Cooperation of two Italian NGOs (Help3 and S.O.S.G.T) in subsaharan areas against "sickle cell disease" and other hematological diseases

Cornelio Uderzo,MD

Pediatric DPT, University of Milan (Italy)

S.Gerardo hospital (Monza) , MBBM Foundation

cornelio.uderzo@help3.it

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SCD in Tanzania up to 2018

- **SCD birth prevalence /year**:

  6-10 per 1000 births (around 20.000)

- **SCD children MR/year** = 10.500 (J. Makani)

- **U5-MR for SCD = 50 to 90%**

- **U5-MR for Malaria = 10 % (WHO data)**

“SCD” and national/international cooperation in “subsaharan area”:

a challenge to reduce U5-MR as claimed by WHO and UNESCO on 2006

Phase 1 (2015-2017) : our initial commitment in SCD children only

- **Starting point :**
  - in TANZANIA (**BMC -Mwanza, **St. Gemma H -Dodoma , **Muhimbili hospital –Dar Es Salaam ,** Zanzibar hospitals)
  - in UGANDA (S.M. Lacor hospital)

  - SCD children treated before our intervention = 60 out of 6000 _

- **Aims of Italian NGOs cooperation :**

  - To improve diagnosis and treatment in SCD children

  - To improve the outcome and QOL in SCD children

Help3 and SOSGT ongoing activities for SCD:

- **From 2015 to 2017**:

➢ **four SCD "outpatients" activated in** 4 Hospitals :

BMC -Mwanza, **St.Gemma H**-Dodoma , and **Mnazi Mmoja H** -Zanzibar

Lacor hospital (*Uganda)*

➢ **Donation of Hydroxyurea** for the treatment **of the first 280 children**

➢ **Donation of a "data base" SCD oriented**

➢ **Donation of one "Electrophoresis of Hb" instrument**

➢ **An Italian hematologyst** available every day for consultation

- **Within 2019** :

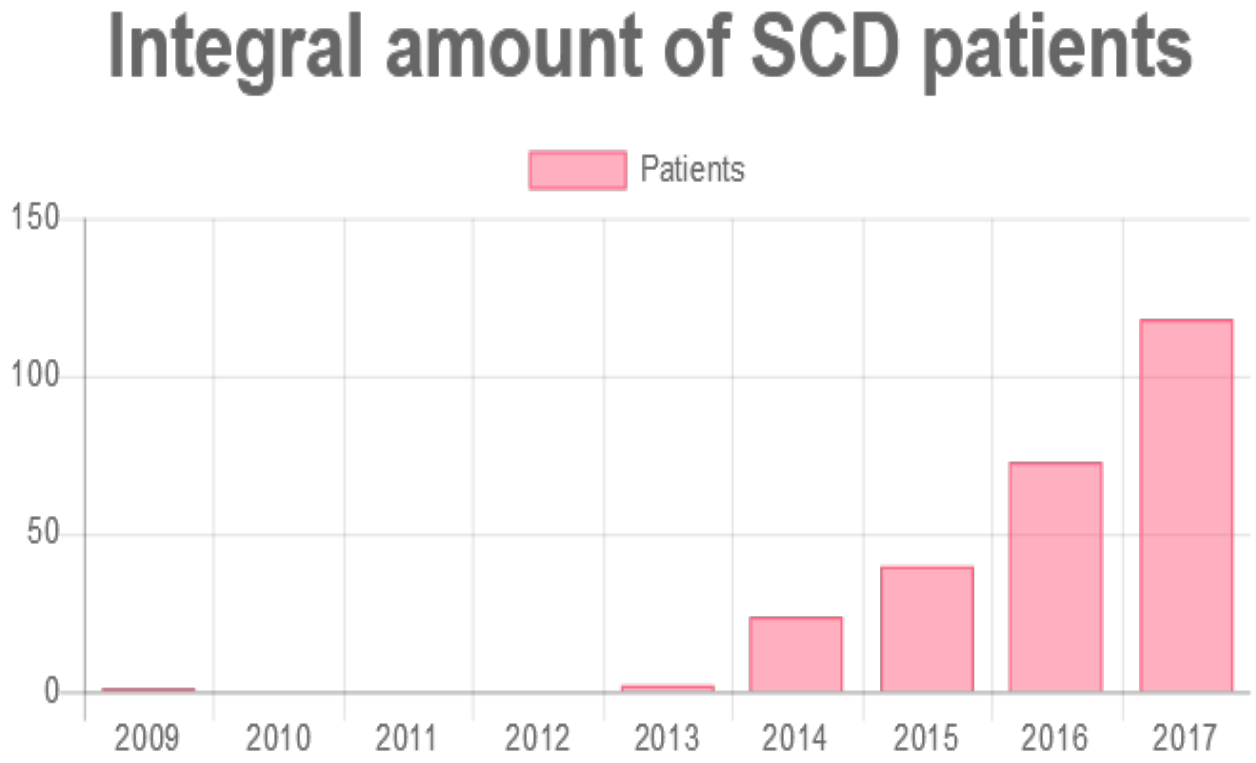
➢ **600 SCD children *on Hydroxyurea therapy***

➢ ***Donation of 2nd "electrophoresis of Hb" or "Rapid Test"***

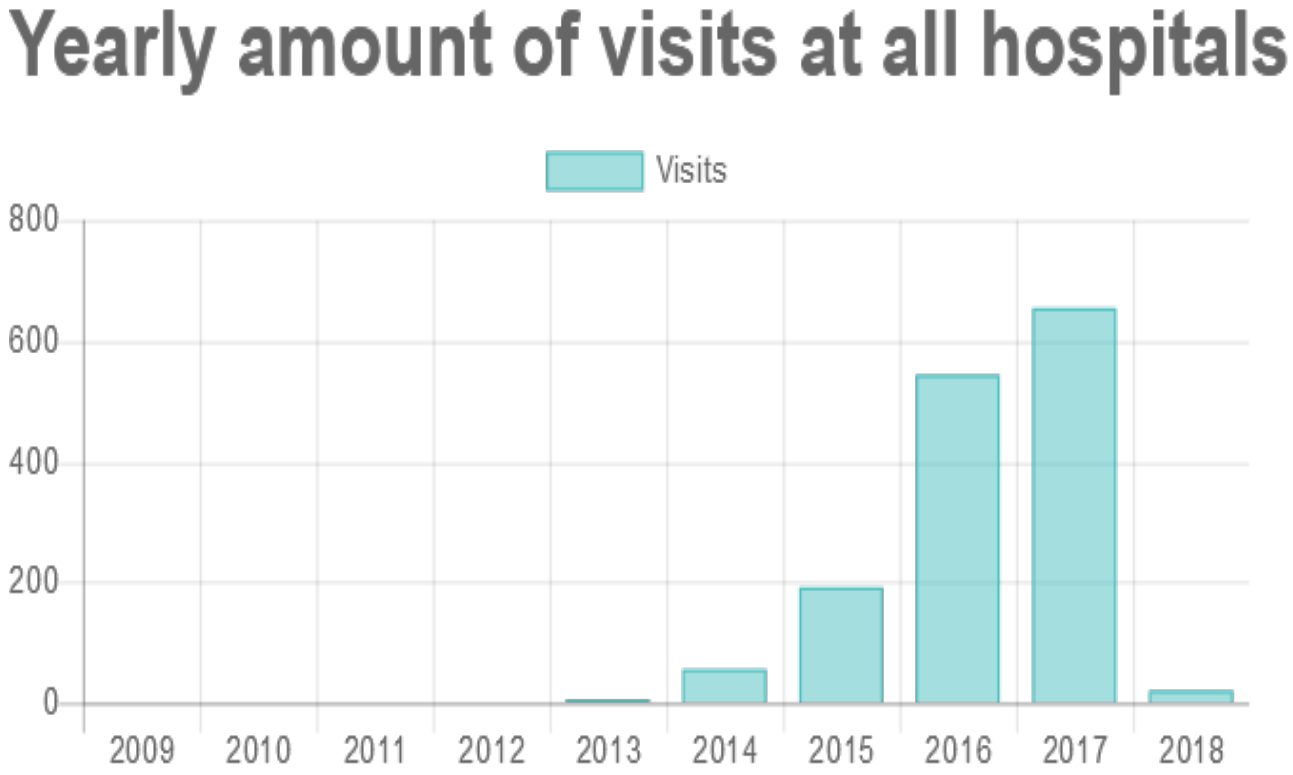
➢ ***Distribution of "Brochures" with SCD INFO***

➢ ***HSCT ?***

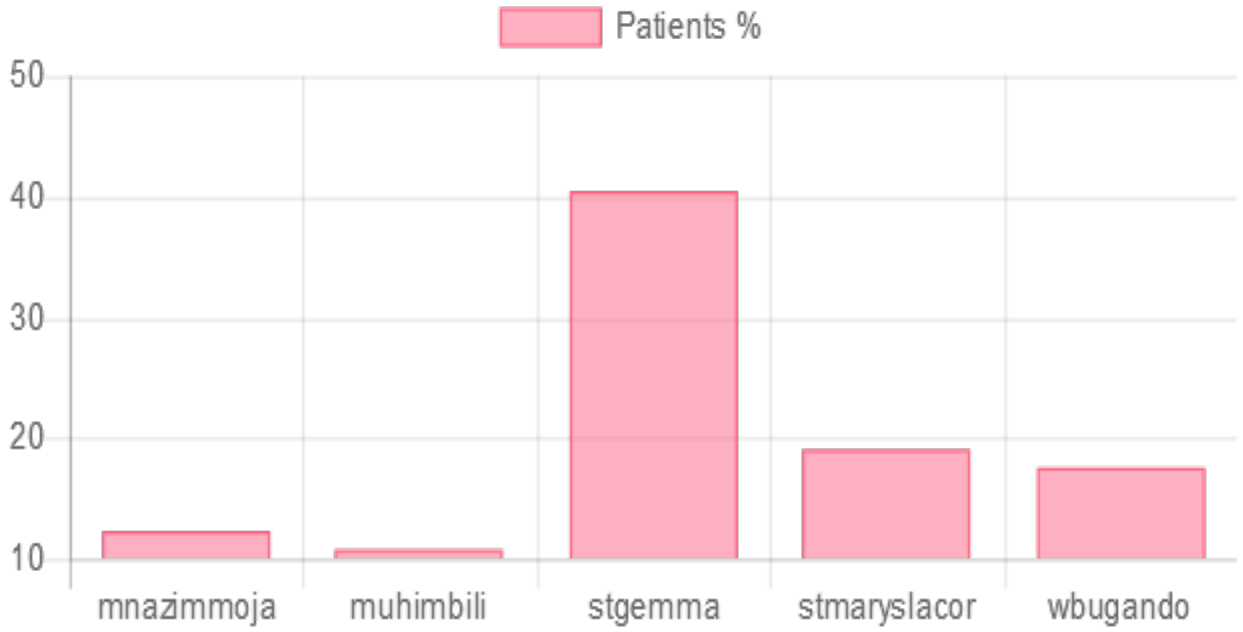
Result 1: 280 registered patients



Result 2= 1468 registered visits

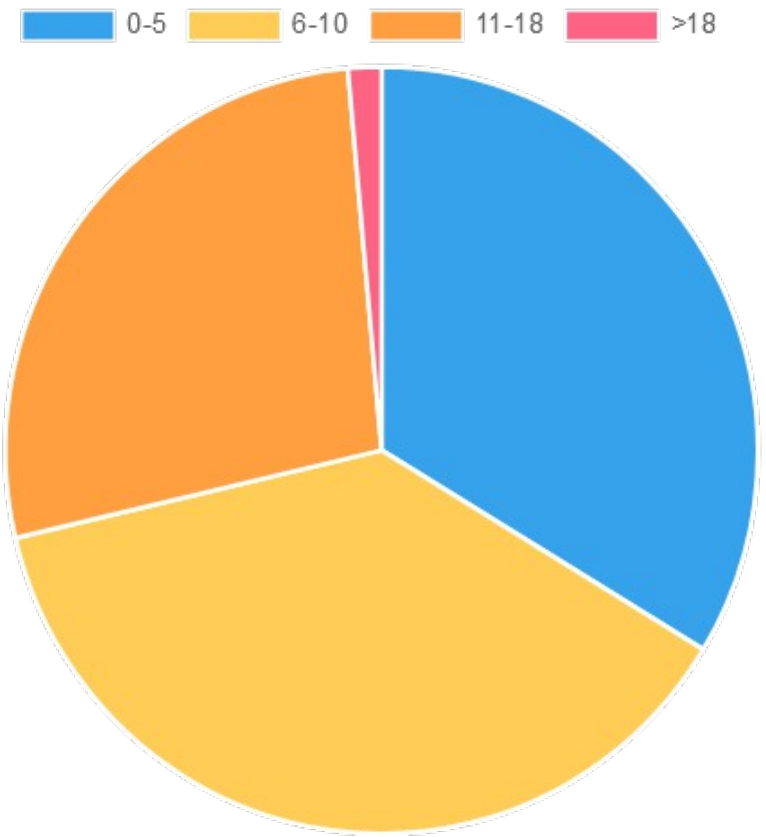


Patients % treated per hospital



Result 3 = age at enrollment

- **AGE**

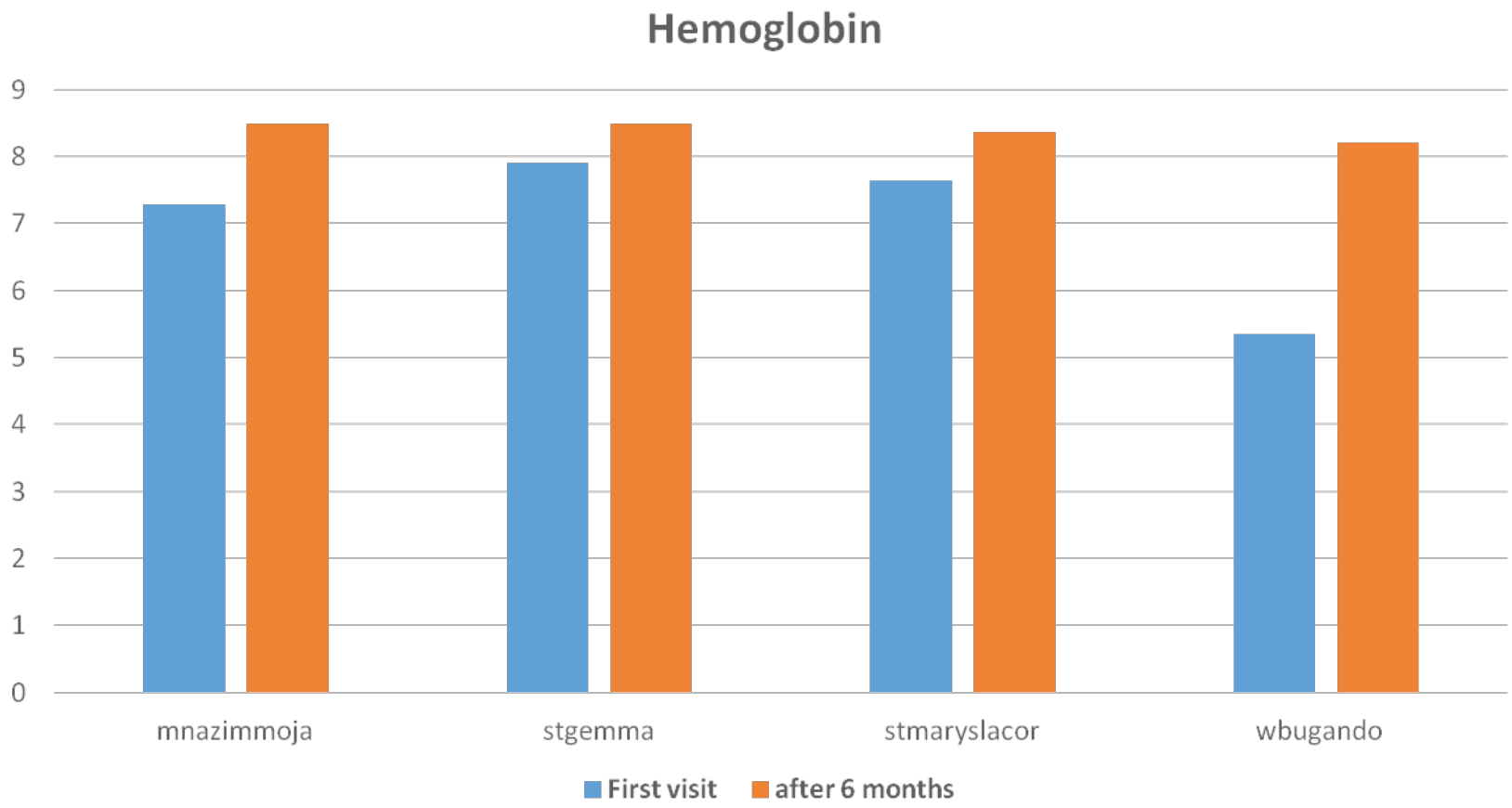


Number / age

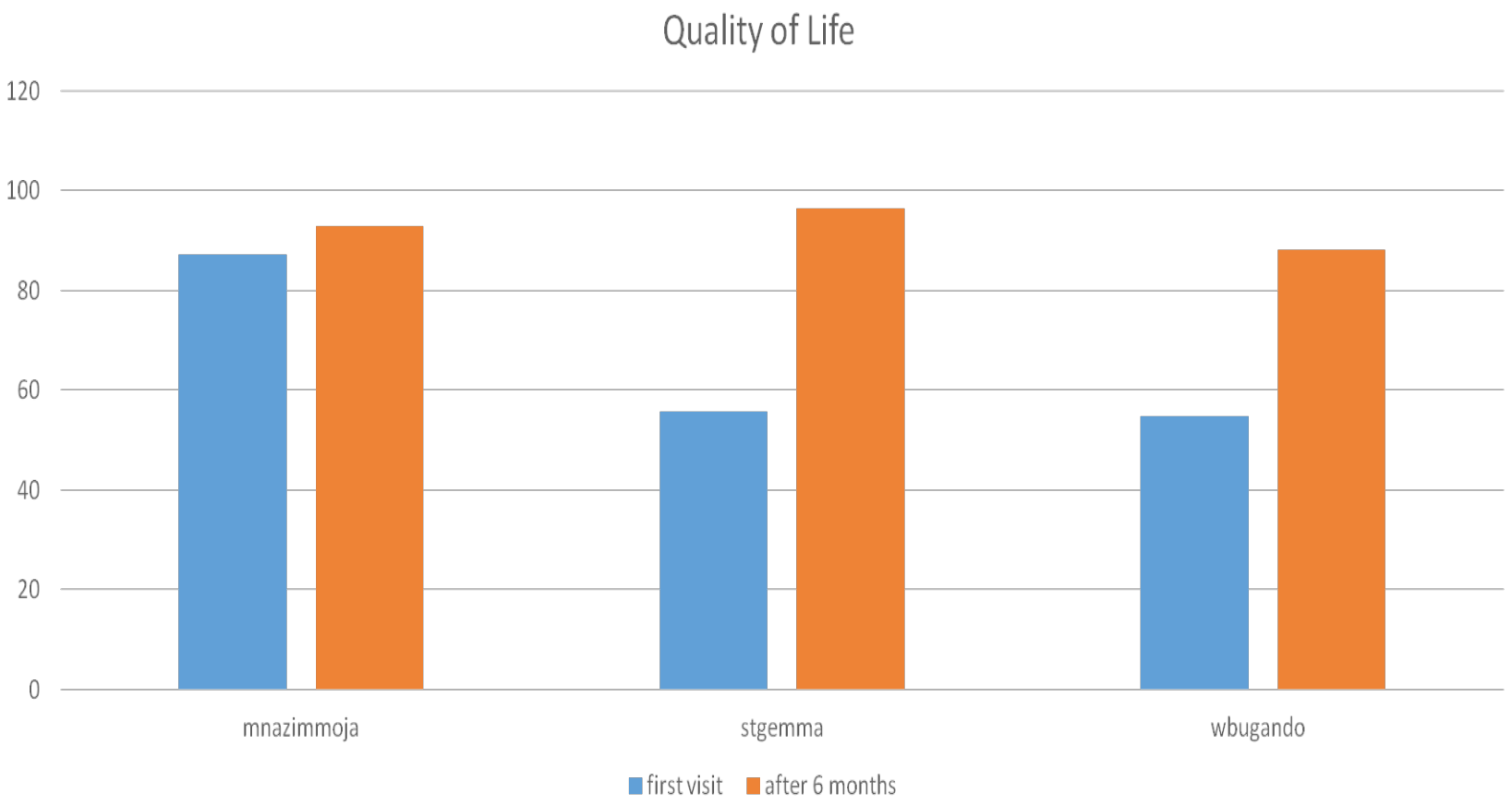
- 94 (0-5 yr)
- 105 (6-10 yr)
- 77 (11-18 yr)
- 4 (>18 yr)

Result 4 = median Hb value in 249 SCD children

pre and post HU



Result 5 = QOL *(by Lansky score) in* ***196 SCD children*** *pre and post HU*



What about HSCT for SCD ?

- **is the only "curative treatment "** for **SCD** since 20 years in "high income countries" *with 95% of EFS* and no *recurrence of clinical "vaso-occlusive crisis"* and no new ischemic lesions after successfull transplant

(F.Bernaudin, BLOOD 2007)

What about "gene therapy" for SCD ?

- ***First positive experience (M.Cavazzana, 2015)***
- **To be confirmed in larger series**
- **Very high costs of the procedure**

HSCT **in "AFRICA"**

- **Situation on 2015**

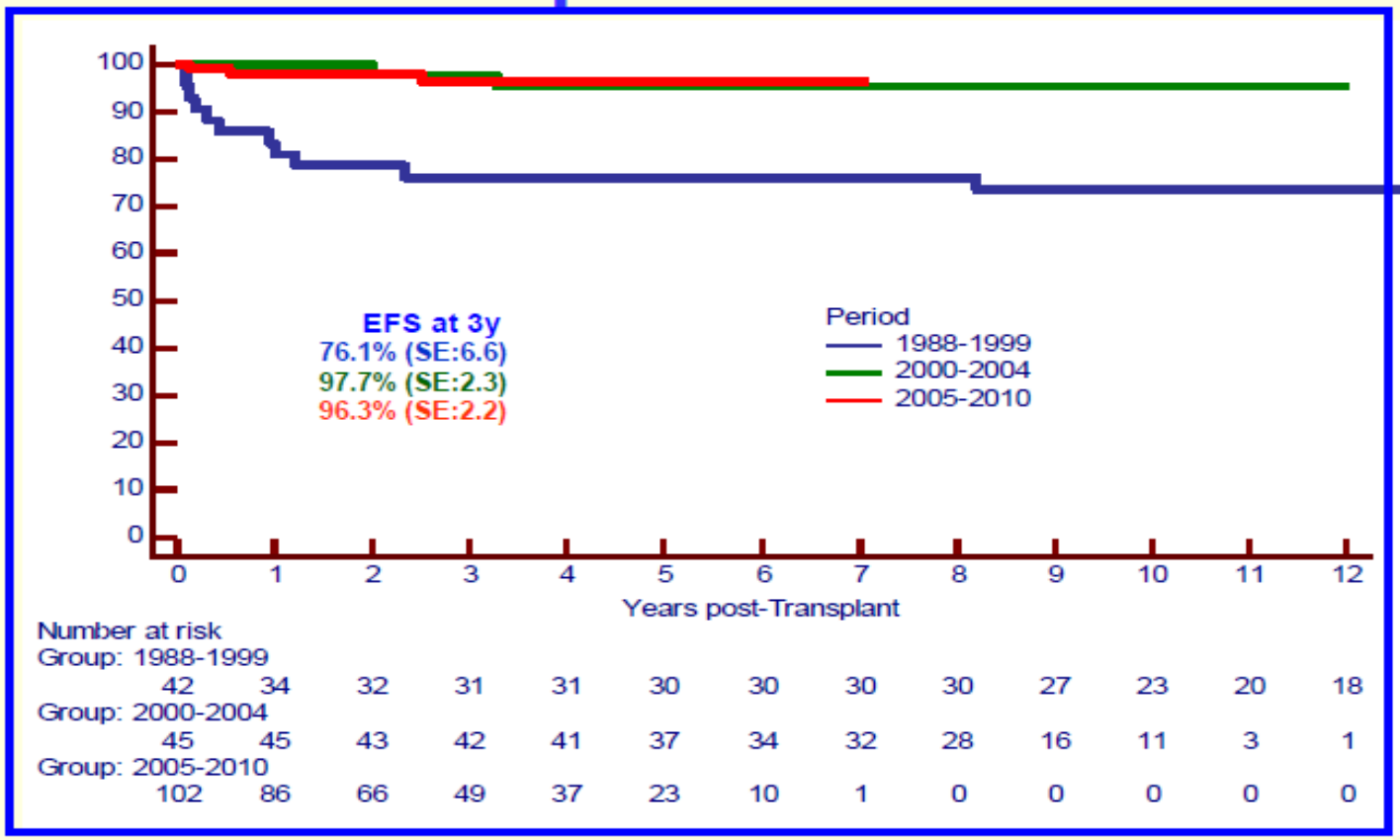
- only **10 HSCT centers** in Africa for 1 milliard of people (*1 in Nigeria, 6 in South Africa,1 in Tunisia,1 in Morocco, 1 in Egypt*) but not experience in SCD
- **need to set up other HSCT centers in *"sub-saharan area"***

- **Probable costs** for building up a Pediatric HSCT Unit in sub-equatorial area : around ***350.000 $***
- ***Probable costs for a HLA identical donor HSCT : 10.000 $***

"EFS" in SCD after HSCT from HLA identical familiar donor : 20 years experience

(F. Bernardin, Blood , 2005)

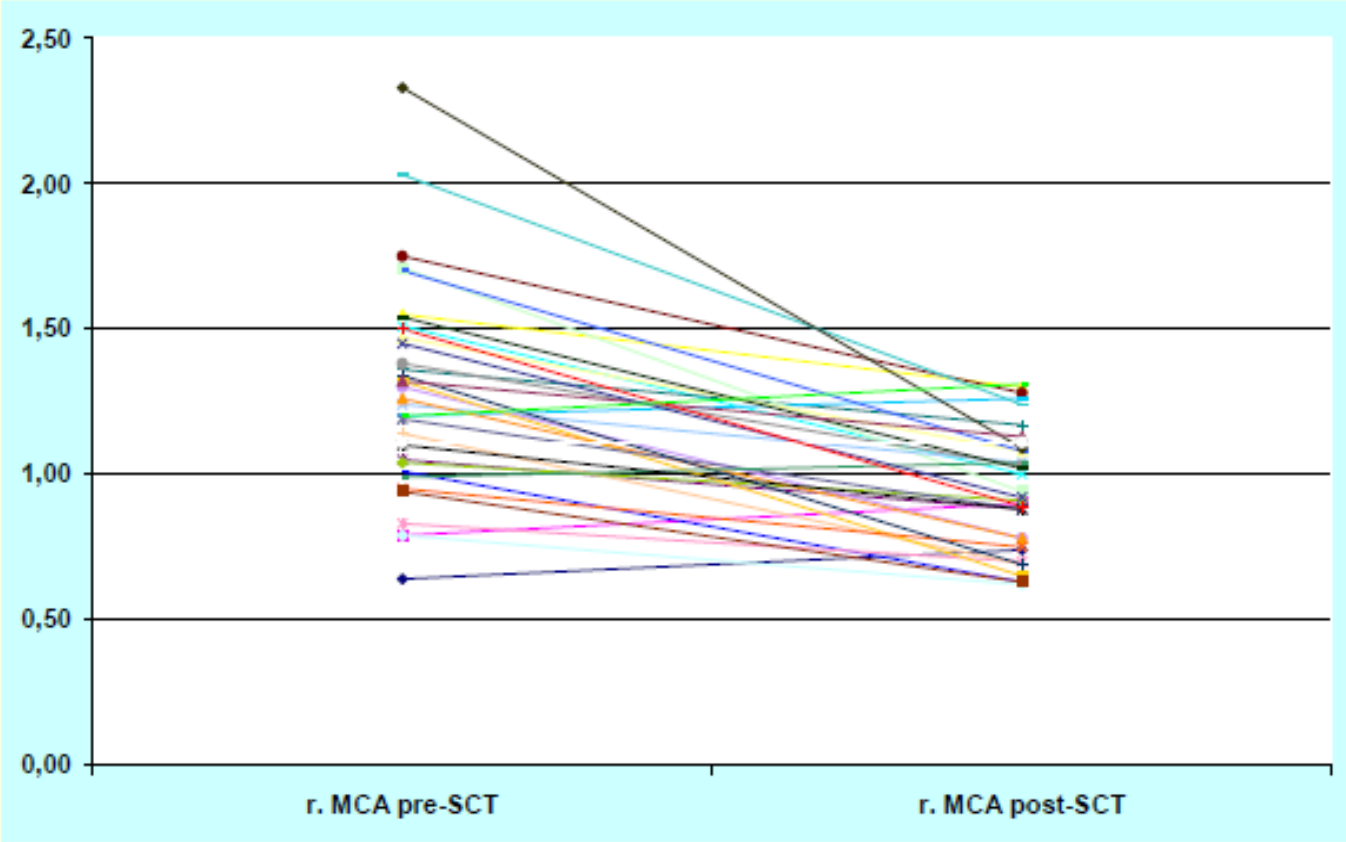
EFS: Improvement with time



Chance of cure at least of 95% since 2000 (n=147)

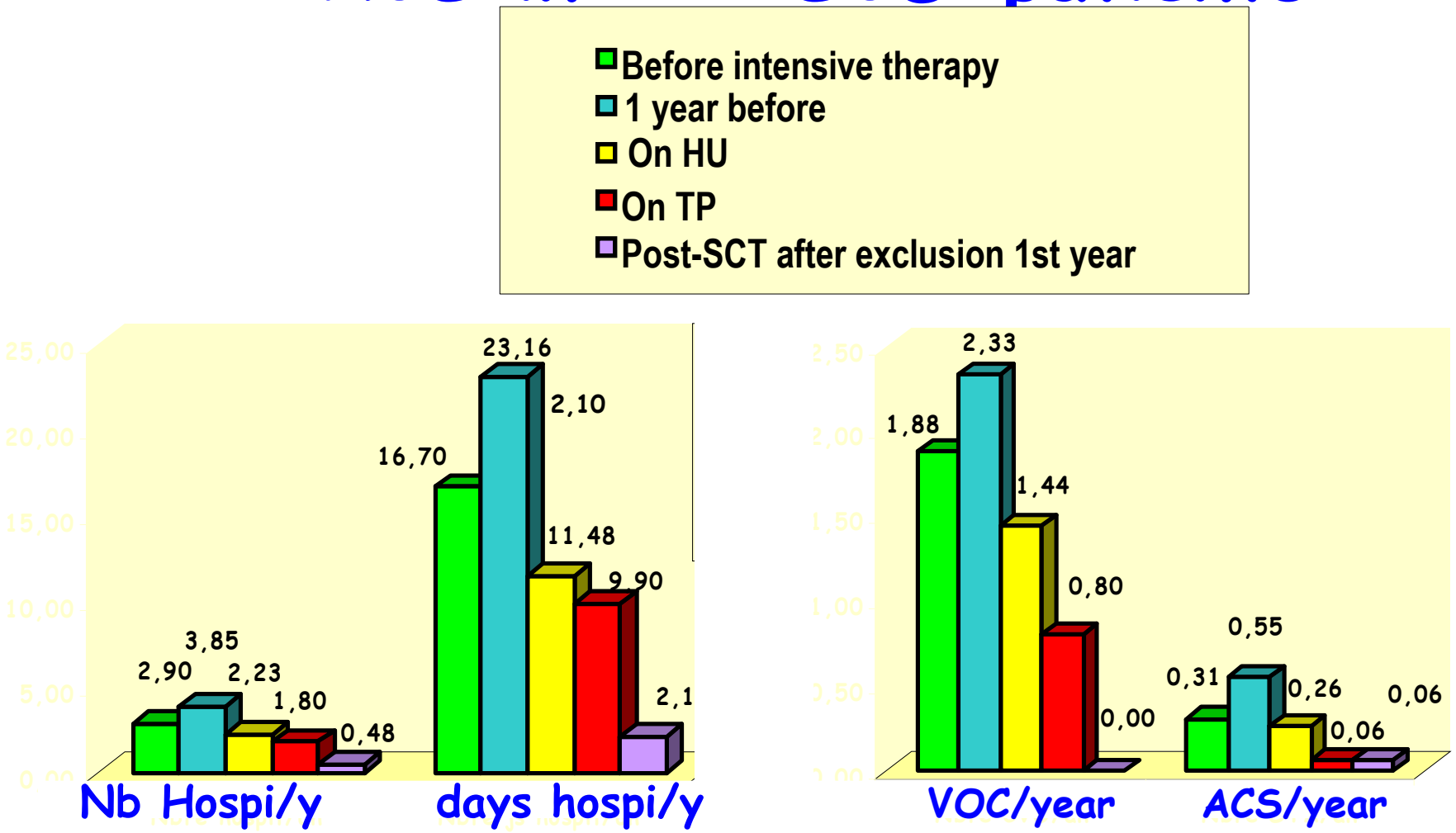
Outcome of arterial velocities

- Significantly reduced 1 year after transplant in 49 assessable patients *(p<0.001)*



Bernaudin et al Strasbourg April 2011

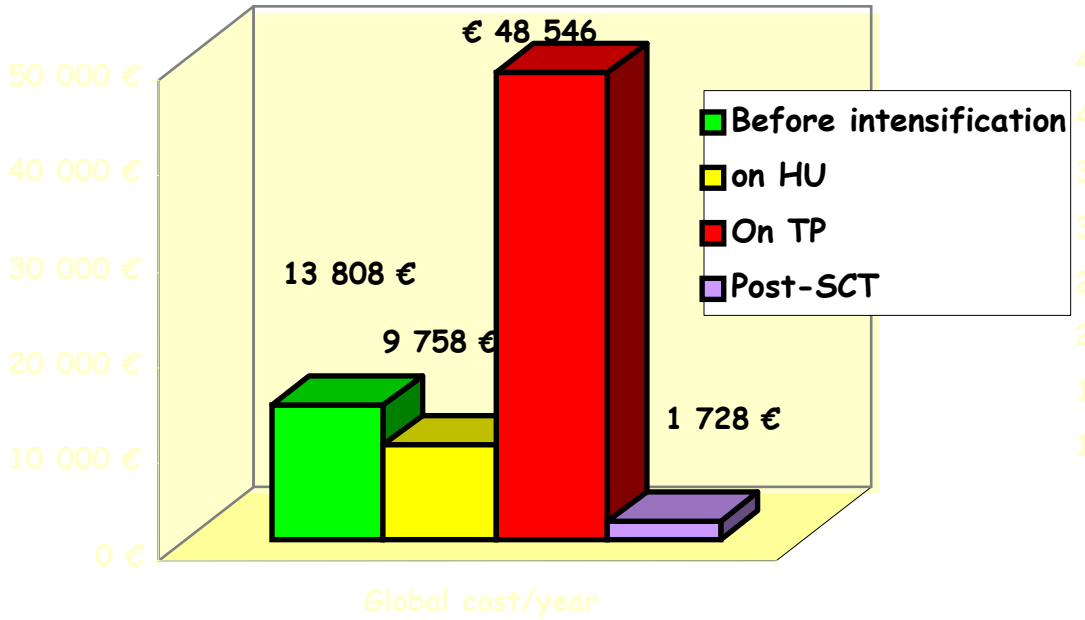
Comparative effects of TP, HU and HSCT on frequency of Hosp, VOC, ACS in 111 SCD-patients



Arnaud et al CHI-Creteil, ASH

Costs in Patients with pre-HSCT frequent VOC/ACS

- HSCT cost (1st year: 77,883 €)
  = 1.6 year of transfusion program
  = 7.9 years of HU
- Annual cost 1 year post-transplant
  = 12 days of TP
  = 64 days of HU



HSCT in "low income countries: lesson from previous experiences

L. Faulkner and C. Uderzo (Blood advances, 2017)

Jaipur (INDIA)

- Period : 2012-2016
- HLA identical sibling donors HSCT in **56 "low risk"** **Thalassemic children**
- Conditioning

  Bu+Cy (Myeloablative)

- 2 yrs overall SV= **95%**
- 2 yrs TFS = **91%**

Islamabad (Pakistan)

- Period :2011-2016
- HLA identical sibling donors HSCT in **125 "low risk"**

  Thalassemic children
- Conditioning

  Bu+Cy (Myeloablative)

- 3 yrs overall SV = **93%**
- 2 yrs TFS = **87%**

HSCT for **SCD** is a reliable objective in subsaharan area too

"Malignant Diseases" vs. "Comunicable Diseases " : "mortality rate" in subsaharan area up to 2030

(Gopal S.: Blood 2012, 5078-5087)

- **Leukemia and Lymphomas**
  - **MR/year**

  = 800.000

- **HIV**
  - **MR/year**=1.2 million
- **Malaria**
  - **MR/year=** 709.000
- **TB**
  - **MR/year=** 250.000

Estimated yearly Incidence of childhood leukemia and lymphoma in "Tanzania"

NEW LEUKEMIAS/YEAR

- **2000** patients (1 to 18 yrs)
- **500**
  in the areas of
  - Mwanza
  - Dodoma
  - Zanzibar

NEW LYMPHOMAS/YEAR

- **2500** patients (1 to 18 yrs)
- **600**
  in the areas of
  - Mwanza
  - Dodoma
  - Zanzibar

Expected prognosis for childhood leukemias/lymphomas after standard therapy and HSCT

In high income countries

❖ **Chemotherapy** :

DFS in standard risk = **85%**

DFS in high risk = **50%**

❖ **HSCT**

DFS in standard risk = **80%**

DFS in high risk = **50%**

In subsaharan areas

❖ **Chemotherapy :**

DFS in standard risk = **60% (?)**

DFS in high risk = **30% (?)**

❖ **HSCT (to be proved)**

DFS in standard risk = **70% (?)**

DFS in high risk = **40% (?)**

Phase 2 (2018-2020) : our current commitment

Strategy :

- **Giving our scientific and training support by our professionals in setting up one " Hematologic and HSCT Unit" in TANZANIA**

- **To establish a continuous education plan for a high level of training and attitude of Tanzanian hematologic team (before and after the Hematologic and HSCT Unit start-up)**

- **to institute in Tanzania a strong collaborations with some Italian Institutes dedicated successfully to hematologic diseases**
  (*S. Gerardo hospital, Monza, University of Milan ;*
  S. Raffaele hospital ,Milan, University of Milan)

HSCT for hematologic patients : general requirements

- To be carried out in eligible patients only
- ***The personnel*** must not only be appropriately qualified, but should be trained according to international agreed standards
- **A strong interactivity** among different structures (Radiology, Pharmacy , Pathology and Hematology Labs , ICU, …….)

  of HSCT program must be encouraged
- Useful to perform at least 10 transplants/year to have and to maintain an adequate experience

HSCT for hematologic patients : specific needs

- Fully sterilized HSCT Unit: no need
- Normal “microbiology” and “virology”
- **Efficient “Blood Bank”** : mandatory
- **ICU and “Dialysis”** : available
- **Blood product irradiation** : mandatory
- **Dosage of Cyclosporin level:** mandatory
- **Monitoring of “CMV” infection**: mandatory

HSCT CENTER
MBBM Foundation
Pediatric Dept. University of Milano-Bicocca
San Gerardo Hospital, Monza,Italy

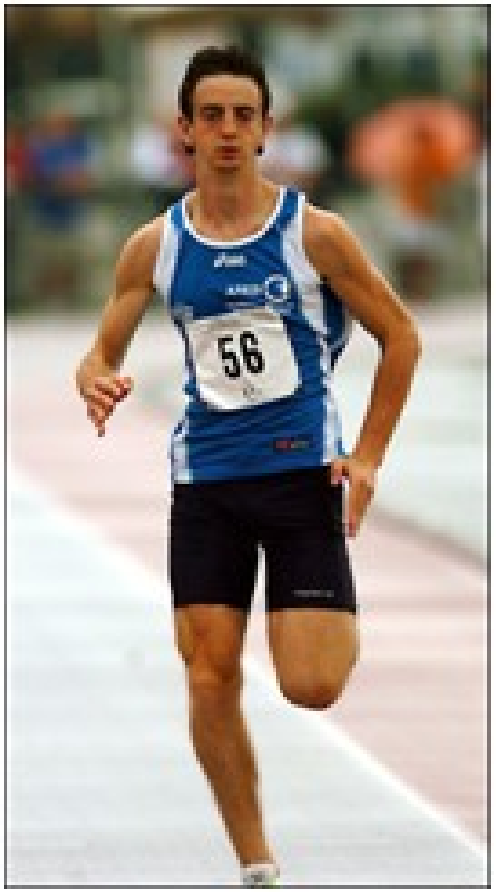
c.uderzo@help3.it

JACIE accredited facility &
AIFA authorized GMP cell factory

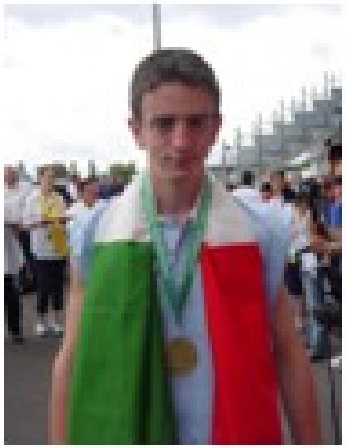
MBBM HSCT Center
Transplant activity 1985-2016

Malattia	AUTO	ALLO	Total
ACUTE LYMPHOBLASTIC LEUKEMIA	46	288	334
ACUTE MYELOID LEUKEMIA	43	114	157
NEUROMETABOLIC DISORDERS	-	45	45
MARROW HYPOPLASIA (SAA 23, FA 10)	-	33	33
MYELODYSPLASTIC SYNDROMES	-	26	26
CHRONIC MYELOID LEUKEMIA	-	26	26
NON-HODGKIN LYMPHOMA	2	20	22
HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS	-	18	18
HEMOGLOBINOPATHIES	-	15	15
JUVENILE MYELOMONOCYTIC LEUKEMIA	-	14	14
HODGKIN LYMPHOMA	13	8	21
METABOLIC DISORDERS		58	58
TOTAL	104	620	724

Monza, 31.12.16



Our patients winners at the BMT Olympic games



London, Canada – July 2005

The new building "Centro Maria Letizia Verga"
Floor 0: Tettamanti Research Center

Centro Maria Letizia Verga
PER LO STUDIO E LA CURA DELLA LEUCEMIA DEL BAMBINO

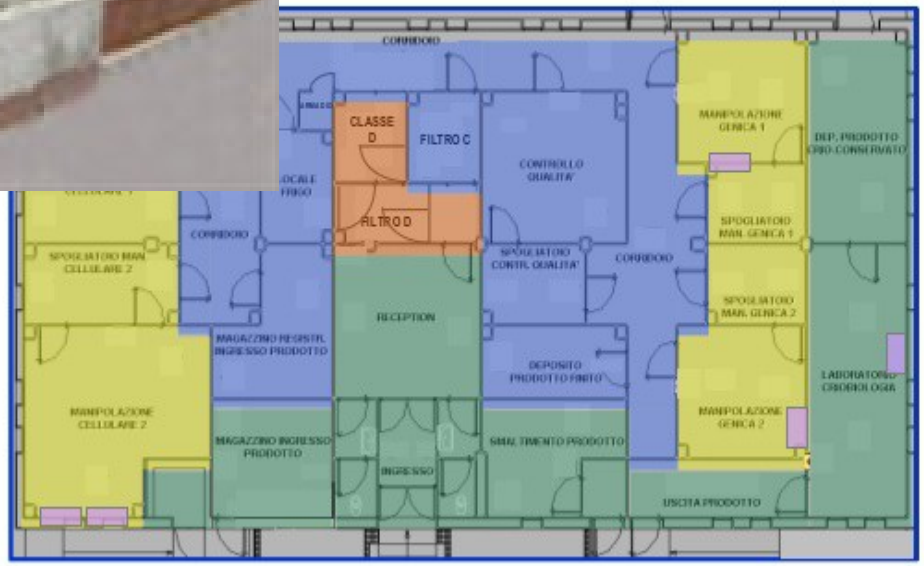
- ➢ **15 diagnostic labs**
- • ***35 lab researchers***

- ✓ **Clinical research**

- • **94 studies (61 active, 33 in start-up)**

(36 profit: Phase I, II, III)

Cell & Gene Therapy Unit “S. Verri”



AUTHORIZED BY

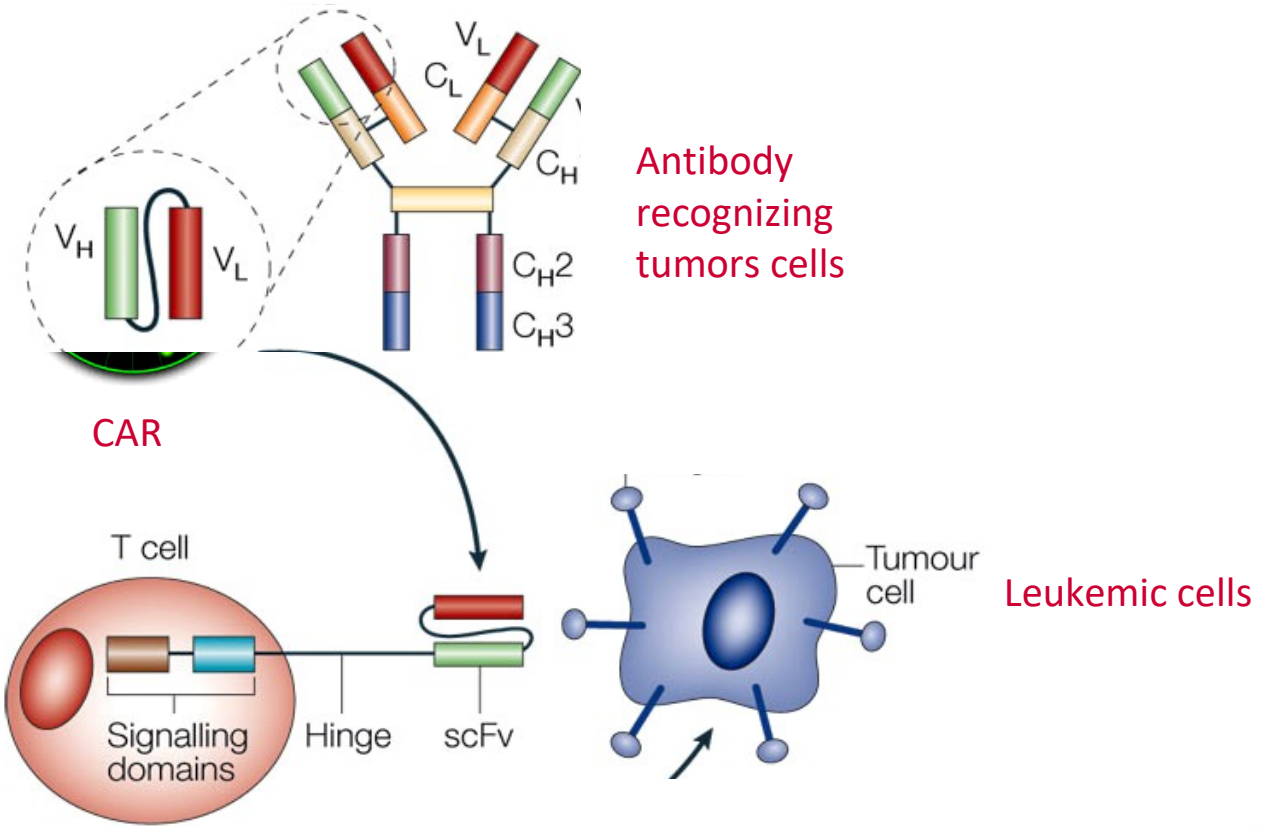
AIFA
Agenzia Italiana del Farmaco

Non classificato Classe D Classe C Classe B Classe A – cabina a flusso laminare

Monza, 06.06.2017

Gene therapy in childhood Leukemia: chimeric artificial receptors (CAR)

T cells ***genetically modified to express*** ***the CAR*** **and then expanded *in vitro , are finally reinfused* into the patient, ready to kill the leukemic cells (CD19+ or CD33+)**



modified from Kershaw M.H. (2005), *Nature Reviews Immunology,* 5, 928-940

Conclusion 1 : why to improve pediatric care in the community ? (T. Stiris et al, **Lancet** ,385, 2015)

According to European Academy of Paediatrics :

- *Children have the right to access the highest possible standards of health care services and facilities both in primary health care and when they need specialised care*

- *Any restriction of provision of appropriate care would contradict article 24 of the UN Convention on the Rights of the Child*

- *Paediatric Services should provide disease prevention and health promotion*

Conclusion 2: targets for childhood hematological diseases in sub-saharan areas

First : to decrease the "U5-MR" *with a sustained collaboration and advocacy by National task force and International NGOs*

Second : to improve the DFS and QOL by standard diagnosis and treatment , decreasing also the "social costs" of the diseases

Third: to cure definitively by standard therapy and HSCT both childhood SCD and other blood diseases

HOPEFULLY !

A big thanks to Donnall Thomas…

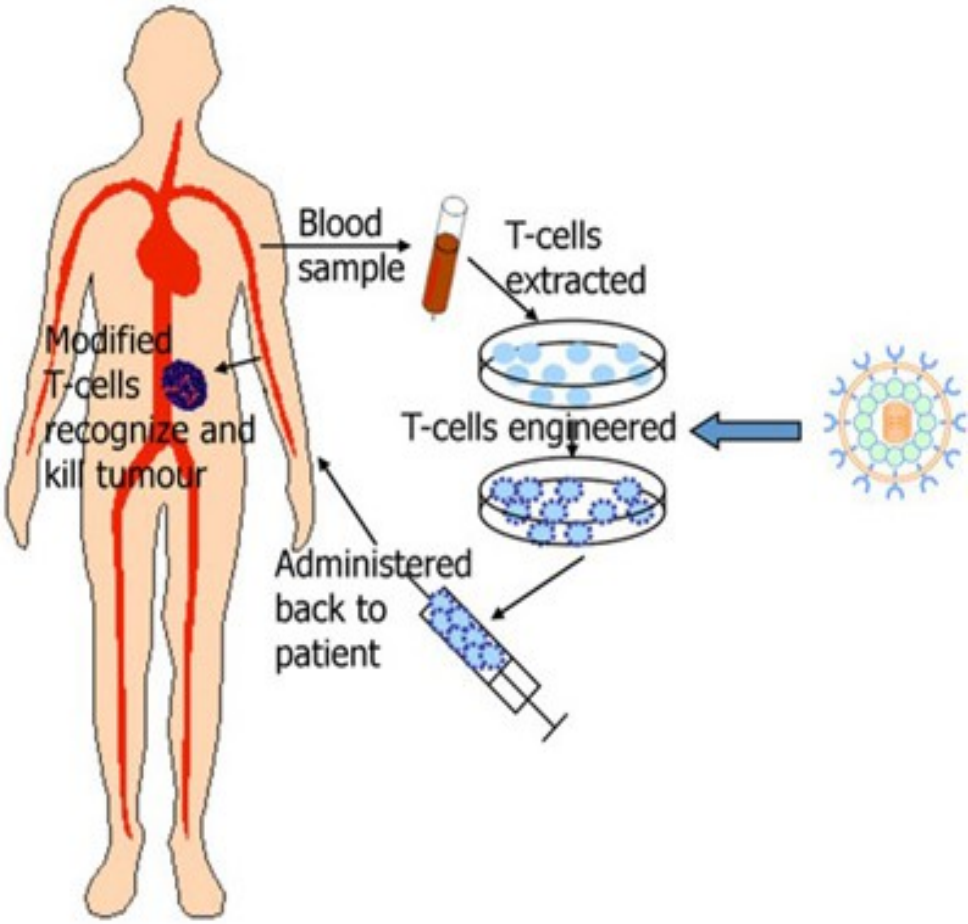
HSCT pioneer, Nobel Prize on 1990 and a great "life coach"

MBBM HSCT Center
Transplantation for rare disorders

Disease	Pts.	HSCTs
MUCOPOLYSACCHARIDOSIS TYPE I-H	17	21
OTHER MUCOPOLYSACCHARIDOSIS	4	4
X-LINKED ADRENOLEUKODYSTROPHY	8	8
GLOBOID CELL LEUKODYSTROPHY	7	7
MITOCHONDRIAL NEUROGASTROINTESTINAL ENCEPHALOMYOPATHY	2	2
OTHER DISORDERS	3	3
TOTAL	41	45

T-CARS : a revolution

- The most common procedure for *CAR-T cell therapy* starts with the extraction of T cells from the own patient, a process called leukapheresis.
- *The T cells are then genetically modified to express a CAR* and expanded *in vitro*.
- *Finally, they are reinfused* into the patient, ready to fight the tumor.



HYDROXYUREA : the TWITCH study

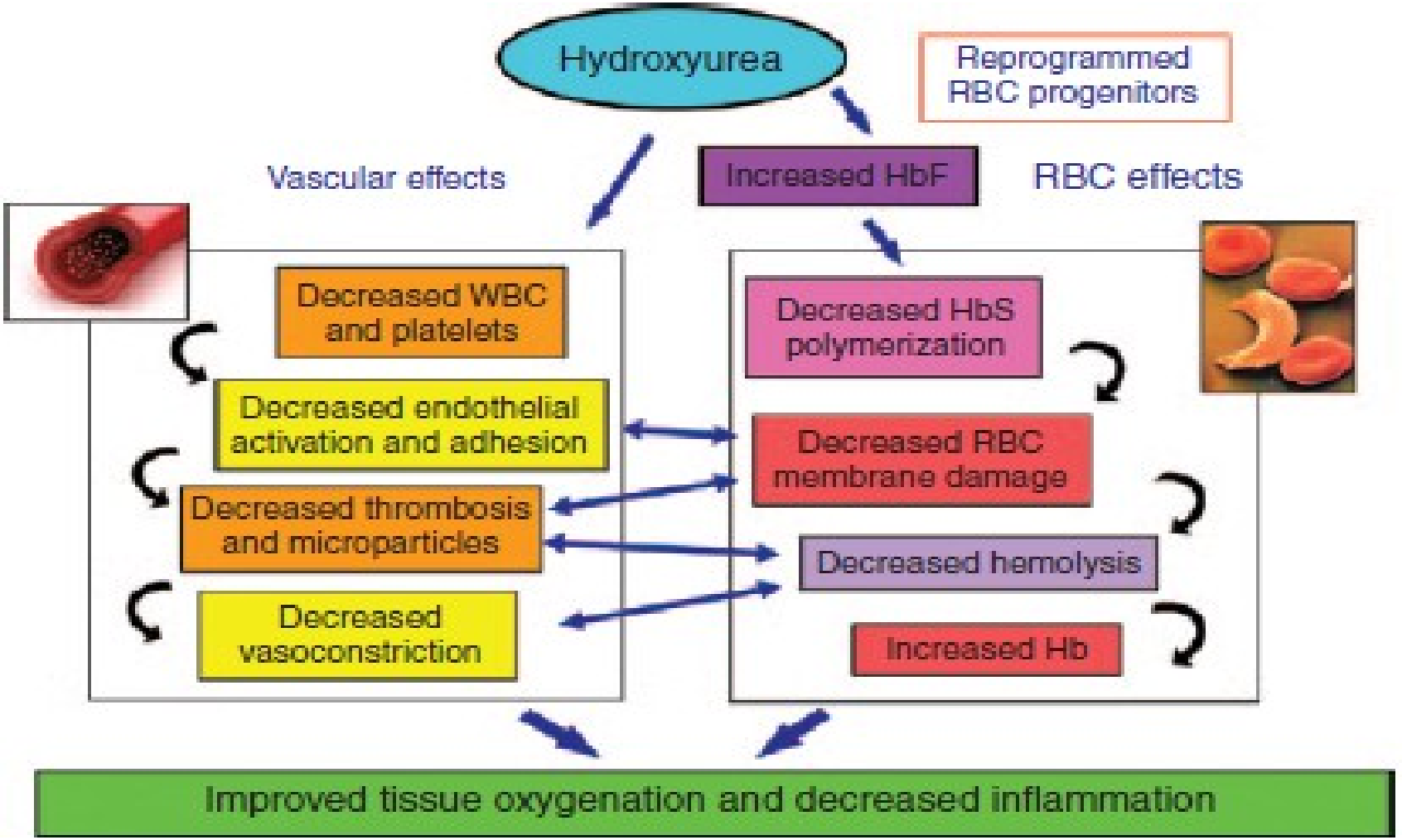
Lancet 2015

- Phase 3 "randomized study" (conducted by 25 USA and Canada Centres) to compare monthly transfusion with standard HU
- 121 SCD children (4-16 yrs old) with abnormal TCD and at high risk of stroke

- *F-up scheduled for 24 months*
- The study was terminated after only half of the children completed the treatment because of an overwhelming evidence of benefit in the group treated by HU

HOSPITALS	0-5yr	6-10yr	11-18yr	>18yr
mnazimmoja	19 (56%)	13 (38%)	**2 (6%)**	0 (0%)
muhimbili	3 (10%)	4 (13%)	**20 (67%)**	3 (10%)
stgemma	42 (37%)	40 (35%)	31 **(27%)**	0 (0%)
StM.Lacor	15 (28%)	27 (51%)	10 (**19%)**	1 (2%)
wbugando	15 (31%)	21 (43%)	13 (**27%**)	0 (0%)

Figure 1. Physiological effects of hydroxyurea on sickle cell disease (SCD). Hydroxyurea has pleiotropic effects in ameliorating SCD, with complex and interacting effects of vascular and red blood cell (RBC) components. Hb, hemoglobin; HbF, fetal Hb; HbS, sickle hemoglobin; WBC, white blood cells.



a plasma cell disorder (n=11 877; 41%). tween participating countries from 48.5 HSCTs were more common (Asia:

Figure 1. Global Distribution of Hematopoietic Stem Cell Transplantations (HSCTs) in 2006

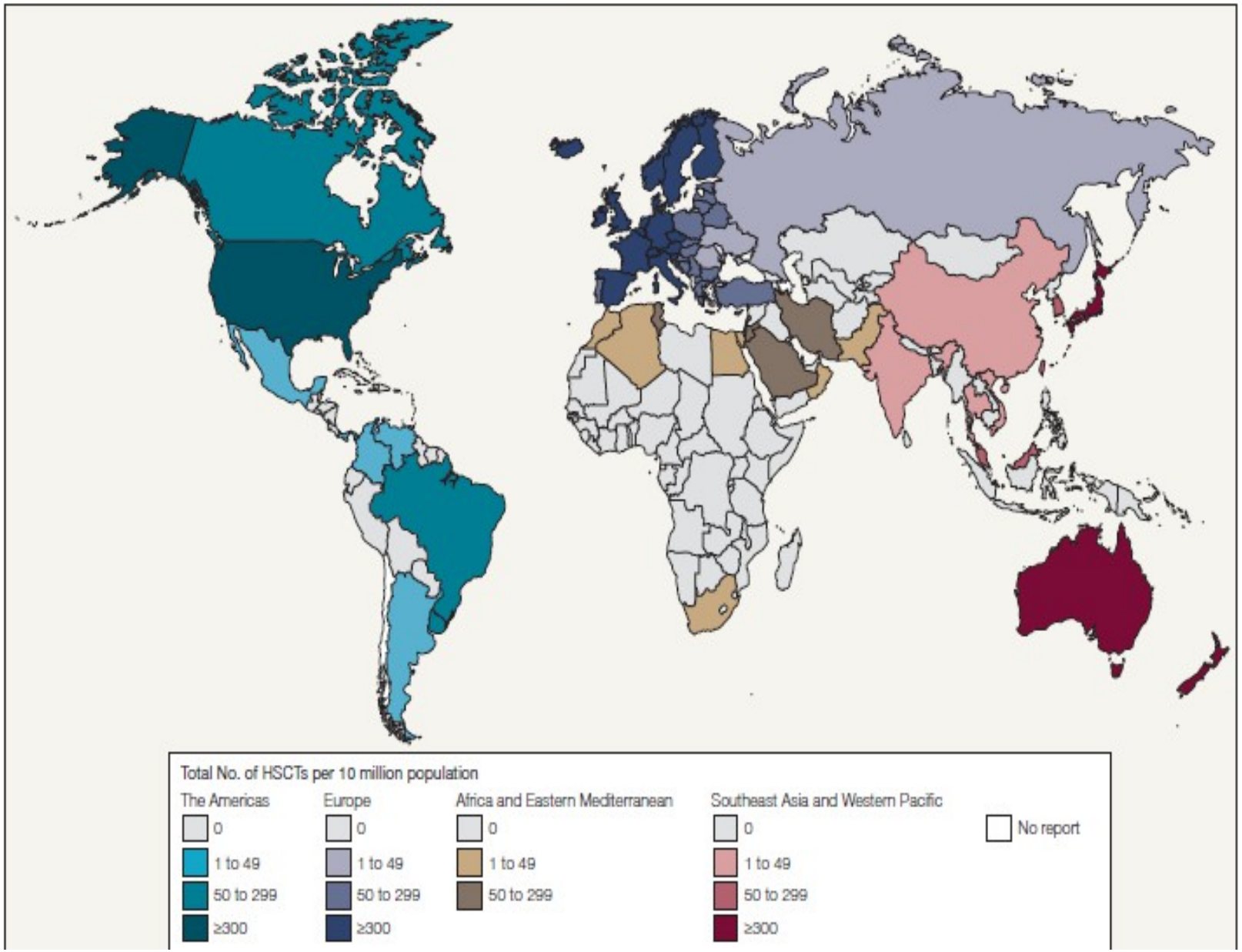


FIgure 2. Fetal hemoglobin (HbF) levels of a teenager with homozygous sickle hemoglobin (HbSS) on hydroxyurea (HU). Before HU use, this teenager had two to three hospitalizations for pain each year. She had no admissions for 1.7 y after beginning HU. Her baseline HbF was 2.4%, and maximum recorded HbF level was 16.9%. She acknowledged intermittent adherence in the years 2 and 3, during which time she had two admissions for acute pain episodes. Blue diamonds refer to HbF data points.