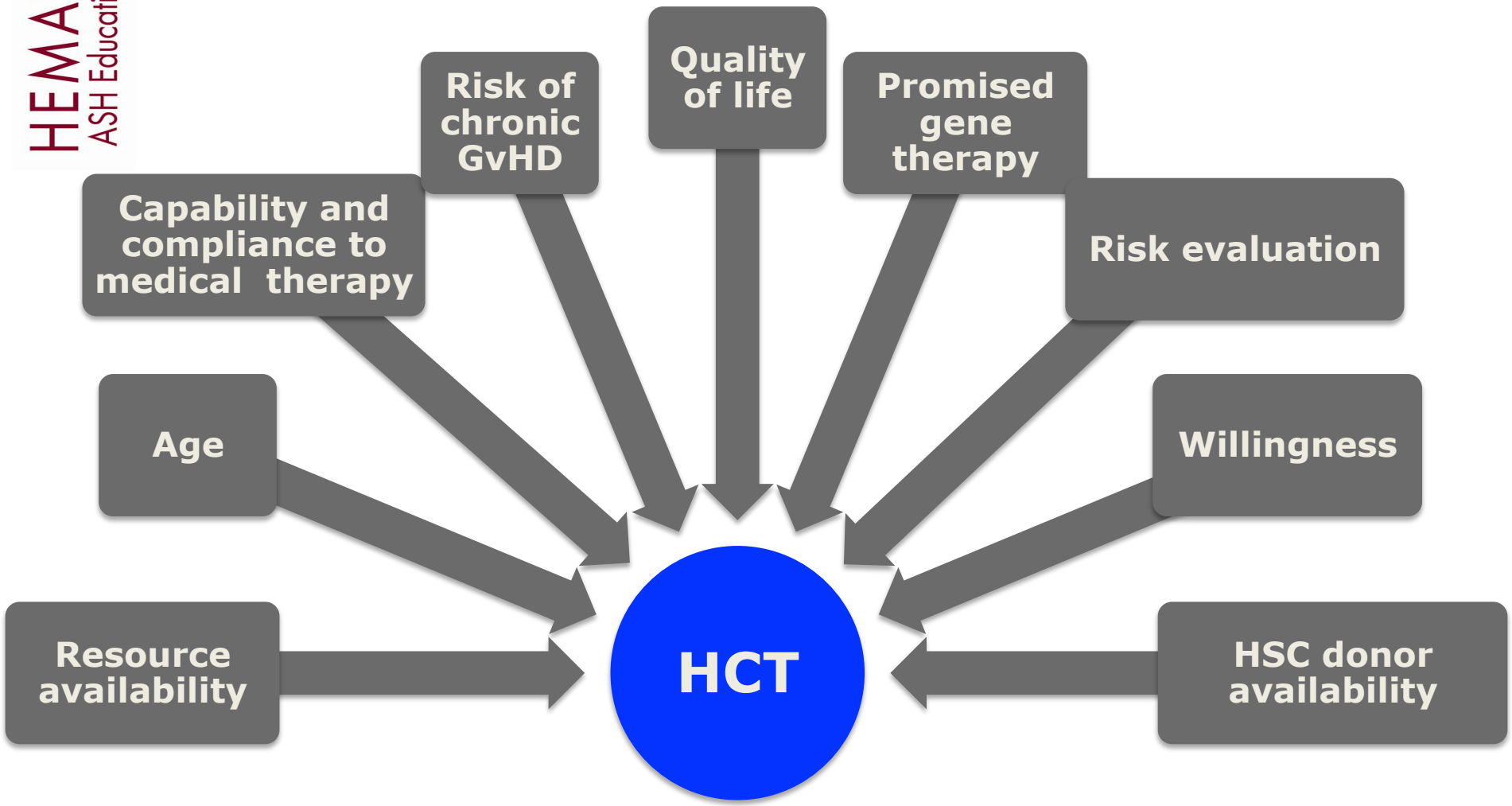
Andreani M. Haematologica. 2010 Nov 11. [Epub ahead of print]

HCT limitations

- Mortality rate
- GvHD
- Adult patients
- Donor availability
  - MUD limited diffusion
  - Haplo experimental
  - Unrelated CB experimental

HEMATOLOGY
ASH Education Program Book

Transplantation in Thalassemia
Individual decision process

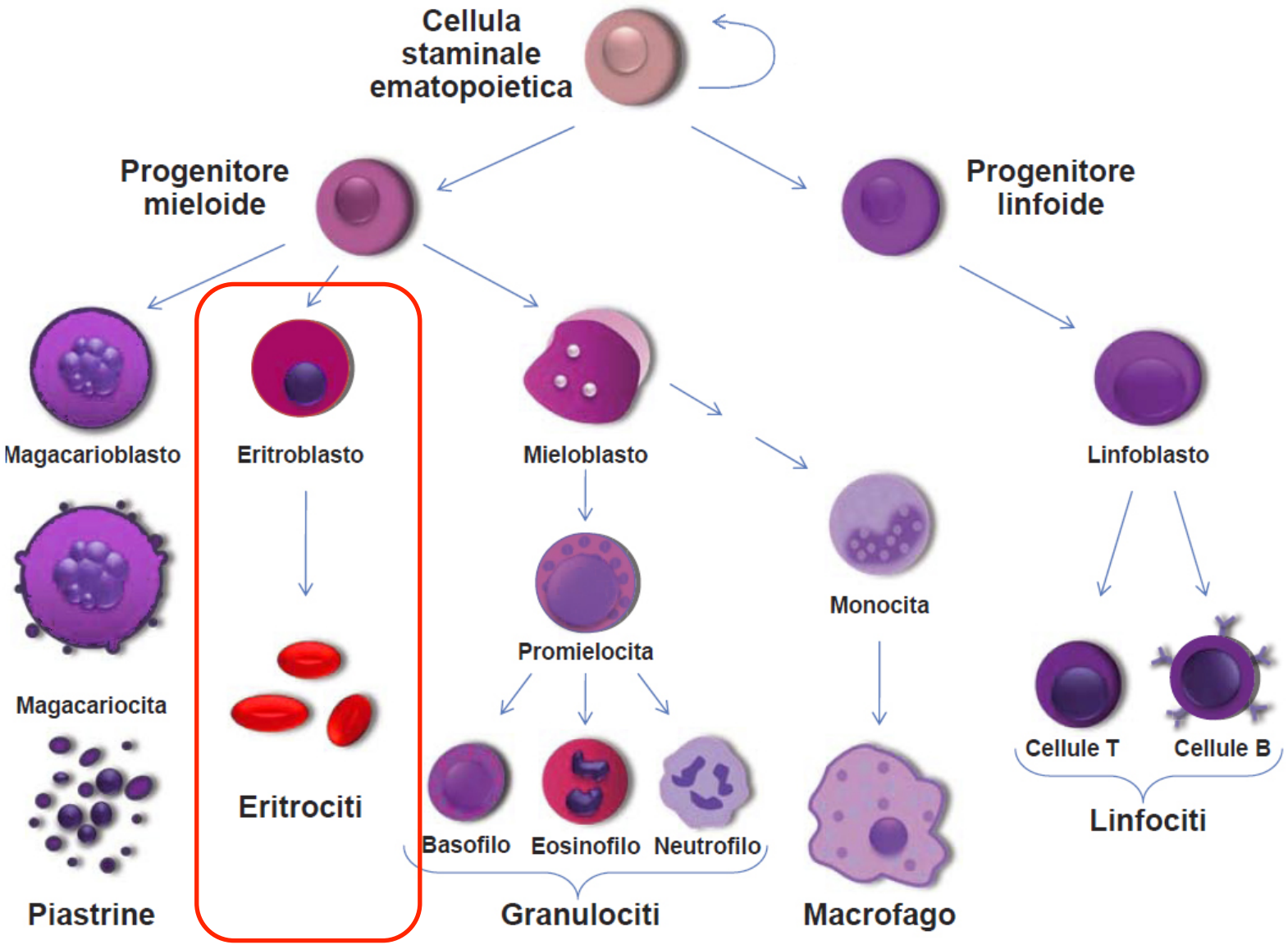


Angelucci, E. Hematology 2010;2010:456-462

Gene therapy:
the use of genes as medicine

- It is based on the transfer of a therapeutic or working gene copy into somatic cells of an individual in order to repair a defective gene copy
- Thus it may be used to replace a faulty gene, or to introduce a new gene whose function is to cure or to favorably modify the clinical course of a condition

HEMOGLOBINOPATY



The success of gene therapy is based on:

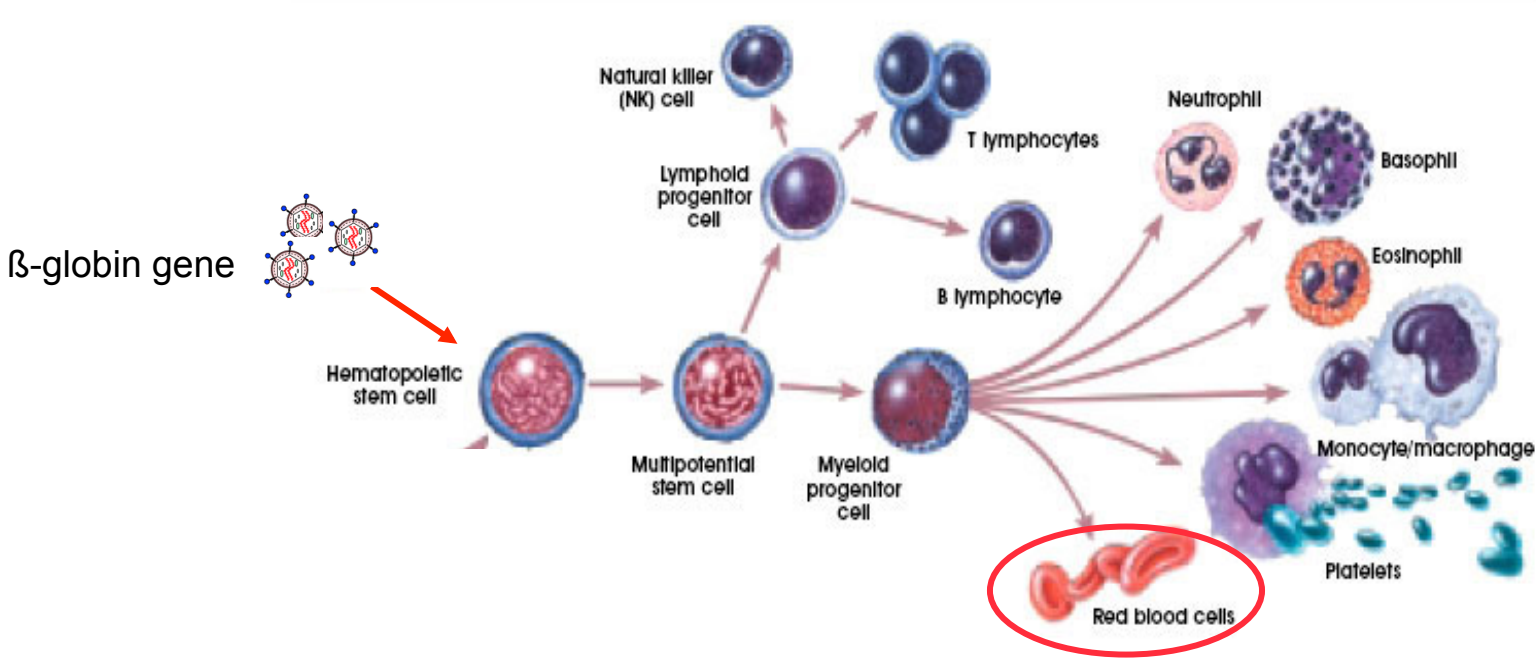
- High titer vector and efficient gene transfer into target cells
- Efficient engraftment of transduced cells and maintenance of “stemness”
- Adequate and persistent level of transgene expression
- Correction of the disease

Safety

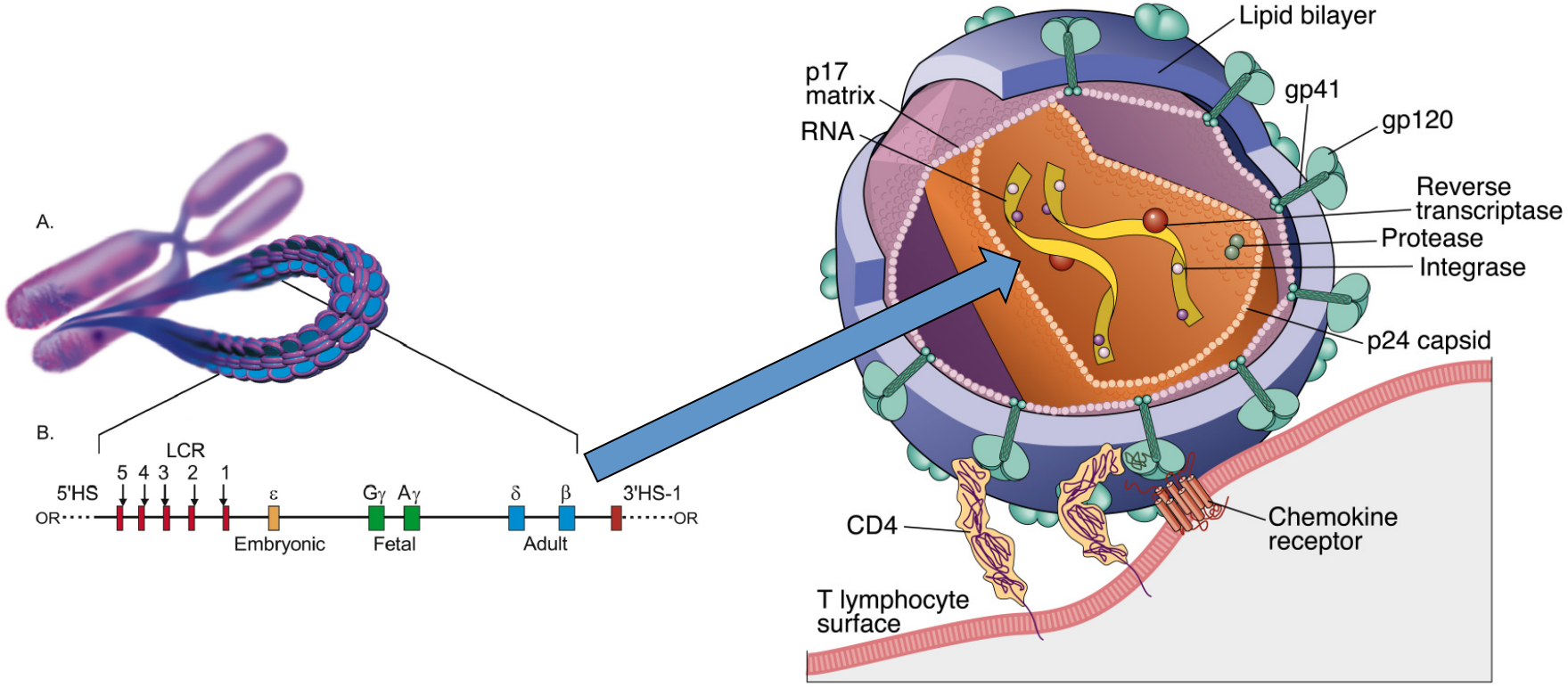
- An intense collaboration between researchers and clinicians
- A deep knowledge of the disease
- Infrastructures
- Grants for research
- Sponsor for trials

Gene Therapy in Thalassemia: Rationale

The ß-globin gene transfer into HSCs reduces globin chains unbalance in erythroid cells



VIRUS
the most suitable transfer

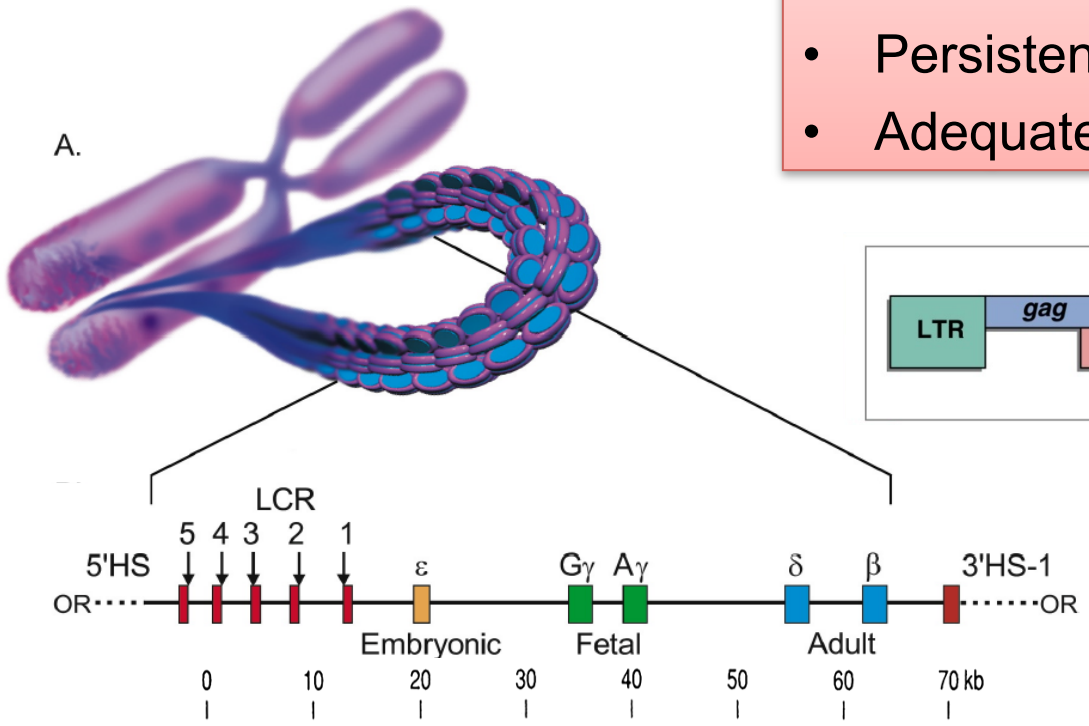


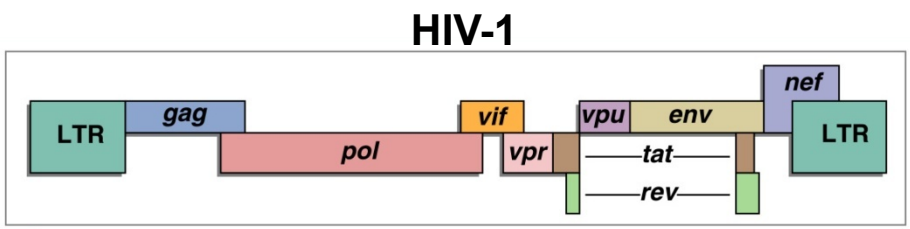
Gene transfer of ß-globin
The challenge of making efficient vectors

- Production of high-titer vectors
- Efficient gene transfer in primary cells

Correction is achieved if:

- Absence of rearrangements
- Persistence of transgene expression
- Adequate level of transgene expression



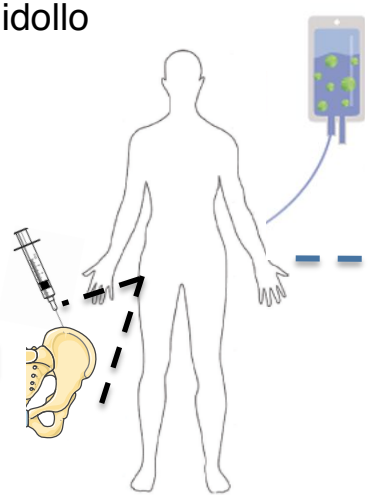


Lentiviral vector

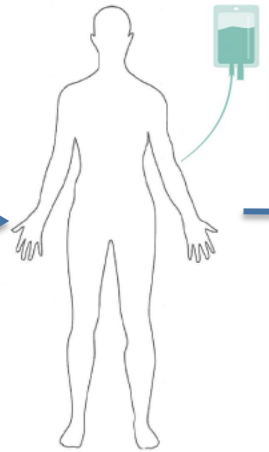
Gene Therapy for thalassemia

Trattamento paziente

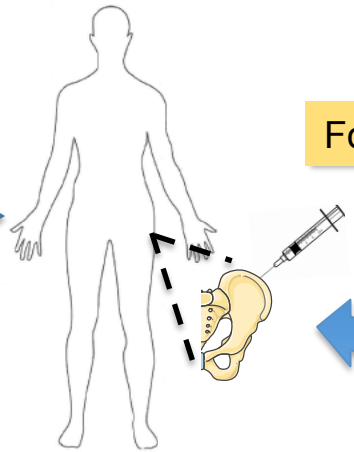
- Mobilizzazione e aferesi
- Espianto di midollo



Condizionamento giorno-5 to -1



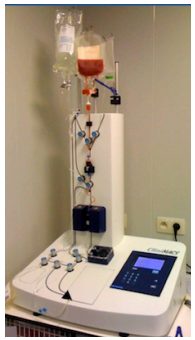
Somministrazione del prodotto (giorno 0)



Follow up

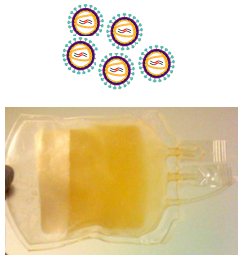
Rilascio prodotto e scongelamento

Produzione



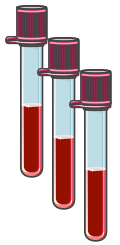
Purificazione CD34+

LV beta globina +



Trasduzione CD34+

60 hrs



Criopreservazione e controlli qualità

Gene Therapy as a Treatment for Patients with β-Thalassemia Major

Pre-clinical Studies:

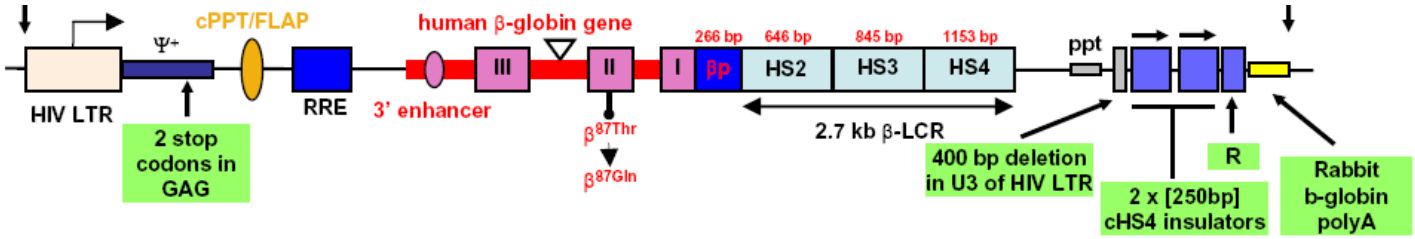
- Mouse models of β-thalassemia *(May et al. Nature 2000)* and sickle cell disease (*Pawliuk et al. Science 2001)* corrected by ex vivo gene therapy using lentiviral vectors
- Lentiviral vector, developed in the Leboulch laboratory *(Science 2001 ; PNAS 2002),* expresses functional $\beta^{A\text{-}T87Q}$ globin

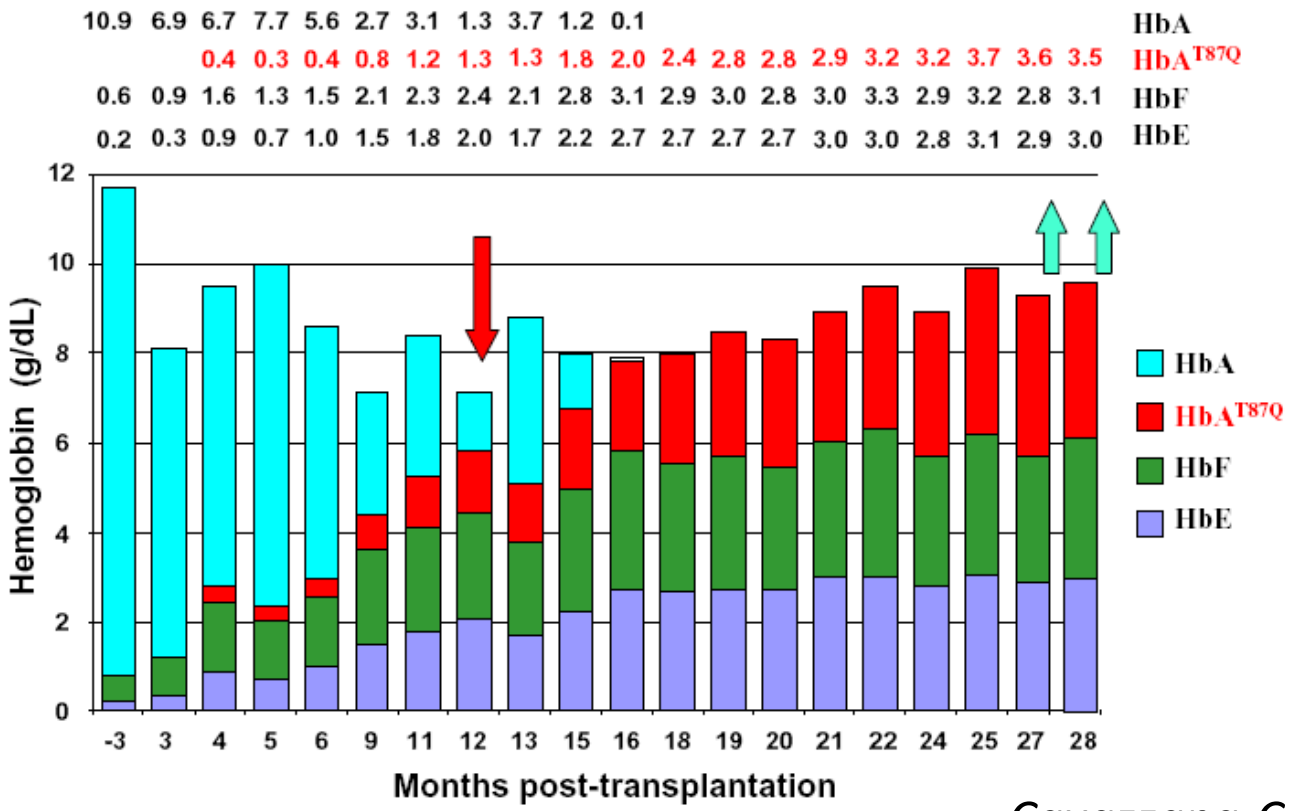
Clinical studies

- Ex vivo gene therapy using a lentiviral vector encoding $\beta^{A\text{-}T87Q}$–globin led to transfusion independence for at least 6 years in a subject with β^0/ β^E-thalassemia (*Study LG001)*
  - *Cavazzana –Calvo et al., Nature 2010;467:318 322*

- Promising results of ex vivo gene therapy using LentiGlobin BB305 Drug Product in 2 subjects with β^0/β^E–thalassemia major *(Study HGB-205)*
  - *Cavazzana et al., 2014, EHA*

Clinical Trial: Gene Transfer of the β^{87} lenti-vector into a β^{E}/β^{0} thalassemia patient promotes transfusion independence





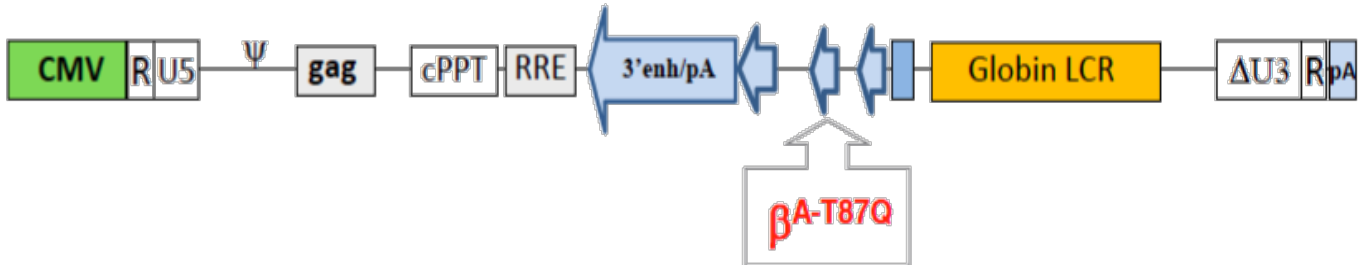
Cavazzana-Calvo,Nature2010

Gene Therapy as a Treatment for Patients with β-Thalassemia

- BlueBird
- Tiget-Thal

Lentiviral gene therapy in Transfusion Dependent β-thalassemia (TDT)

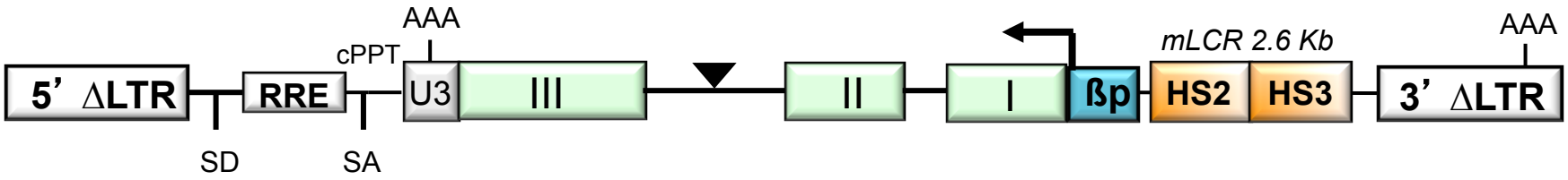
BB305 vector schematic



- Preclinical studies[1]: expression of functional $\beta^{A\text{-}T87Q}$-globin corrected mouse models of β-thalassemia[2] and sickle cell disease[3]
- HSC transduction and $\beta^{A\text{-}T87Q}$-globin expression eliminated RBC transfusions in some thalassemia subjects (ASH 2014)[4]

1. Takekoshi et al. PNAS 1995; 2. May et al. Nature 2000, Imren et al. PNAS 2002; 3. Pawliuk et al. Science 2001; 4. Cavazzana et al. Nature 2010, ASH 2014, EHA 2015

Terapia genica di BTHAL
Studi preclinici: **proof of concept**



Validazione del potenziale terapeutico del vettore GLOBE nei modelli disponibili:

- **topo mutante talassemico**

  (Miccio et al., PNAS 2008; Miccio et al. PlosONE, 2011)

- **cellule da pazienti talassemici**

  (Roselli et al., EMBO MolMed 2010)

Transfusion-dependent β Thalassemia (TDT) Ongoing Clinical Trials

NORTHSTAR STUDY

(Beta-thalassemia major)

(HGB-204)

Phase 1/2, multi-center, global study

- N=18 subjects (including 3 adolescents)
- Centralized transduction for drug product manufacturing
- Positive data presented at ASH 2014 and 2015
- Enrollment completed

HGB-205

(Beta-thalassemia & sickle cell disease)

Phase 1/2, single-center study in France

- N=7 subjects (4 beta-thalassemia)
- Positive data presented at ASH and EHA in 2014 and 2015
- First patient with SCD ever treated with gene therapy in 2014
- Enrollment completed

Subject and cellular product characteristics

N=13 infused subjects

Subject Parameters at Enrollment	
Gender	**11 female/2 male**
Age	**Median 21y** (range 16-35)
***HBB* Genotype**	**β^0/β^0 N=6** **β^E/β^0 N=4** **Other (1 each): β^+/β^0, β^+/β^+, β^x/β^0**
Pre-study pRBC transfusion vol (mL/kg/ month)	**Median 14.0** (range 11.0-19.0)
Splenectomy	**Yes in 5 (39%)**
Drug Product Parameters	
Drug Product Vector Copy Number (VCN)	**Median 0.7** (range 0.3-1.5)
Drug product cell dose (CD34+ cells x10^6/kg)	**Median 8.1** (range 5.2-14.0)

Next steps: Additional β-thalassemia clinical trials

HGB-207

Transfusion-dependent β-thalassemia, non-β0/β0 genotype

Phase 3, multi-center, global study

- N=15 adults and adolescents, and N=8 pediatric patients
- Launched in September 2016
- Primary endpoint = transfusion independence
- LentiGlobin manufacturing using transduction enhancers

HGB-212

Transfusion-dependent β-thalassemia, β0/β0 genotype

Phase 3, multi-center, global study

- N=15 adults, adolescents and pediatric patients
- Initiation planned for 2017
- Primary endpoint = transfusion reduction
- LentiGlobin manufacturing using transduction enhancers

TIGET BTHAL Protocol

Promoter: Ospedale San Raffaele
Sponsor: Telethon Foundation

Project Leader: Giuliana Ferrari

Principal Investigator:
Alessandro Aiuti
Co-Principal Investigators:
Maria Domenica Cappellini
Fabio Ciceri
Sarah Marktel

SR-Tiget
San Raffaele Telethon Institute for Gene Therapy

Stem cell program

Ospedale San Raffaele

Fondazione IRCCS Ca' Granda
Ospedale Maggiore Policlinico

Gene Therapy in Thalassemia
The long way to go

GSK Alliance

GMP prod GLOBE plasmid

GLP Toxicology (th3 mice)

GMP LV lots (MolMed)

GLP Biodistribution (CD34 cells in NSG)

2003 **2004** **2008** **2010** **2012** **2013** **2014**

PHASE I/II TRIAL

3Q2015

Development β-globin LVs

IME-HSR Network BMT in Thal pts

Correction of thalassemic mouse
Miccio et al., PNAS 2008
PloSONE 2011

Correction of thalassemic patients' cells
Roselli et al., EMBO Mol Med 2010
Frittoli et al., HGT 2011

Mapping splice sites in GLOBE LV
Moiani et al., JCI 2012

Exploring new HSC source in thalassemic patients
AMD-THAL TRIAL

✓ EMA SA IMPD/IB Master Protocol

✓ Pre-enquiry mtg (ISS)

Nov 2014
Submission to AIFA/ISS
Submission to Ethical committe
Dec 2014
Ethical committe meeting
AIFA/ISS meeting
Apr 2015
Approval

TIGET-BTHAL **Disegno dello studio**

G-CSF + plerixafor PBSC:
Cell production
cryopreservation, QC tests
Back-up ≥ 2 x 10^6/kg

If unfeasible:
BM HARVEST

intraosseous injection
of Drug Product

i.v. infusion autologous
CD3+ 5x10^7 /kg

days ≤-42 -5 -1 0 +3

Treosulfan (14 g/m2 x3)
Thiotepa (6-8 mg/kg)

Follow-up phase
2 + 8 yrs

Clinical, regulatory,
scientific monitoring

3 consecutive age groups:
Group 1 (n=3) ≥ 18 yrs
Group 2 (n=3) 8-17 yrs
Group 3 (n=4) 3-7 yrs

TIGET-BTHAL strategia a steps

GRUPPO 1.
N=3 adulti
≥ 18 aa

GRUPPO 2.
N=3 pediatrici
8-17 aa

GRUPPO 3.
N=4 pediatrici
3-7 aa

Il trial può procedere all'inclusione del GRUPPO 2 e poi del GRUPPO 3 in base al raggiungimento dei seguenti criteri in almeno 2 pazienti su 3 del gruppo precedente:

1. Assenza di SAE legati alla mobilizzazione
2. Assenza di SAE legati all'infusione intraossea
3. Assenza di SAE precoci legati al prodotto (entro 60 giorni)
4. Attecchimento ematologico entro il giorno +60
5. Presenza delle cellule trasdotte nel midollo a +30/+60d

TIGET BTHAL
CONCLUSIONI PRELIMINARI SICUREZZA

- ✓ Buona tollerabilità della procedura incluso condizionamento
- ✓ Buona tollerabilità dell'infusione intraossea
- ✓ Rapido attecchimento ematologico
- ✓ Assenza di eventi avversi seri legati alla terapia genica
- ✓ Attecchimento policlonale senza segni di dominanza clonale ne integrazione in siti a rischio oncogenico

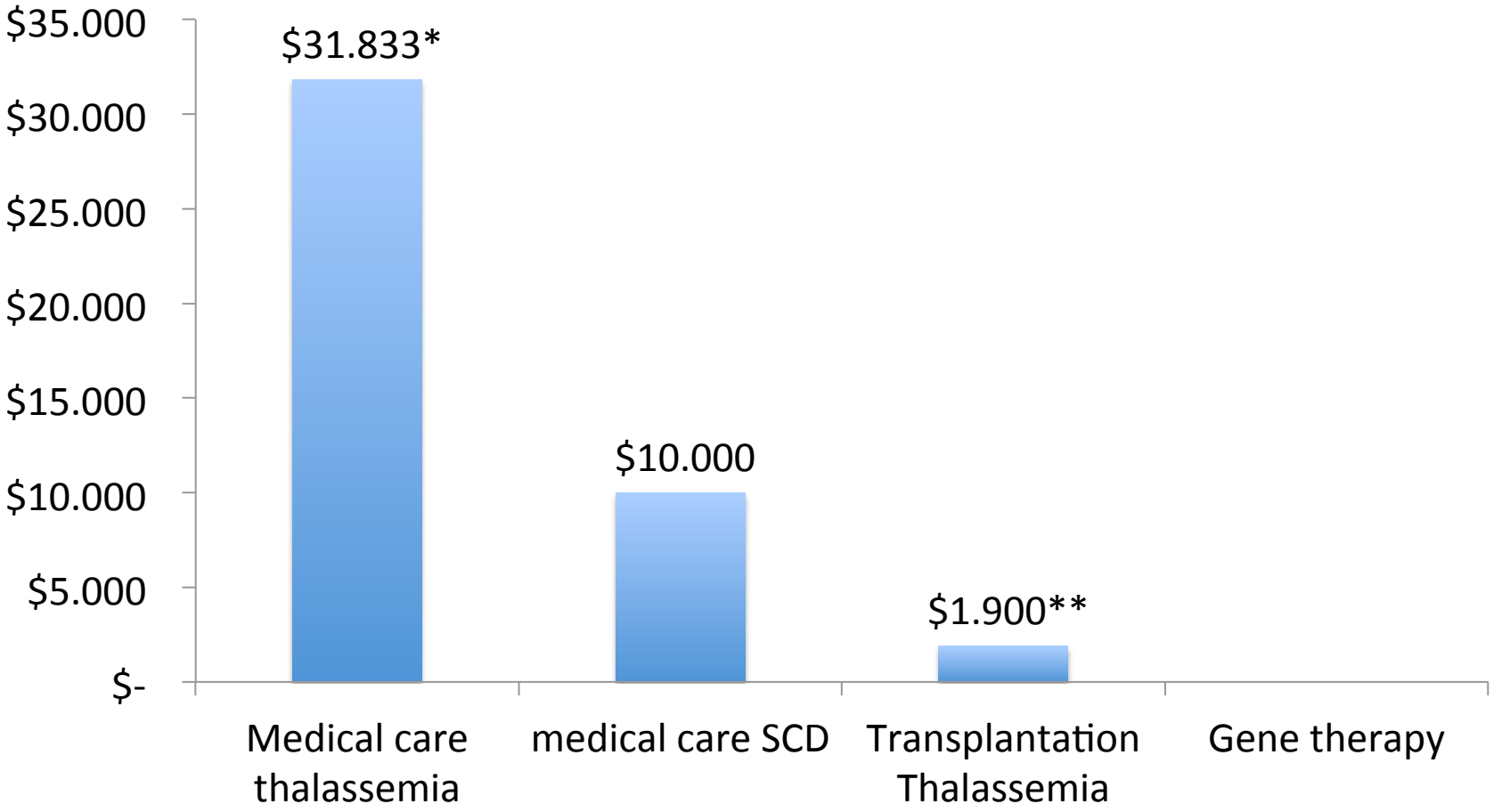
TIGET BTHAL :
CONCLUSIONI PRELIMINARI EFFICACIA

- ✓ In tutti: ottima raccolta di cellule staminali e trapianto di alto numero di cellule trasdotte
- ✓ Presenza cellule geneticamente modificate in tutte le linee ematopoietiche nel midollo osseo e sangue
- ✓ Riduzione fabbisogno trasfusionale negli adulti
- ✓ Dati preliminare di efficacia incoraggianti nei bambini

The challenge

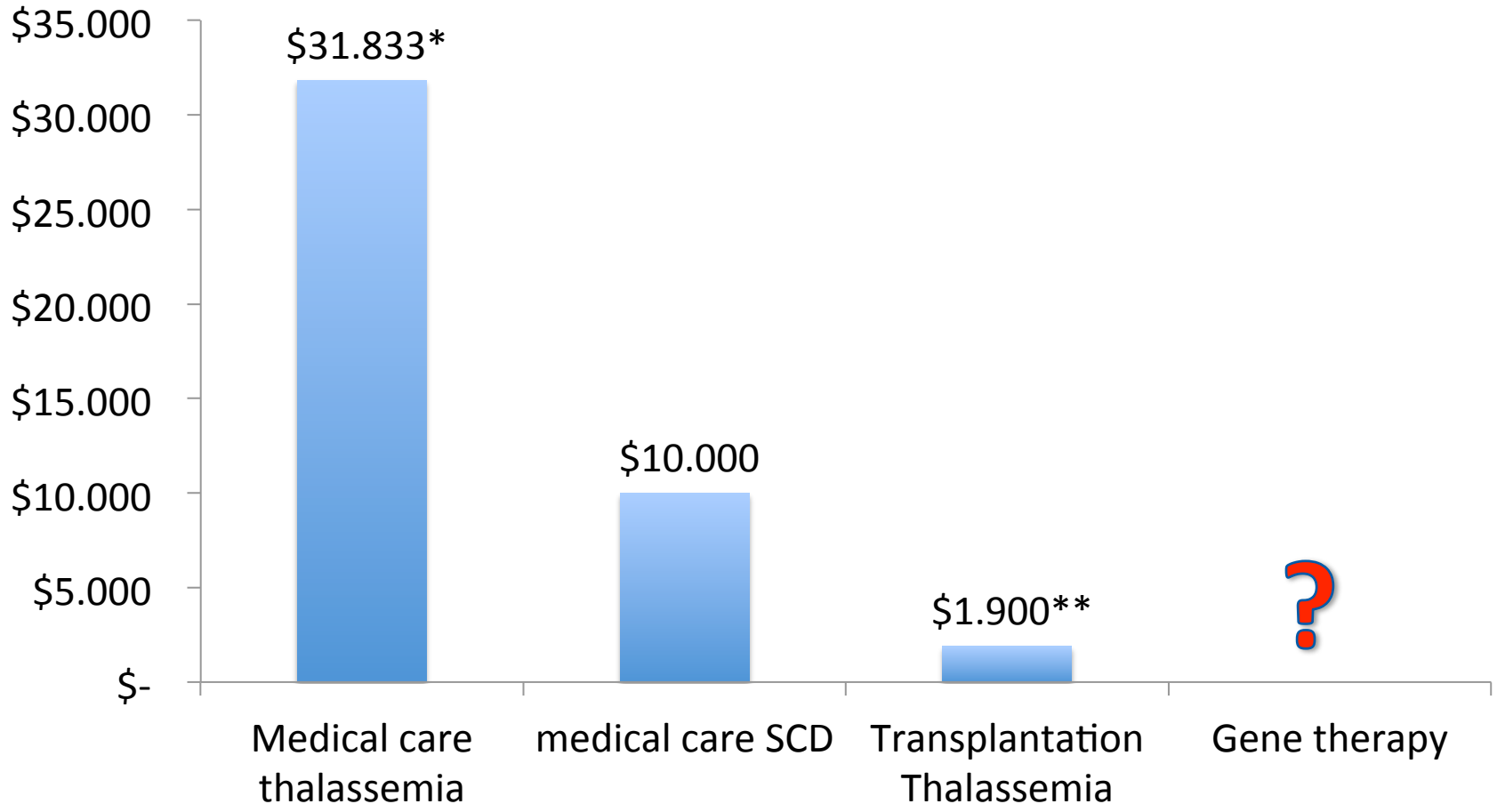
- Is gene therapy a cure for thalassemia or just a treatment to improve transfusion dependence ?

Cost-effectiveness of HCT vs Medical care in Thalassemia and SCD. USD per expected life year.



*Angelucci et a. Direct Medical Care Costs Associated With βThalassemia Care in Italy. ASH 2017
** Steiner CA, Miller JL. Sickle Cell Disease Patients in U.S. Hospitals, 2004: Statistical Brief #21. 2006.
Kauf TL, Coates TD, Huazhi L, Mody-Patel N, Hartzema AG. The cost of health care for children and adults with sickle cell disease. Am J Hematol. 2009;84:323-327.
***Orsi C et al Bone Marrow Transplant 2007; 40: 643-9. Matthes-Martin S, Potschger U, Barr R, et al. Costs and Cost-Effectiveness of Allogeneic Stem Cell Transplantation in Children Are Predictable. Biol Blood Marrow Transplant. 2012.

Cost-effectiveness of HCT vs Medical care in Thalassemia and SCD. USD per expected life year.



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Kauf TL, Coates TD, Huazhi L, Mody-Patel N, Hartzema AG. The cost of health care for children and adults with sickle cell disease. Am J Hematol. 2009;84:323-327.
***Orsi C et al Bone Marrow Transplant 2007; 40: 643-9. Matthes-Martin S, Potschger U, Barr R, et al. Costs and Cost-Effectiveness of Allogeneic Stem Cell Transplantation in Children Are Predictable. Biol Blood Marrow Transplant. 2012.

Thank you for your kind attention

OSPEDALE POLICLINICO SAN MARTINO

Sistema Sanitario Regione Liguria