Post ASH Meeting
January 2011
Red Blood Cell disorders

Sickle cell disease

Thalassemia

Inherited Bone Marrow Failure Syndromes

Sickle cell disease

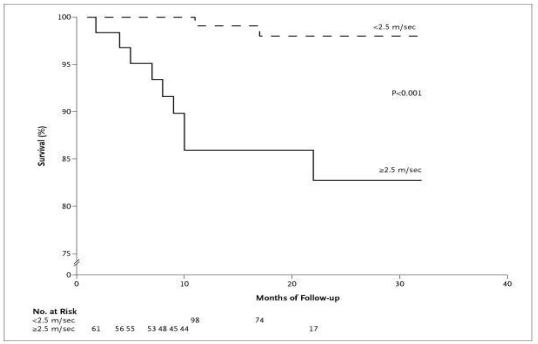
In children	VOC, infection, Acute Chest Syndrome, anemia and stroke
In adults	IDEM + Organ failure (kidney, heart, lung, eye, bone,…) and sudden death

- >75.000 SCD pts in US and 1st inherited disease in Brussels Area

- 1980-2009:
  - Survival at 18y: 95.6%
  - Stroke free survival at 18y: 86%
  - 10y mortality for 20y old patients: 15%
  - But if >100days of pain/y: 65%
  - Improved 10y survival with HU: 86 versus 65%

The lung is a target organ in Sickle Cell disease

K. Hassell. 2011



- TRV > 2.5m/sec associated with ↑mortality
  - >2.8: higly indicative of PH*Gladwin M. 2004*
- 6 min Walk Test correlates with TRV, mPAP, anemıa
- Walk-PHaSST(randomized placebo controlled Treatment for Pulmonary HTand SCD With Sidenafil)
  - Sildenafil for pt with TRV>2.7m/s – change in 6min walk-test?
  - Premature end of the trial < ↑pain episods (NO: role in nociceptive pain?)
  - But some pts with PH have improvment with NO donors

PH screening recommanded in symptomatic SS and Sβ° pts	
If TRV > 2.5m/sec	→ Right heart catheterization
Treat associated conditions	Asthma, Infection, Cardiac failure, Sleep apnea
Disease modifying therapy?	HU, Chronic tranfusion, HSCT
If PH confirmed	Bosentan

Is Primary Prophylaxis possible for SCD?

- Hydroxyurea ↓ pain rate, ACS and need for transfusion in children and adults
- Chronic treatment with HU ↓ the risk of death
- Hydroxyurea in very young children appear to be safe but do'nt prevent kidney or splenic damage

- **BABY-HUG Study** *(Z. Rodgers; # 7, and P. McGann; # 8*)
  - RDZ trial HU – Age: 9-18 mo
  - Not met primary endpoints: Preservation of spleen and kidney function
  - But less transfusion, dactylitis, VOC, ACS, febrile illness
  - Role in prevention of stroke risk or SI? To be assessed
  - No genotoxicity (no ↑ chr. breaks, micronucleated reticulocytes, VDJ recombination in the treatment arm when compared to no HU arm)

Increased incidence of hematological malignancies among Californians with SCD *(A. Mahajan; #1073)*

- High cellular turn-over and inflammation are associated with the development of malignancies
- ↑ risk of malignancy already suggested previously
- SCD pts linked to California Cancer registry

	Observed cases	Expected cases	SIR Standardized incidence ratio
All hematopoietic	46	1.2	37.9
Lymphomas	18	0.7	25.2
Myeloma and CLL	8	0.2	47.7
Acute Leukemia	11	2.4	45.7

Predictors of Morality in SCD (# 515, 339, 1081, 2070 ….)

- Morality is 6% up to 18y and 30% in the 18 – 30 age group
- Main cause of death is children and adolescent: **STROKE**
- **TRANSITION PERIOD** from PED to ADULT care is critical (↑↑deaths)
- In-Hospital mortality: 844 deaths/166.084 admissions

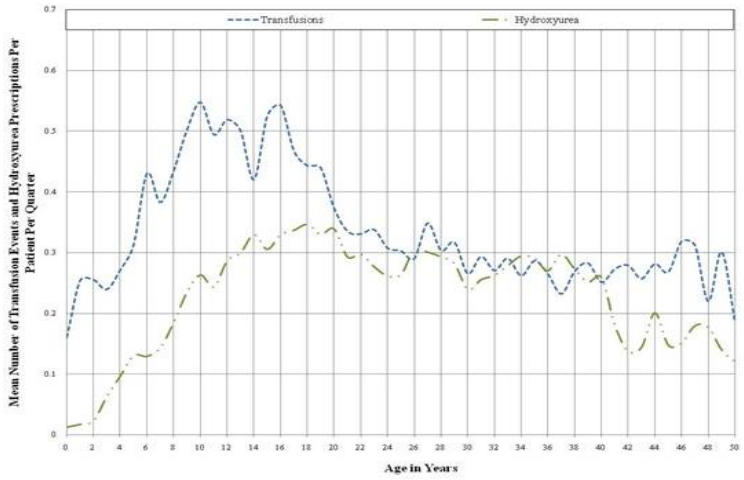
  - Male gender (OR 1.6)
  - Every 10 y increase of age (OR 1.6)
  - Transfusion or ExTf (OR 1.7 or 4)
  - Acute Chest Syndrome (OR 2.6)
  - Sepsis (OR 11.2)

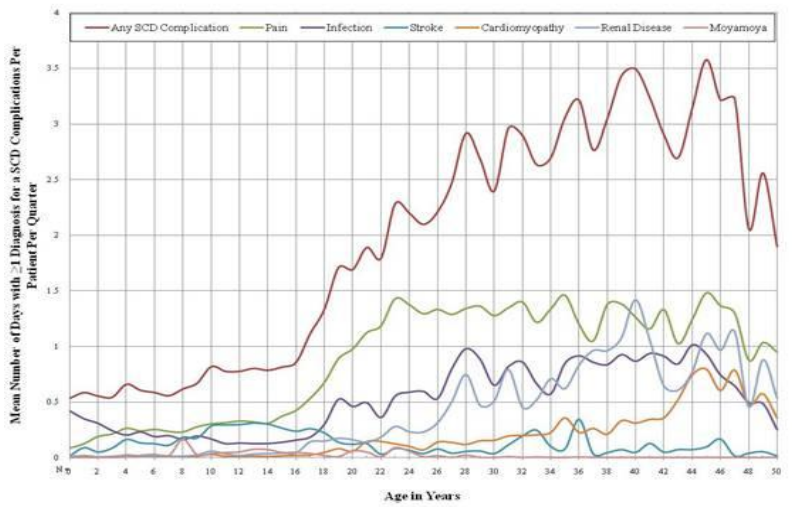
- SCD patients wait longer in the Emergency Dept while they should be prioritized
- Frequent **ED** visits associated with ↑↑ mortality

Age related treatment patterns in SCD: more complications at age of transition to adult care and less transfusion, chelation and prescription of HU

M. Blinder; #12 and #338

- The dramatic increase in complications with decline of Tf, HU prescription and chelation is due in part to inadequate transition to adult care





Preoperative transfusion in SS patients reduces Serious Adverse Events *(J. Howard et al; #9)*

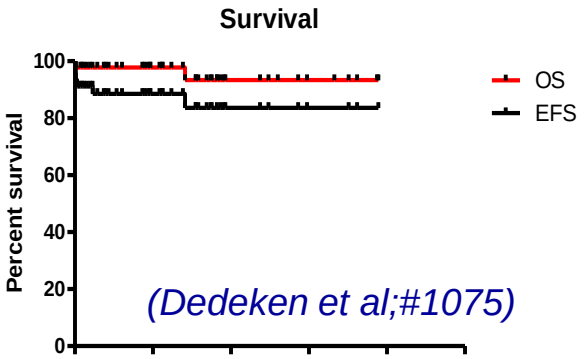
- Surgery associated with high rate of complications
- Better outcome if preoperative tf but variable practice
- RDZ study for medium risk surgery (abdominal, ENT, orthopedic,…)

If Hb < 9g/dl	Top-up transfusion
If Hb > 9 g/dl	Exchange transfusion

Preoperative transfusion strongly recommanded

	No Transfusion	Transfusion
Patients	34	36
Complications	39%	14% **
SAE'S	30%	2.9% **
Acute Chest S.	27.3%	2.9% **
Peri-op transfusion	38%	**
Almost no alloimmunisation (both arms)		

HSCT for SCD



- Excellent results with MAC with MSD (#3103)
- Improves SNC disease and cognitive outcome (#11)
- Also in Brazil (13/16 pts alive and cured) (#1064)

- Adults with severe organ dysfunction do not tolerate MAC → Need for alternative approach
- Most patients lack a MSD → Need for alternative donor
  - In US: only 7% of donor/ CBU < African origin - Very few 6/6 match
- Novel approaches tested in trial setting:
  - Non-Myeloablative allo-HSCT for adults (# 11)
  - Haploidentical Tx
  - Scurt STUDY – ongoing for <19y with MUD 8/8 with RIC (alemtuzumab-Fluda-TT)

Non Myeloablative allo-HSCT for adult patients with severe SCD is feasible

M. Hsieh; #11

Patients with severe disease	**Stroke or vasculopathy, Nephropathy, PH, AVN,… Most had > 1 organ damage**
Conditioning	Alemtuzumab + 300 cGy TBI
GVH prophylaxis	Sirolimus > >1y
Donor	MSD
23 patients evaluated • 20 engrafted • 3 rejection Survival 100% No GVHD	
Donor CD3 chimerism: 40% at 48 Mo	
Some reversal of end-organ damage (PH, kidney, etc…)	

Thalassemia and Iron Overload

Safe Iron load

- Liver Iron Content < 7 mg Fe/g dry dw liver
- Ferritin < 1500 ng/mL but no cardiac death if < 2500 ng/mL

Why combination therapy? ↓ toxicity, ↑organ-specific iron removal, additive or synergestic effect

- 3 chelators available (deferoxamine, deferiprone and deferasirox)
- DFO+DFP: synergestic effect and effective to ↓ cardiac iron load
- DFO+DFX: scarce data – no additive effect??

- DFP+DFO more effective to improve ventricular function
- DFX alone more effective to reduce hepatic siderosis
  → TT according organ *A. Pepe; #1087*
- In Non transfused Thalassemic pts (Thal Intermedia, HbE-β°, HBH):
  Low dose DFX effective to reduce iron overload

BMT for Thalassemia Major – Report of EBMT Registry *(Baronciani et al; #905)*

EBMT survey on Tx performed these last 10 years in 1953 pts from 134 centers in 28 countries.

- Most of patients are < 18y and the majority Tx with a BM from a MSD.
- Thalassemia Free Survival at 81%

- Optimal results in < 14y and worse outcome with ↑ age
- Less good in Iran Turkey,… (suboptimal prior therapy)
- EFS according to donor:

MSD: 91%
MFD: 88%
MMUD: 74%
MUD-MMFD: in between

Tx with alternative donor must be carefully evaluated

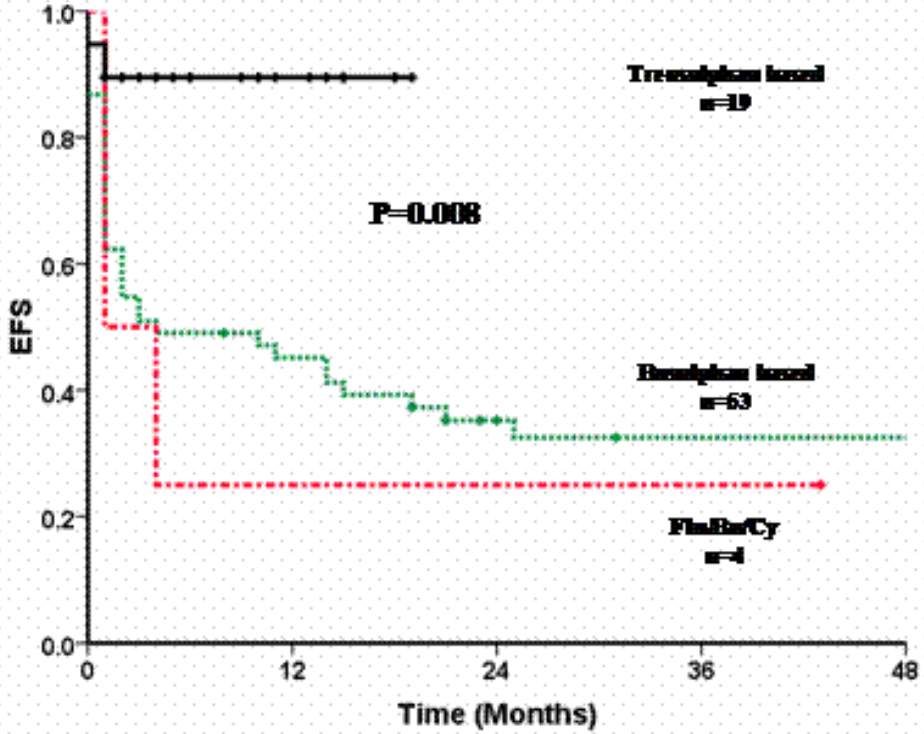
BMT for Thalassemia Major

- HSCT from Alternative Donors with conditioning with CPM, Bu, Fludarabine and Thiotepa achieved OS, DFS and TRM of 92%, 90% and 8% in 61 Chinese pts *(C Li; #3034)*

- Treosulfan based regimen less toxic for high risk patients in 30 Indian pts *(V. Mathews, #1017)*

- Unrelated BMT with selection of donor based on HR HLA typing (10/10 or 9/10 with locus C MM) provides TFS of 84% *(Locatelli et al; #149)*

Figure 1: Event free survival of Class III high risk patients with different conditioning regimens



Bone Marrow Failure syndromes