HELP3 Cooperation 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

February 2019, BMKH-Dodoma

SCD in Tanzania up to 2019

- **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 (2015-2018) : HELP3 commitment in SCD children

- **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 NGO cooperation :**
  - **To improve diagnosis and treatment in SCD children**
  - **To improve the outcome and QOL in SCD children**

Help3 ongoing activities :

- **SINCE 2015 :**

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

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

Lacor hospital (*Uganda)*

➢ **Donation of Hydroxyurea** for the treatment **of the first 350 children**

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

➢ **Donation of two "Electrophoresis of Hb" instruments**

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

- **SINCE 2019 to 2021:** :

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

➢ ***Collaboration with BMKH***

➢ ***Start up of Haematologic and BMT Unit at BMKH for the diagnosis and treatment of SCD and other hematologic diseases***

Hydroxyurea for Children with Sickle Cell Anemia in Sub-Saharan area

Tshilolo et al. NEJM, December 2018

Hydroxyurea treatment in SCD children reduced the rates of :

** Painful events (and VOC)

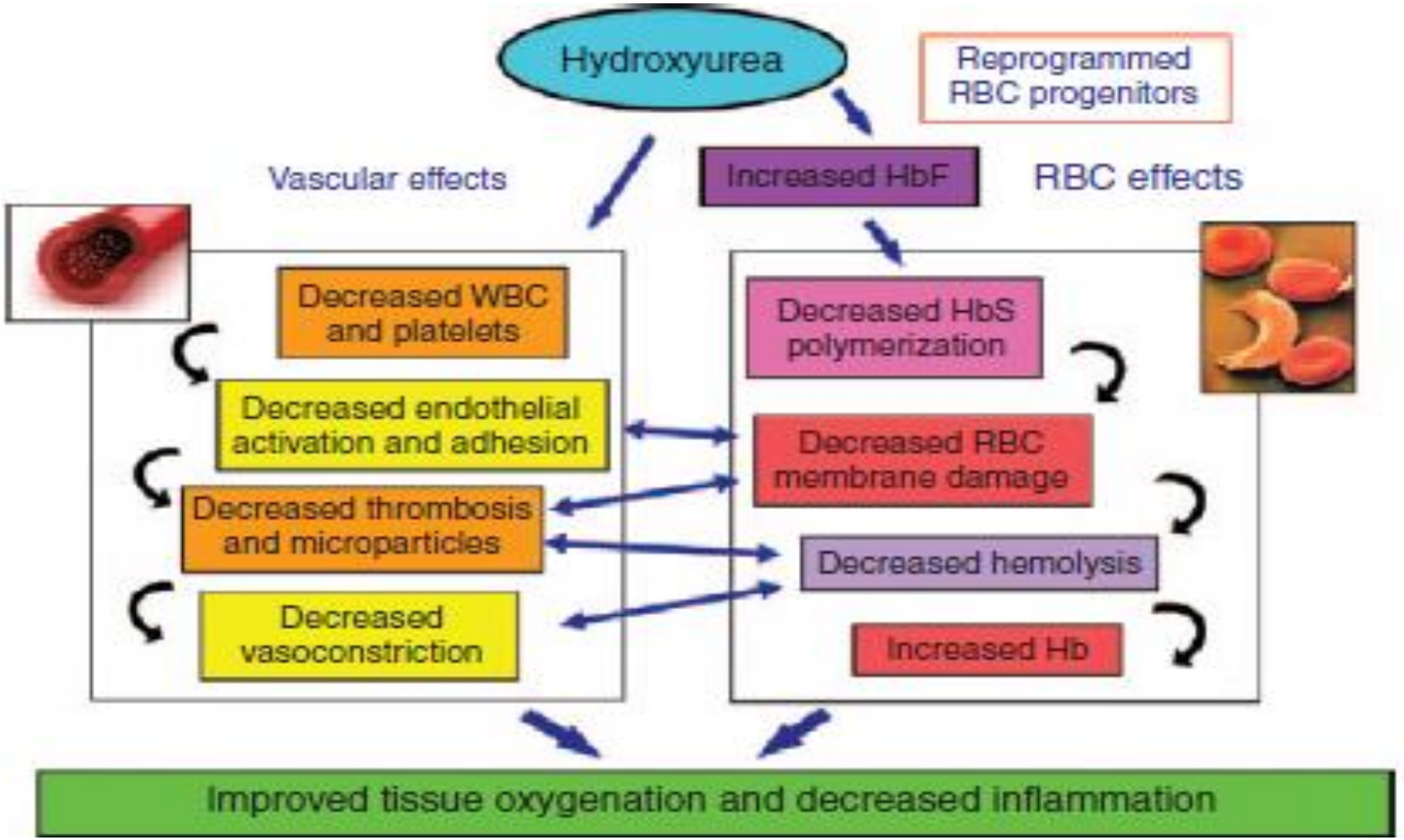
** Bacterial infections

** Malaria

** Transfusion regimen

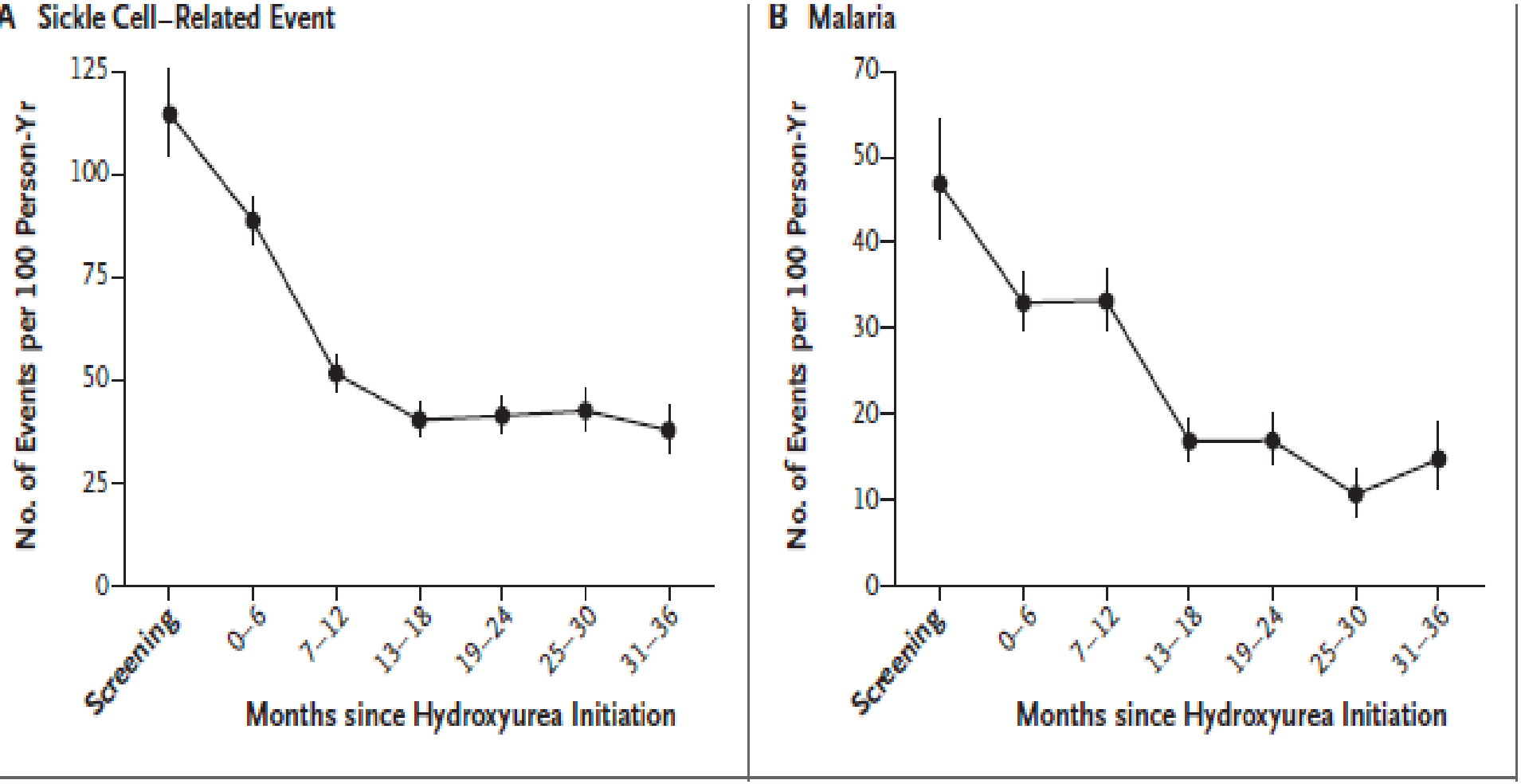
** Mortality rate

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.



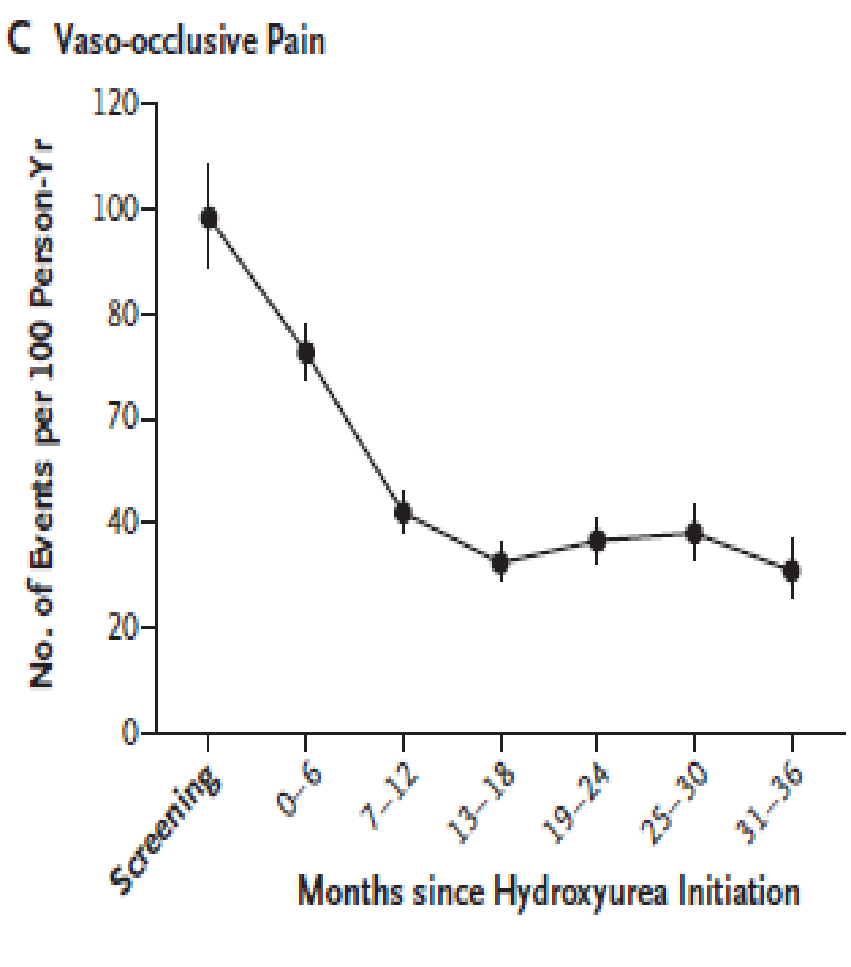
Hydroxyurea for Sickle Cell Anemia in Africa

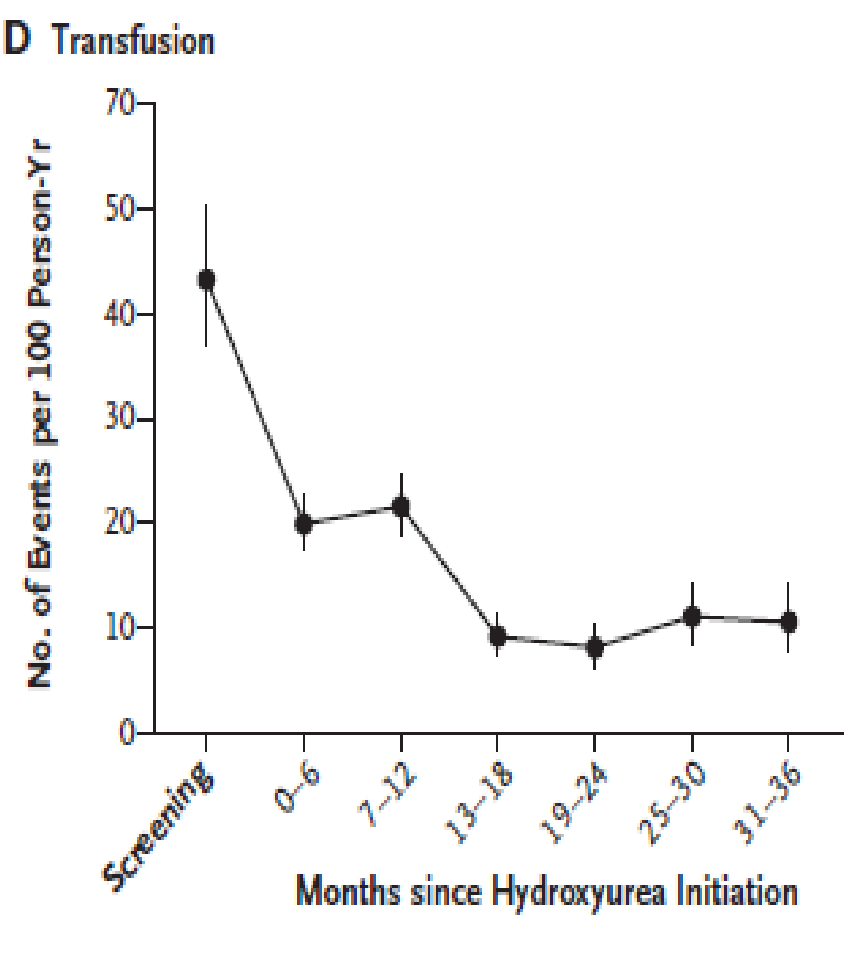
Tshilolo et al , NEJM, December 2018



Hydroxyurea for Sickle Cell Anemia in Africa

Tshilolo et al , NEJM, December 2018





Hydroxyurea for Sickle Cell Anemia in Africa

Tshilolo et al , NEJM, December 2018

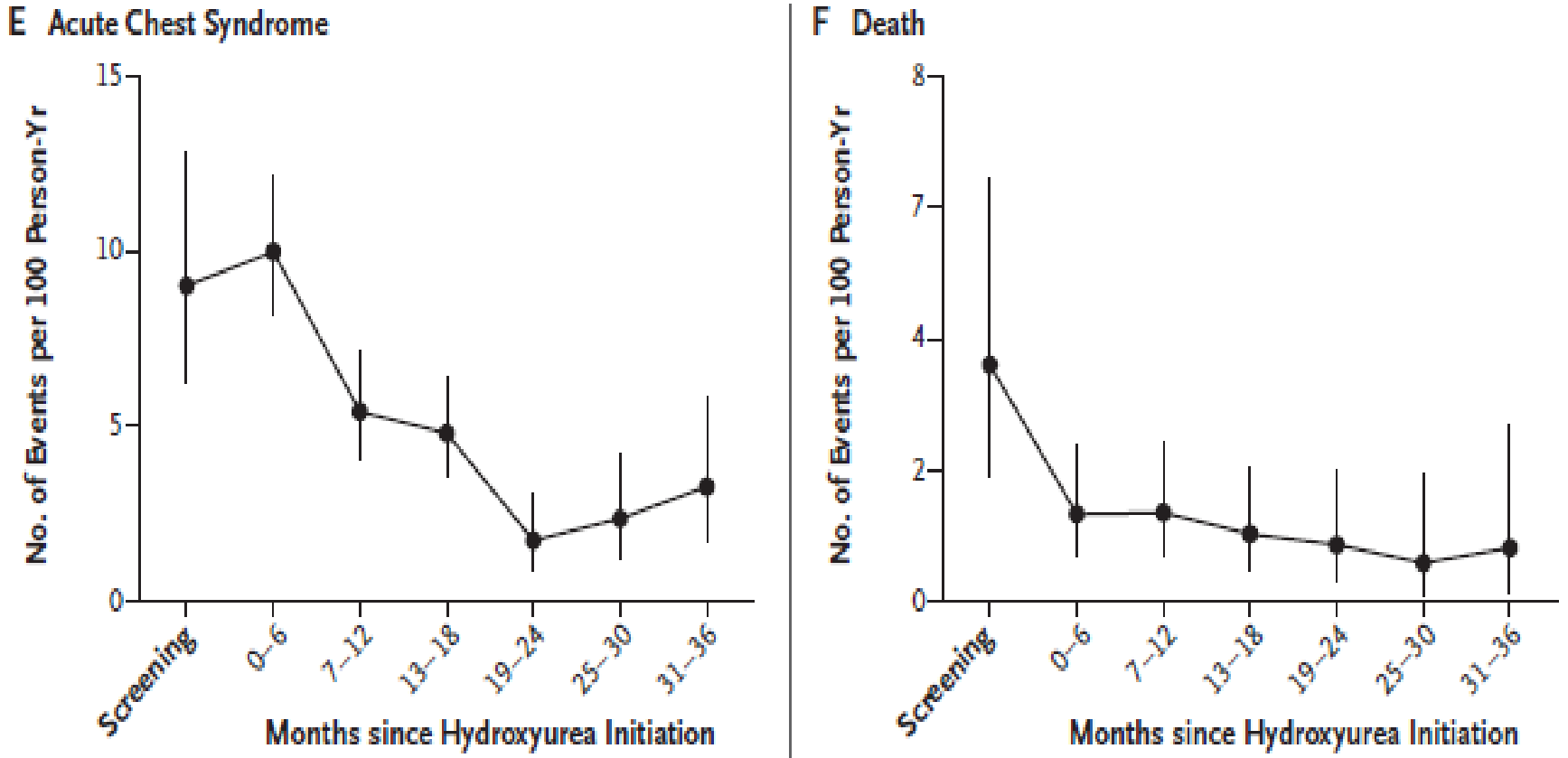


Figure 3. Adverse Events before and during Hydroxyurea Treatment.

Error bars indicate 68% confidence intervals, which correspond to approximately 1 standard error.

HELP3 experience on SCD

- **Period of treatment** : **2015-2018**
- **Enrolled Patients** : **350**
- **Evaluable Patients** : **230**

- **Hospitals** : 4 in Tanzania, 1 in Uganda

- **Age (median) :**
  - **78% below 10 yrs old
  - **22% over 10 years old
- **Median Follow up: 18 months (6 to 40)**

The most cooperative hospitals

St. Gemma Hospital

**General hospital

**Council designated H

- 120 beds
- **SCD PTS = 176**

- Pediatric ward (15 beds)
- **SCD dedicated personnel = 2**

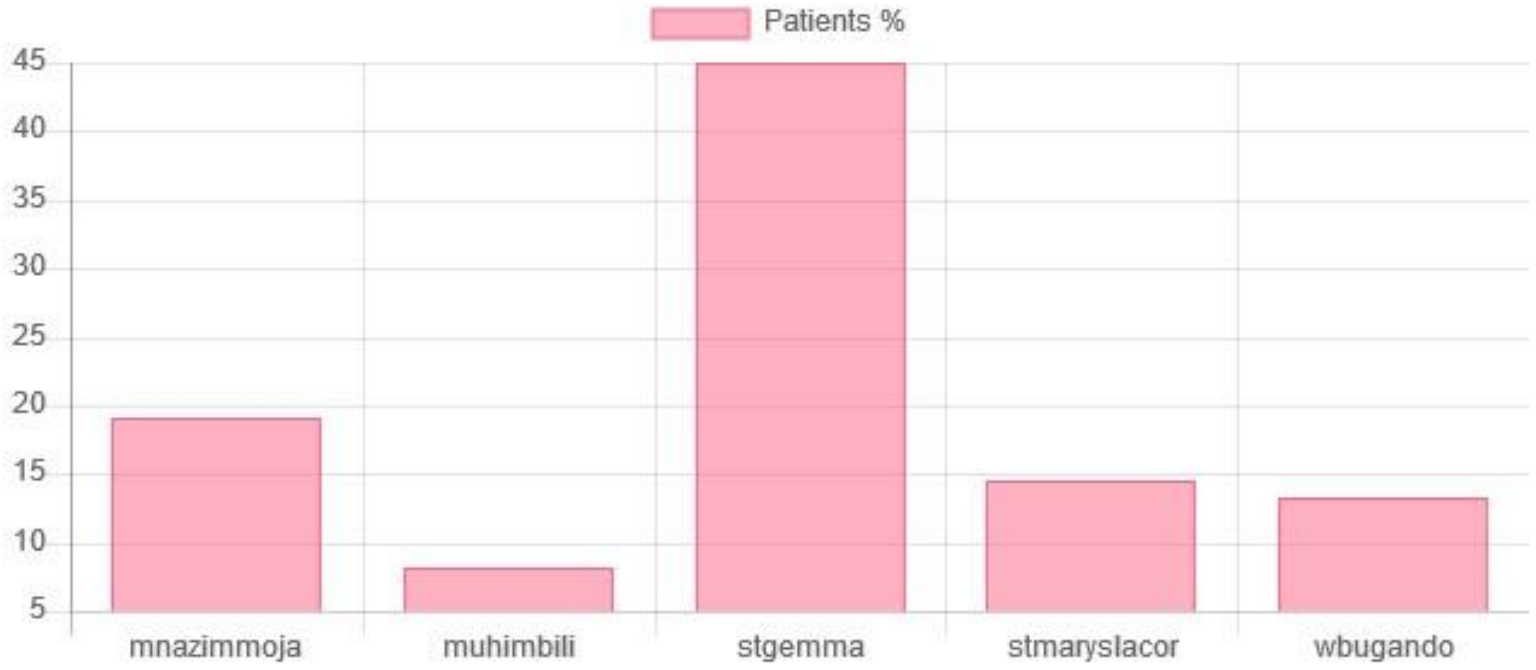
Mnazi Mmoja Hospital

**General and Governative hospital

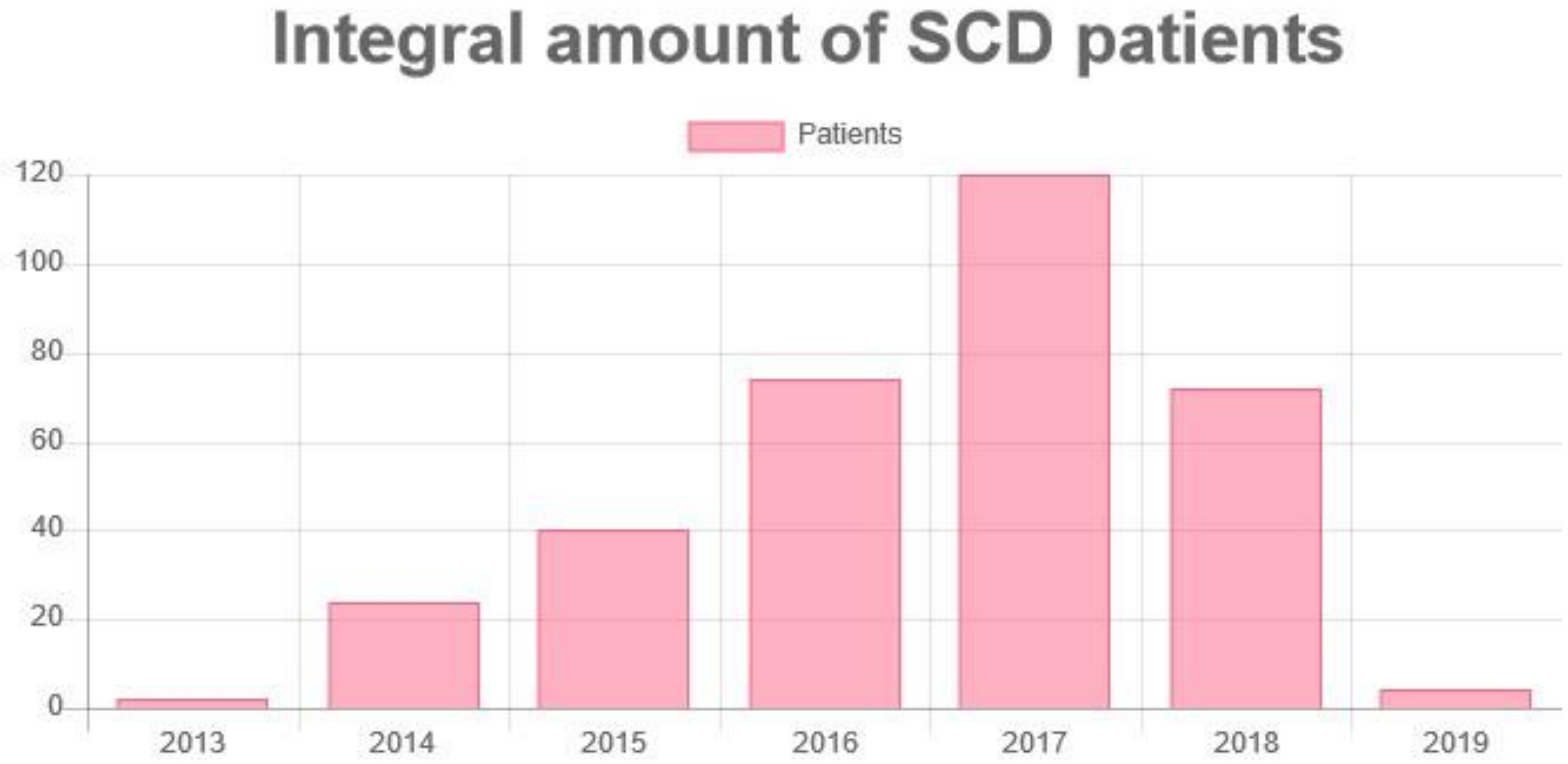
- 400 beds
- **SCD PTS= 70**

- Pediatric ward (40 beds)
- **SCD dedicated personnel = 2**

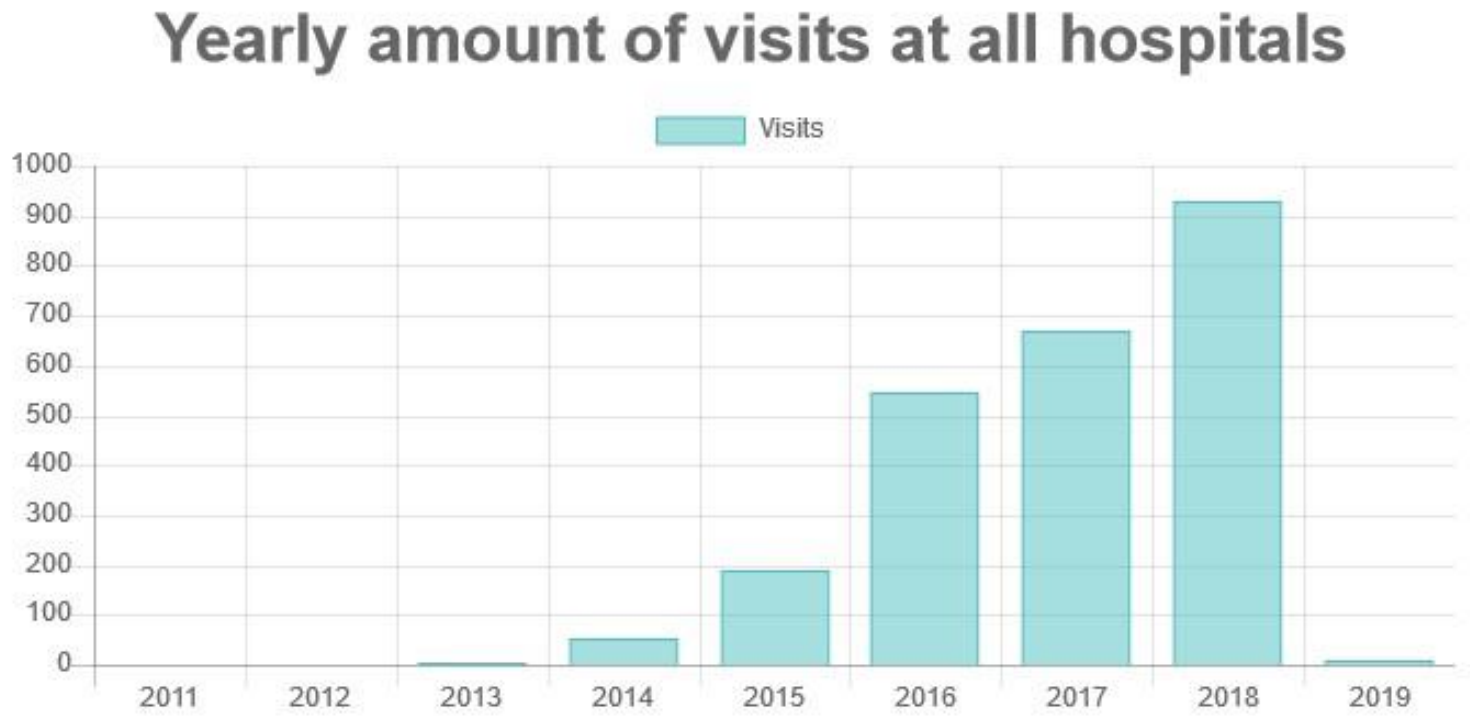
Patients % treated per hospital



Result 1: 352 registered patients

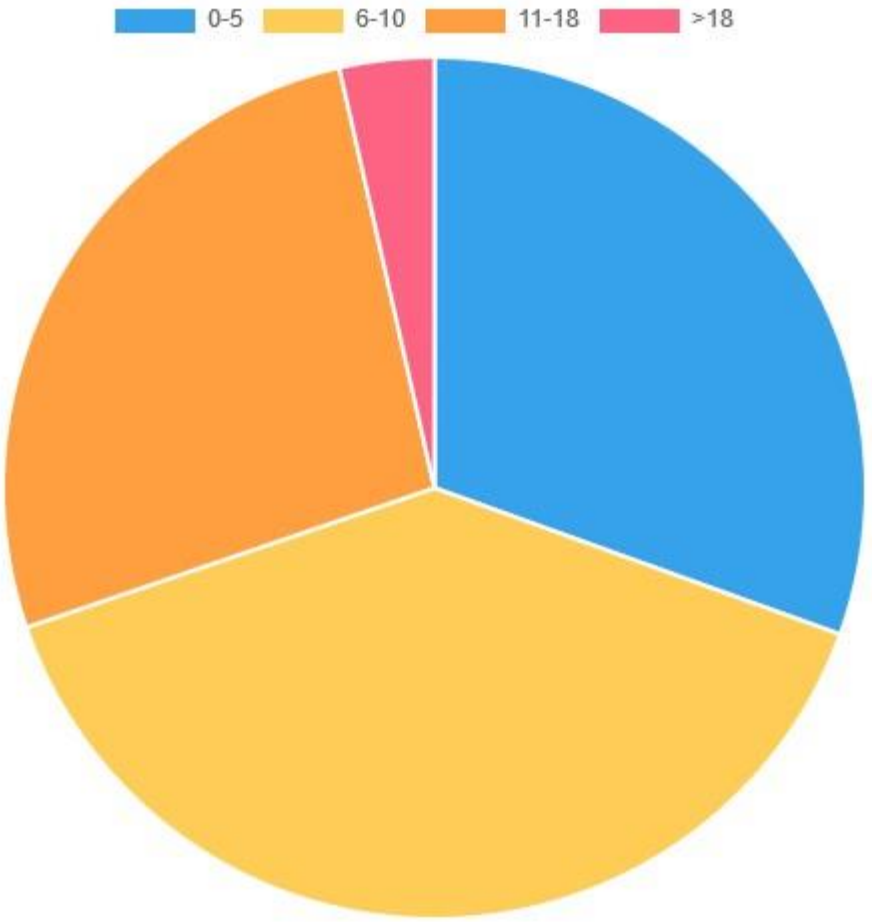


Result 2 = 2510 registered visits



Result 3 = age at enrollment

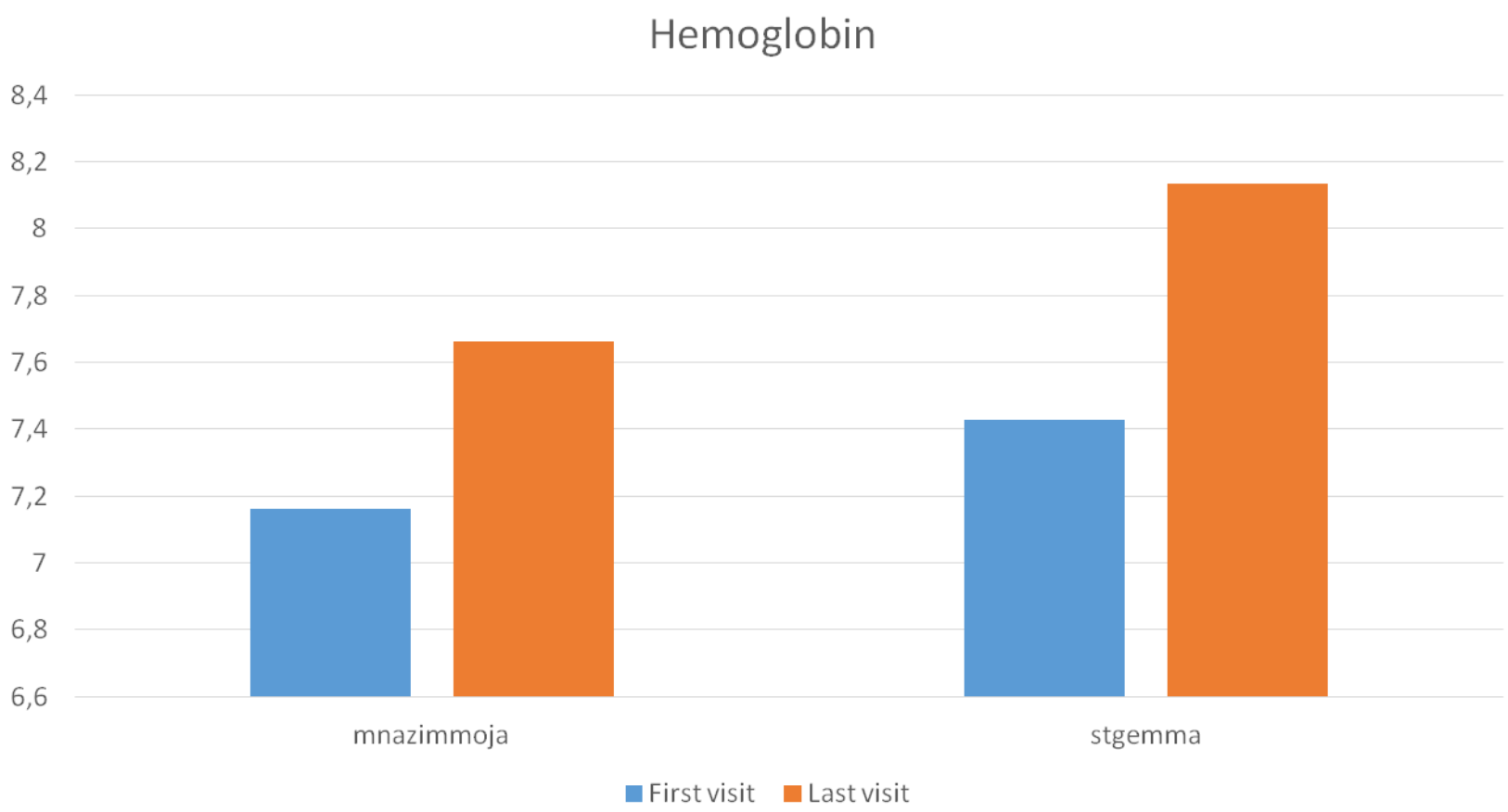
- **AGE**



Number / age

- 112 (0-5 yr)
- 144 (6-10 yr)
- 98 (11-18 yr)
- 13 (>18 yr)

Median Hb value in **195 SCD** children pre and post HU (at St.GH and MMH)



Median QOL in **180** SCD children pre and post HU (at St.GH and MMH)

What about BMT 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***
- **To be confirmed in larger series**
- **Very high costs of the procedure**

(M.Cavazzana, 2015)

WHY BMT CENTERS for childhood hematological diseases in "TANZANIA " ?

- **SITUATION in AFRICA up to 2018**
  - **10 BMT centers in Africa** for 1 milliard of people (*1 in Nigeria, 6 in South Africa,1 in Tunisia, 1 in Morocco, 1 in Egypt*)
  - **BMT centers needed in *"sub-equatorial area"* : (15 ??)**
  - **BMT centers needed in TANZANIA : 3 (??)**

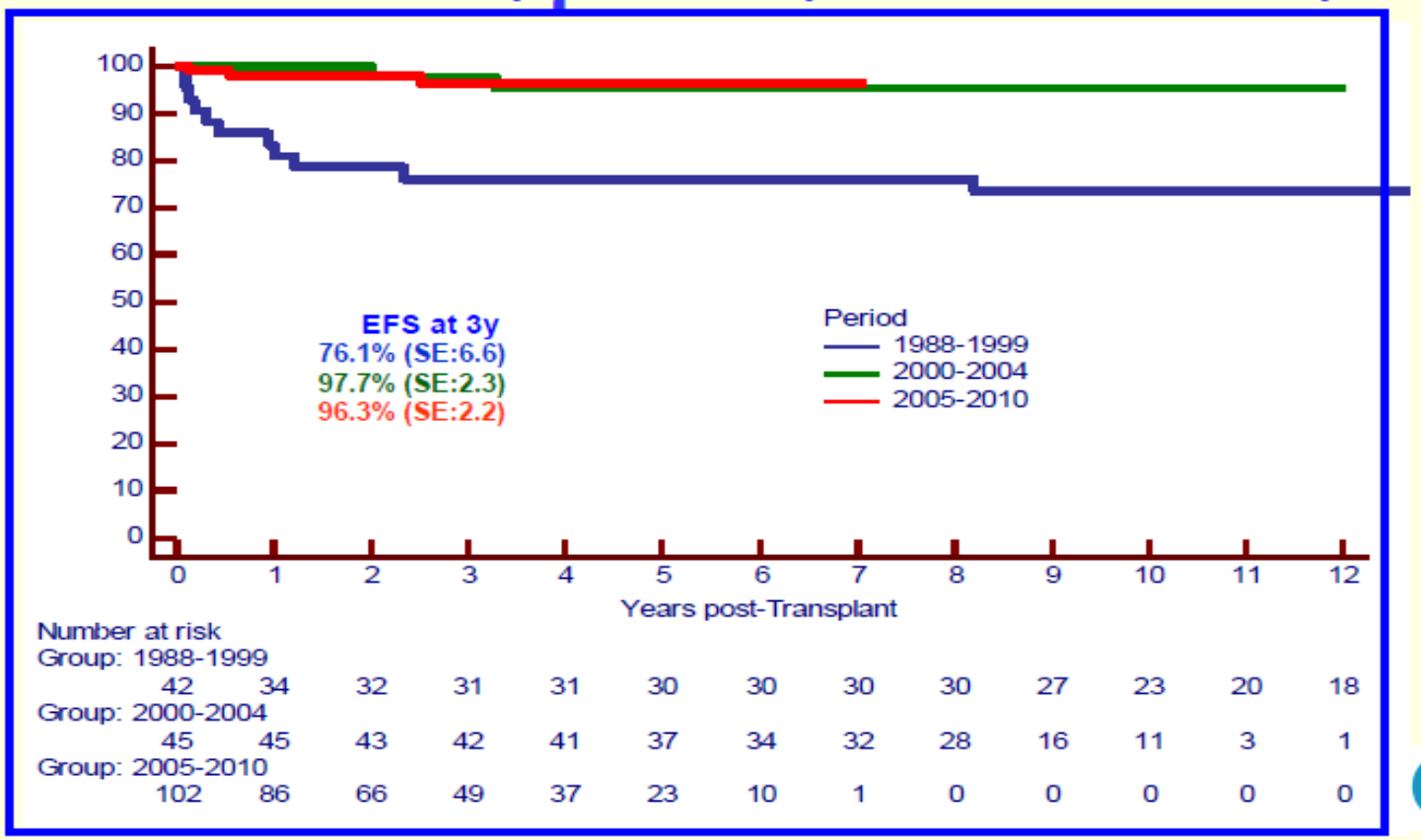
- **Probable costs** for building up a Pediatric BMT Unit in sub-equatorial area (excluding personnel) : ***350.000 $***

- ***Probable costs for 1 allogeneic BMT in Tanzania : 10.000 $***
- ***Probable costs for 1 allogeneic BMT overseas: 40.000 to 150.000 $***

- ***Probable costs of 5 to 7 years of "SCD" standard treatment : 10.000 $***

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

(F. Bernardin, Blood , 2005)



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

BMT 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%**

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

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

NEW LEUKEMIAS/YEAR

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

NEW LYMPHOMAS/YEAR

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

"Malignant Diseases" vs. "Comunicable Diseases " : yearly"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

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

In high income countries

❖ **Chemotherapy** :

DFS in standard risk = **85%**

DFS in high risk = **50%**

❖ **BMT**

DFS in standard risk = **80%**

DFS in high risk = **50%**

In subsaharan areas

❖ **Chemotherapy :**

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

DFS in high risk = **20% (?)**

❖ **BMT (to be proved)**

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

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

Phase 2 (2019-2021) :
Help3 current commitment

Strategy :

- **To establish a continuous education plan for a high level of training and attitude of Tanzanian hematologic team (locally in TANZANIA and /or in ITALY, by Telemedicine as interactive "bridge")**

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

- **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)***

Bone marrow transplantation (BMT) : definitions

** **Bone Marrow Transplantation** is a modern treatment consisting on the substitution of *"patient hematopoietic stem cells"* with " HLA compatible donor" stem cells

** **BMT donor** is generally a *family HLA identical donor*

** The new bone marrow is harvested in an operating room and infused intravenously to the patient previously conditioned

****BMT is the most complex organ transplant** due to the multiple complications (rejection…) *if not done by a very expert transplant team and in an adequate structure*

BMT 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 is mandatory
- Useful to perform at least 10 transplants/year to have and to maintain an adequate experience

BMT 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

BMT 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 1985-2018

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

HELP3 current commitment (2019-2021) :

STRATEGY :

- To establish a continuous education plan for a high level of training of hematologic team (locally in DODOMA and /or in ITALY, and by Telemedicine as interactive "bridge")

- Giving a high level of scientific and training support by our professionals in setting up the first " Hematologic and BMT Unit" in TANZANIA

- to institute at BMKH a strong collaborations with some Italian Institutes dedicated successfully to hematologic diseases
  (*S. Gerardo University hospital, Monza, and S. Raffaele University Hospital in Milan*)

HELP3 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 BMT both childhood SCD and other blood diseases

Brave action for a better world…

We are fully confident !

BMT at BMKH? …

Yes we can

WITH A DEDICATED TEAM at BMKH !

After 1- 2 years of strong "training" to doctors/nurses and Lab staff

Only in the setting of specific BMT structure and collaborative support facilities

Only if there is a strong maintenance of the training to the BMT staff members

Only if there is a continuous and sustainable program of all the BMT procedures

BMT "starting point" at BMKH

- FIRST STEP :

❖ *allogeneic BMT* in **SCD** children
and with HLA identical sibling donors

❖ *autologous BMT* in **leukemia,lymphomas**

- SECOND STEP :

❖ *allogeneic BMT* in other hematological diseases **(SAA, Leukemia…….)** with HLA identical sibling donors

❖ *Haplo identical BMT* in malignancies **(Leukemia, Lymphomas..**

THANKS

- **To all the tanzanian haematologic children** who will permit us to offer our experience/commitment
- **To all BMKH dedicated professionals** to whom this project is addressed
- **To the colleagues** of "S.Gerardo" University Hospital in Monza (Italy) committed to the project

Thanks to the Italian Charities

pediatric hematology ELP3

8 per mille CHIESA VALDESE
UNIONE DELLE CHIESE METODISTE E VALDESI

Azienda Ospedaliera San Gerardo

ISTITUTO MARIA LETIZIA VERGA
Per la salute del Bambino e della Mamma

A big thanks to

Donnall Thomas…

HSCT pioneer,

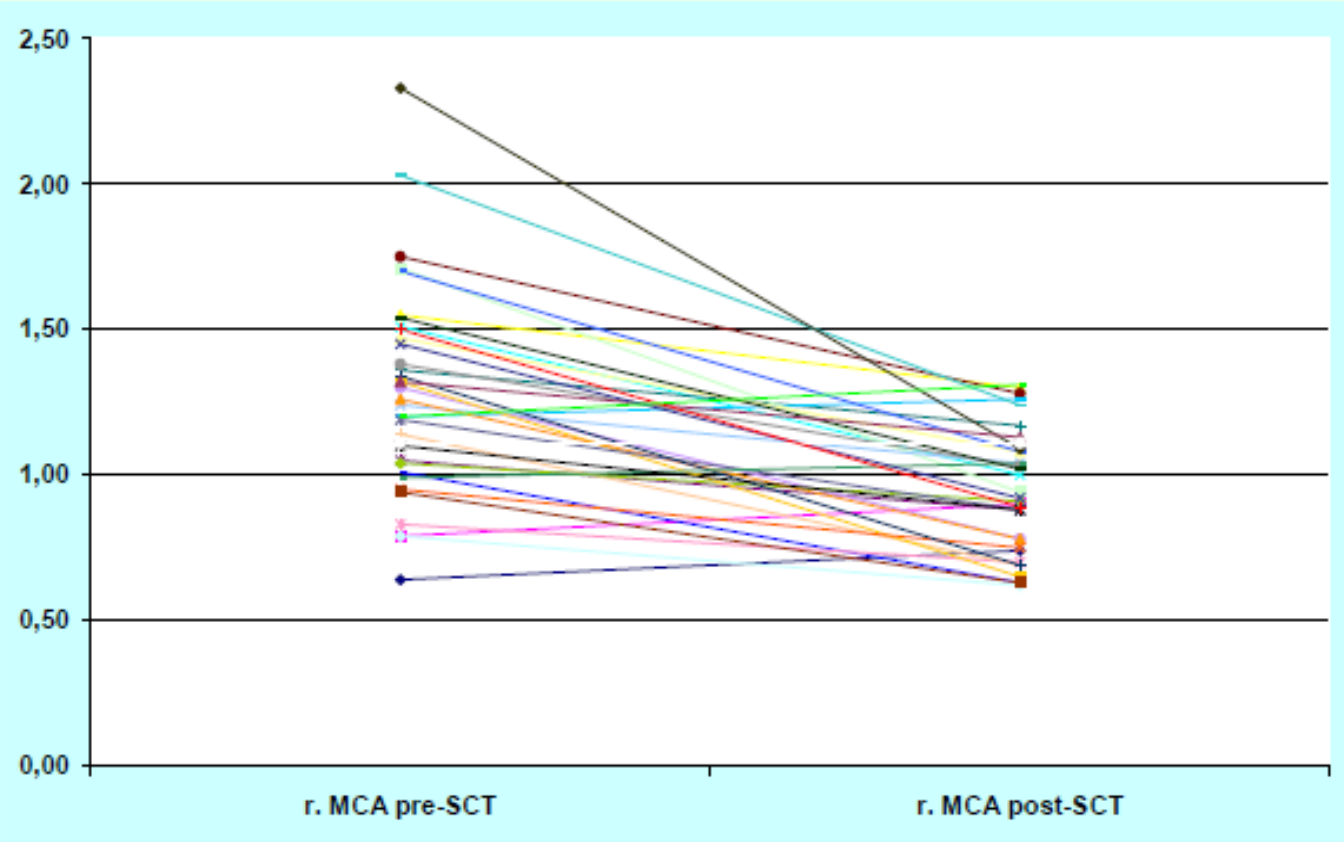
Nobel Prize on 1990

and

a great "life coach"

Outcome of arterial velocities

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



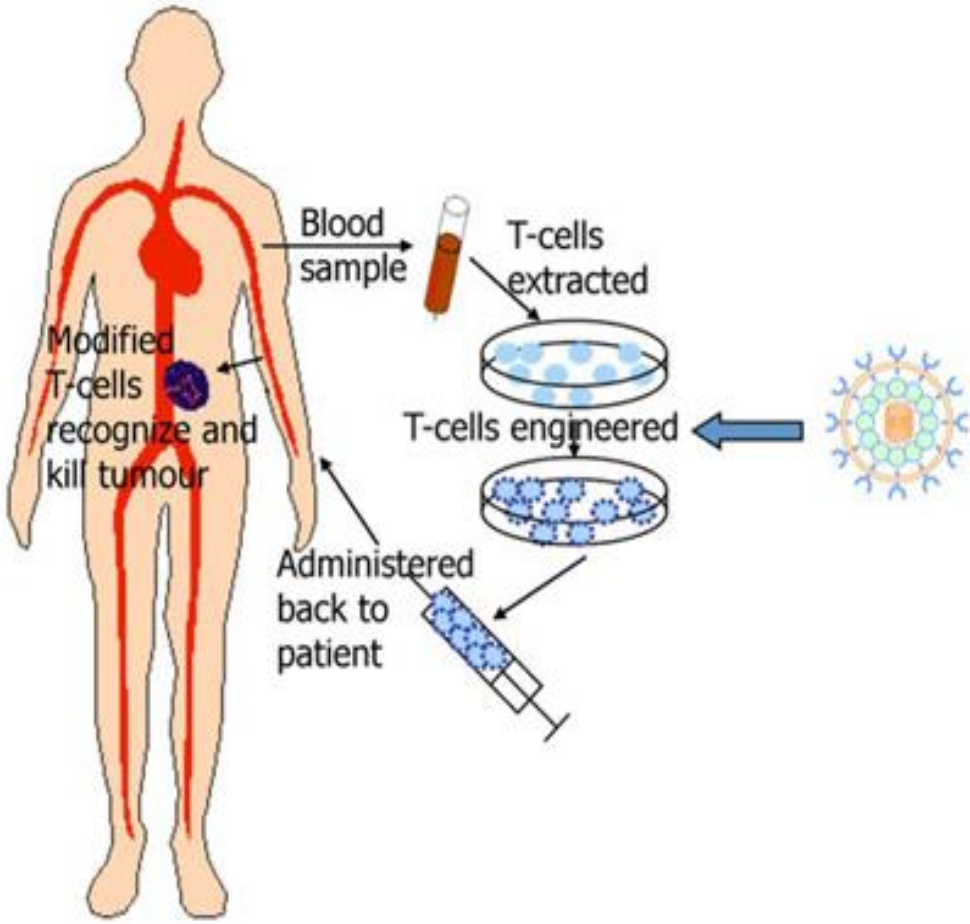
Bernaudin et al Strasbourg April 2011

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

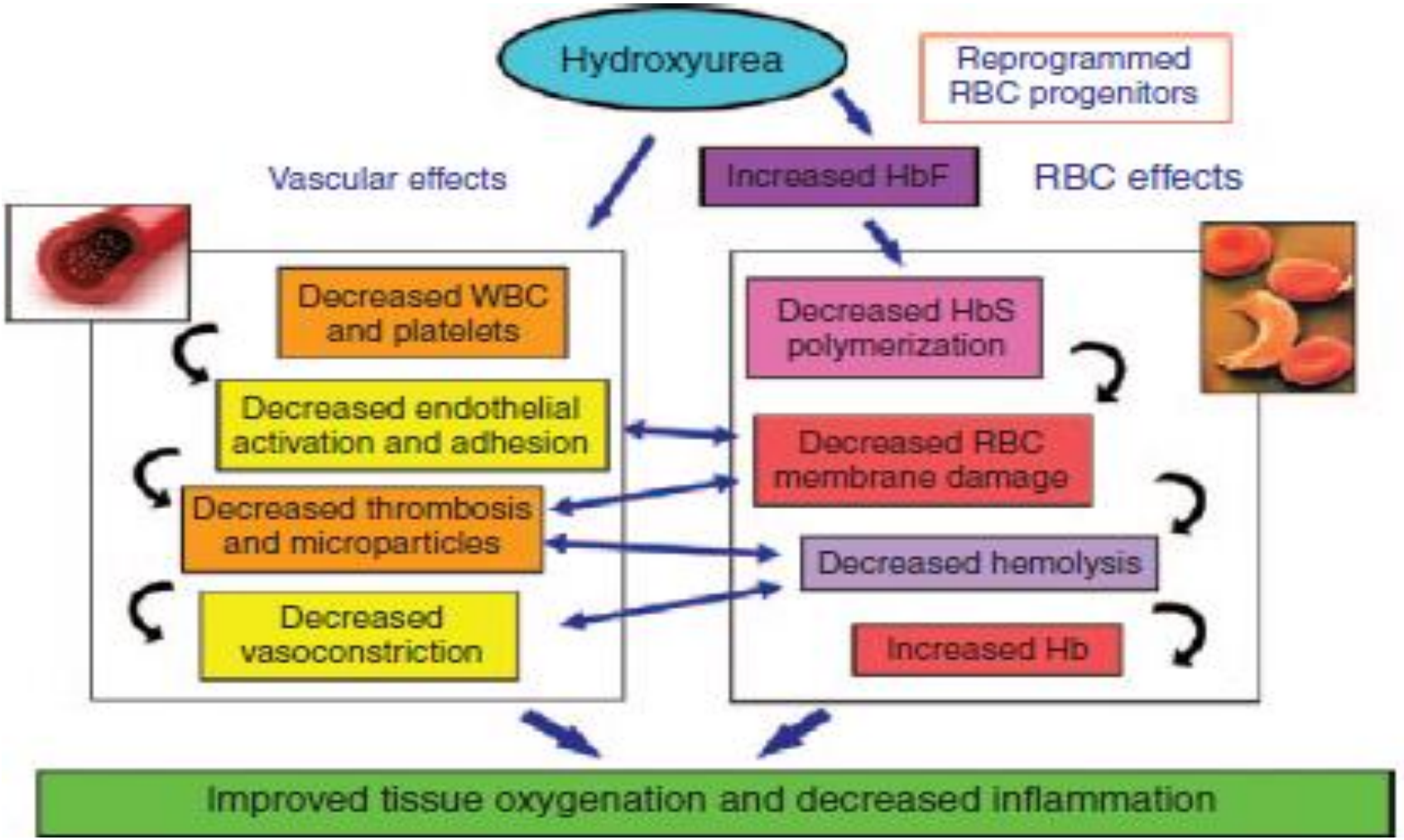
Lancet 2015

- 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

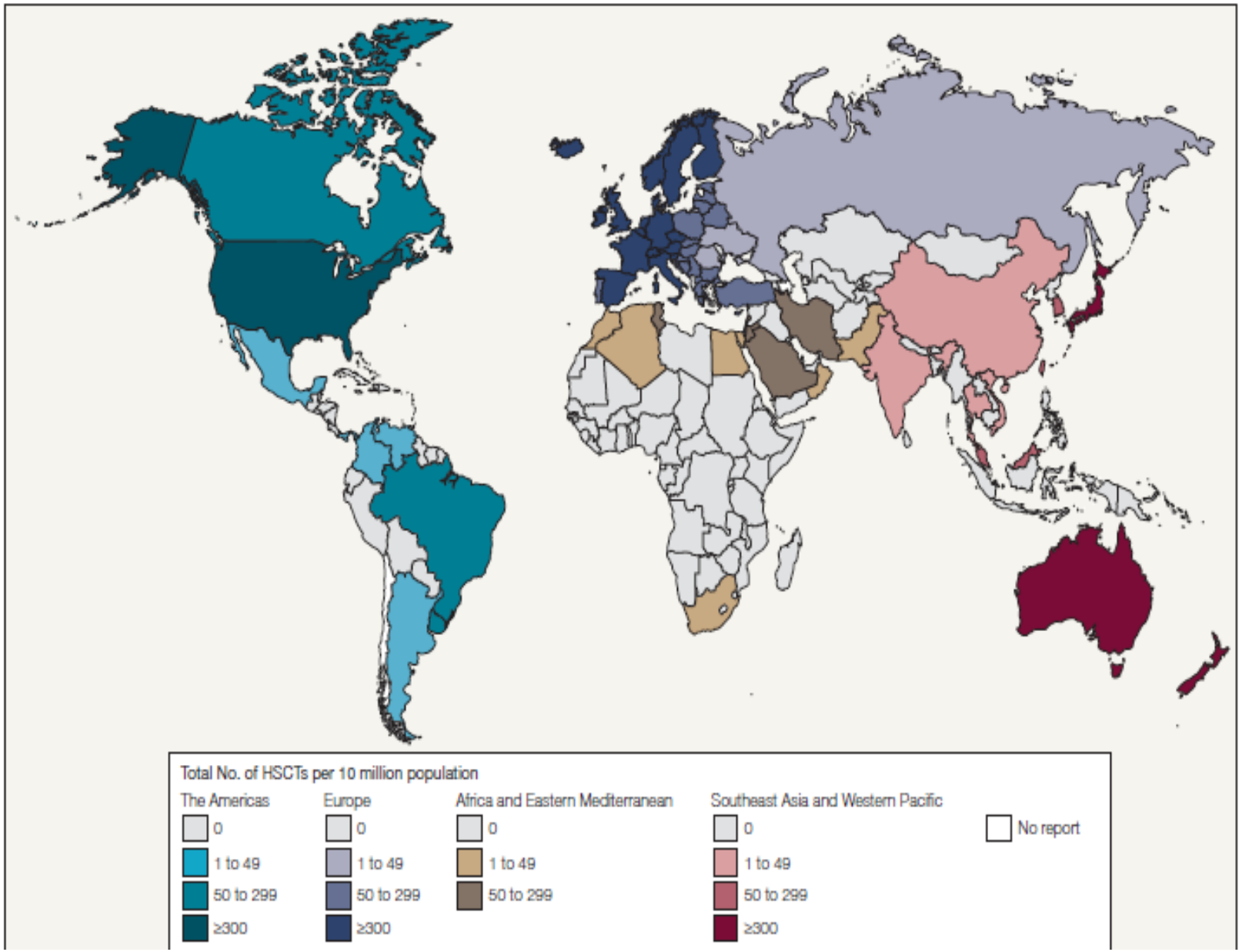
HOSPITALS	0-5yr	6-10yr	11-18yr	>18yr
mnazimmoja	19 (56%)	13 (38%)	**2 (6%)**	0 (0%)
muhimbili	3 (10%)	4 (13%)	**20 (67%)**	3 (10%)
stgemma	42 (37%)	40 (35%)	31 **(27%)**	0 (0%)
StM.Lacor	15 (28%)	27 (51%)	10 (**19%)**	1 (2%)
wbugando	15 (31%)	21 (43%)	13 (**27%**)	0 (0%)

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.



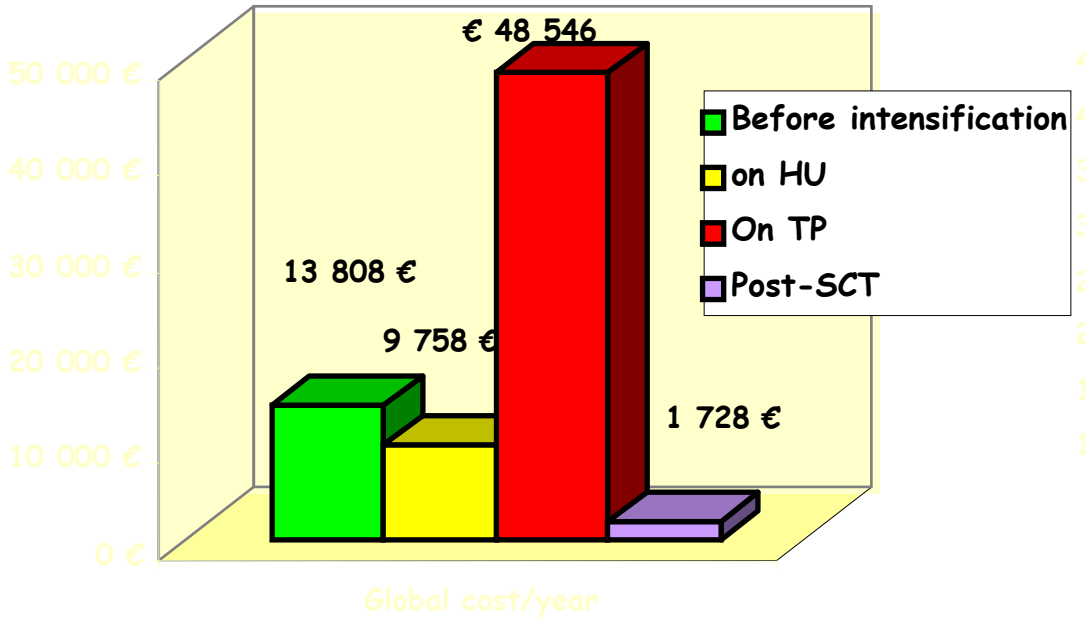
a plasma cell disorder (n=11 877; 41%). tween participating countries from 48.5 HSCTs were more common (Asia:

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

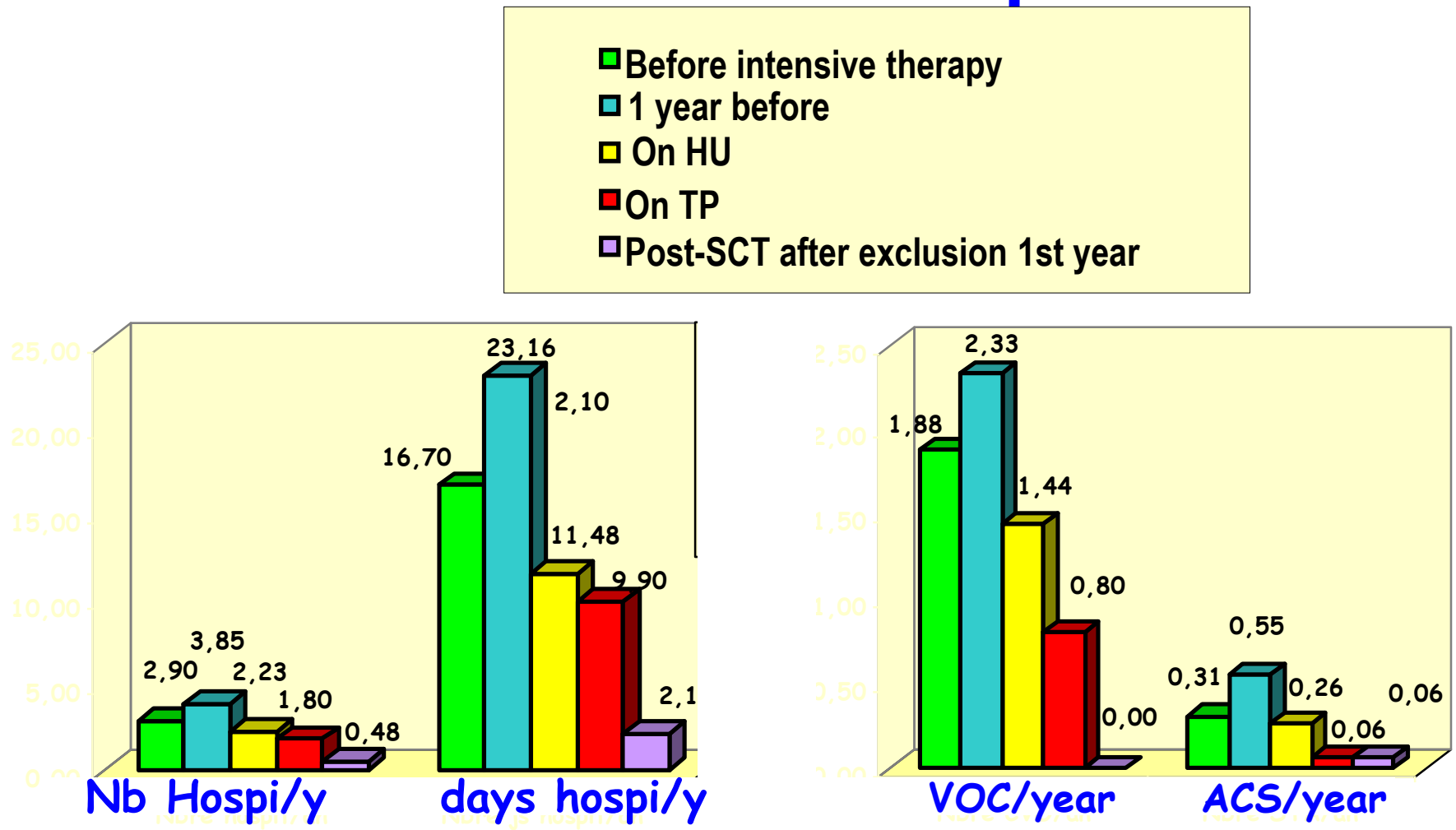


Costs in Patients with pre-HSCT frequent VOC/ACS

- 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

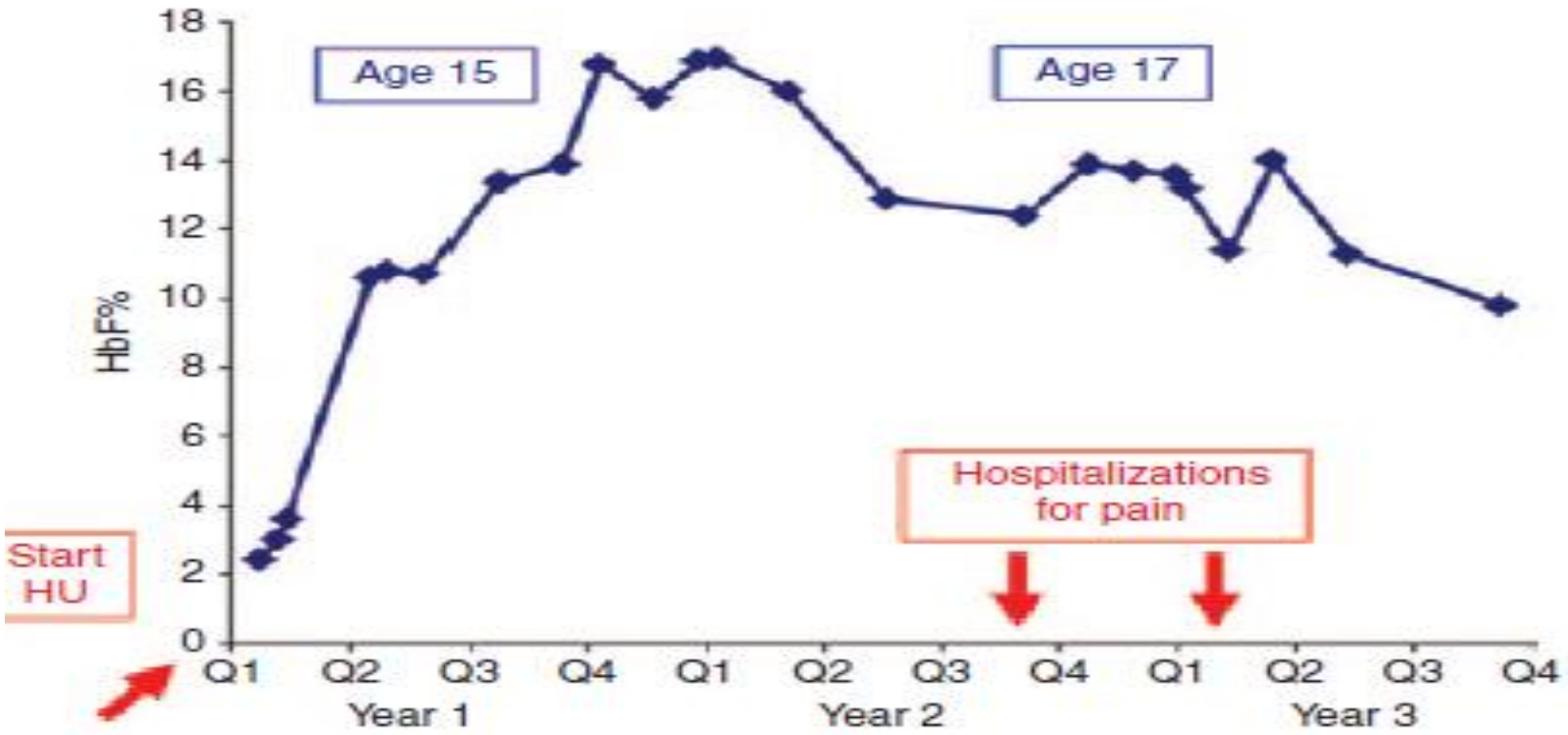


Comparative effects of TP, HU and HSCT on frequency of Hosp, VOC, ACS in 111 SCD-patients



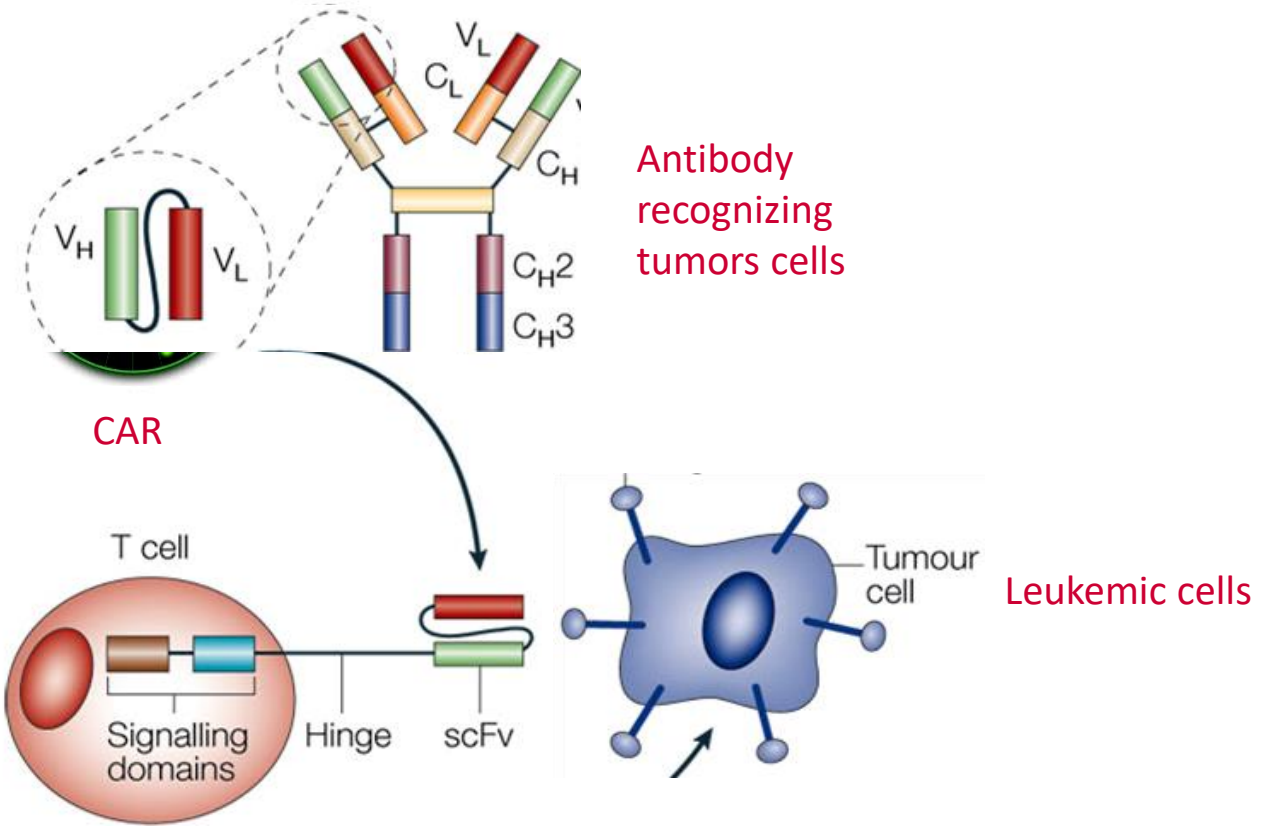
Arnaud et al CHI-Creteil, ASH

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.



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

BMT "starting point"

- FIRST STEP :

❖ *allogeneic BMT* in **SCD** children
and with HLA identical sibling donors

❖ *autologous BMT* in leukemia,lymphomas

- SECOND STEP :

❖ *allogeneic BMT* in other hematological diseases (SAA, Leukemia…….) with HLA identical sibling donors

❖ *Haplo identical BMT* in malignancies (Leukemia, Lymphomas..