Hematopietic Stem Cell Transplantation in Sickle Cell Disease

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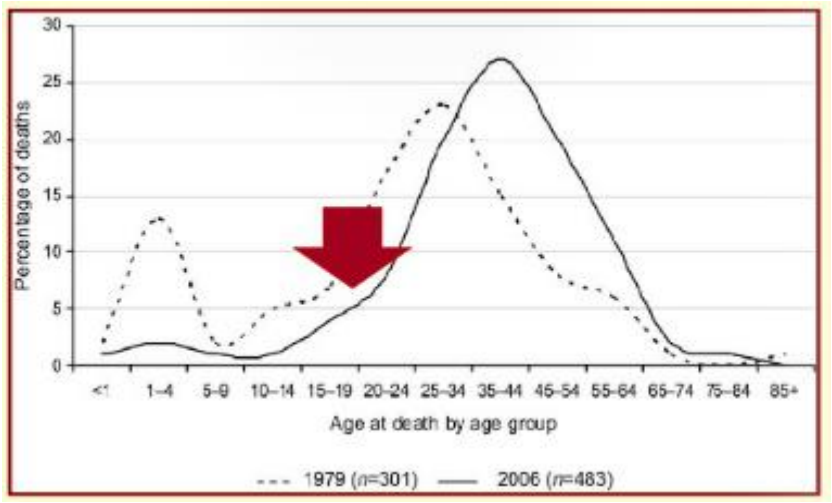
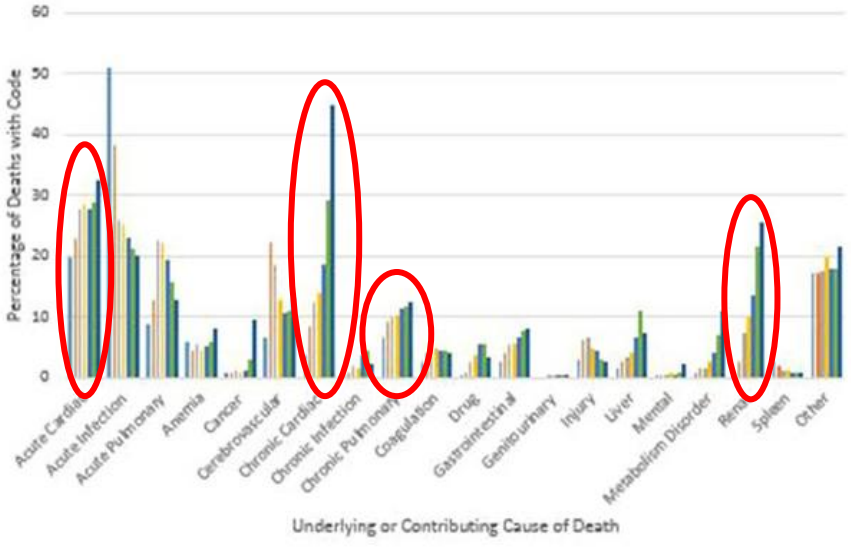
In developed countries SCD is a systemic vasculopathy



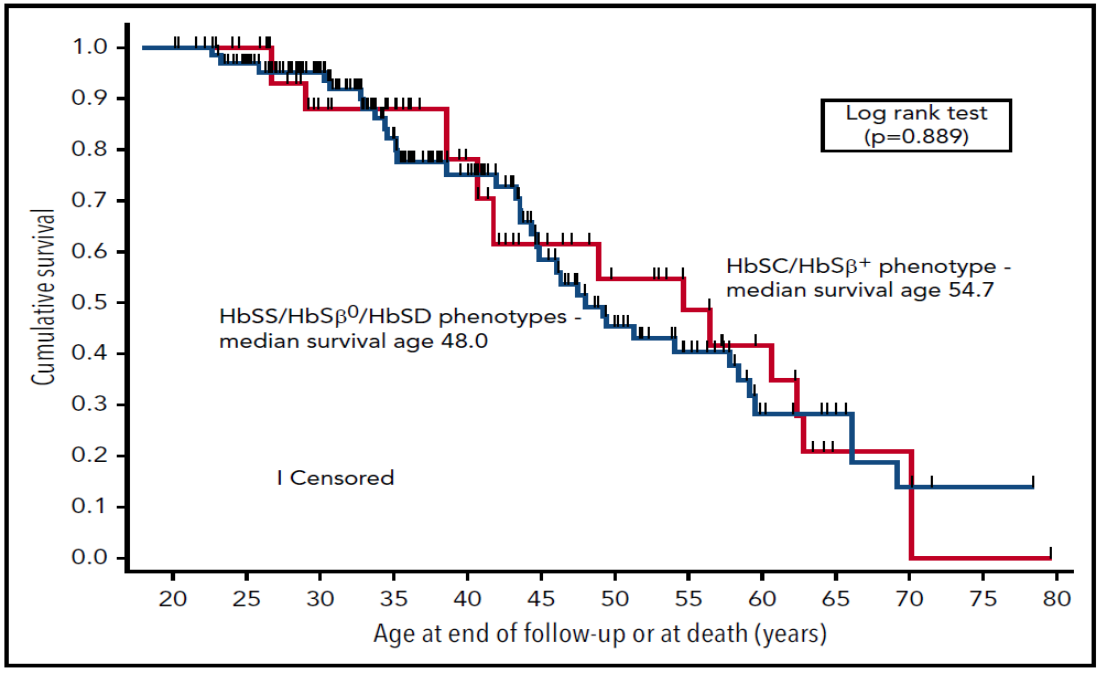
Hassel et a, Am J Prev Med, 2010



Payne A, et al. Blood 2017;130:865

Background

Persistently poor survival with conventional care



Median survival for adults with SCD is ≥20 years shorter than for African Americans living in the United States

DeBaun et al. Blood. 2019 Feb 7;133(6):615-617.

Novel non-curative treatment options offer promising improvement of short-term parameters…

Voxelotor

- HbS polymerization inhibitor to stabilize the oxygenated hemoglobin state
- Trend in der reduction of vaso-occlusive crises
- Reduction of acute anemic events
- Reduction of hemolysis
- Licensed in the USA in 2019

Dufu et al., Hematol Rep 2018
Oksenberg et al., BJH 2016
Howard et al., Blood 2019
Vichinsky et al.,NEJM 2019.

Longterm Impact on systemic vascular complications?

Crizanilizumab et al

- P-selectin antagonist
- Reduced adhesion of erythrocytes, leukocytes and PLT
- Licensed in 2019

Kapoor et al., Mayo Clin Proc, 2018
Ataga et al., NEJM, 2017,
Kutlar et al., Am J Hematol, 2019a

L-Glutamine

- Glutamine increased NAD redox potential
- Decrease endothelial adhesion
- Reduced frequency of crises and hospitalization
- Benign adverse event profile
- Licensed in 2017

Neumayr et al. 2019, Am L Manag Care
Quinn 2018, Blood
Niihara et al. 2018, NEJM

Costs: app. 11000$/months

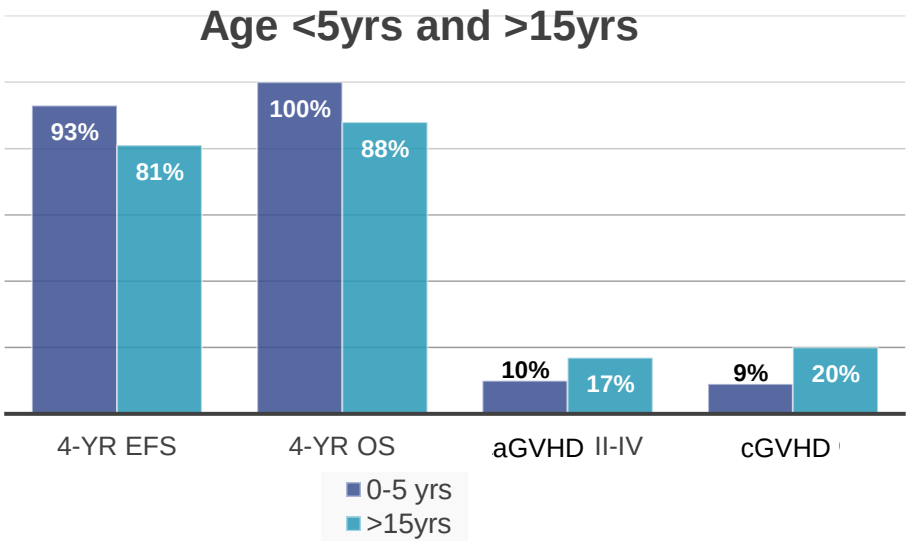
Marilyn J. Telen Blood 2016;127:810-819

MSD ≧ MUD > MMUD$^{9/10}$ > Haplo

Balduzzi et al, BBMT 2019

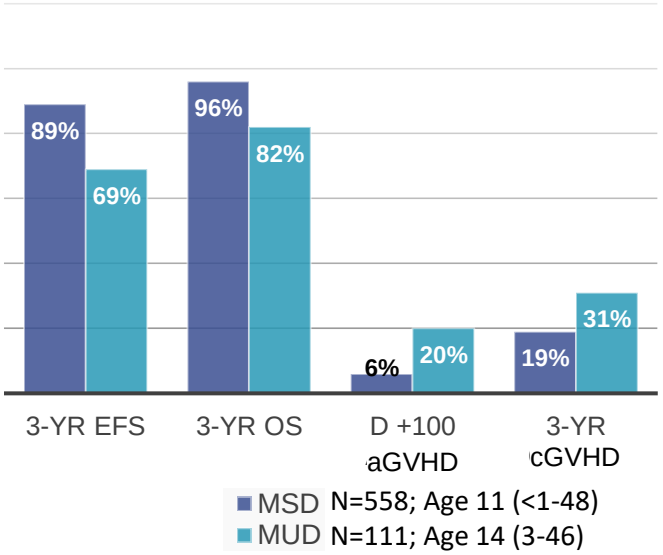
Is the donor hierarchy in SCD identical to malignant diseases?

MSD is the standard of care...



Cappelllini et , Hematologica, 2019

MSD = MUD?



M. Eapen et al, Lancet Hematology, 2019

But:

- MSD/MUD Donor availability <20%
- Key outcome indicator decline significantly >15yrs (>13<yrs)

Unmet Need!

Haploidentical HSCT for SCD

Posttransplant Cyclophosphamide

comparison	pre-conditioning	no pre-conditioning
Number	23	10
Median age	11 (3-19)	13 years (3-19)
Survival Months (median)	12.9	9.7 (1.5-21.6`0
Grat failure	3 (13%)	0
Neutrophil engraftment	17 (15-29)	17 (15-21)
Platelet engraftment >50	34.5 (20-64)	34.5 (28-38)
aGvHD Grade I	4 (17.4%)	3 (30%)
aGvHD Grade 2-4	3 (13%)	5 (50%)
cGvHD >D+100 Limited	2 (8.7%)	1 (10%)
cGVHD >D+100 Extensive	5 (21.7%)	4 (40%)
cGVHD >18 months	0	0
Deaths	5 (21.7%)	1 (10%)
VOD	2 (8.7%)	0
TMA	2 (8.7%)	3 (30%)
MAS	7 (30.2%)	1 (10%)
Median cessation of immunosuppression	174.5 (95-656)	171 (160-191)

Preconditioning:

- Azathioprine 3 mg/kg/d
- Hydroxyurea 30 mg/kg/d
- Hyper-transfusion

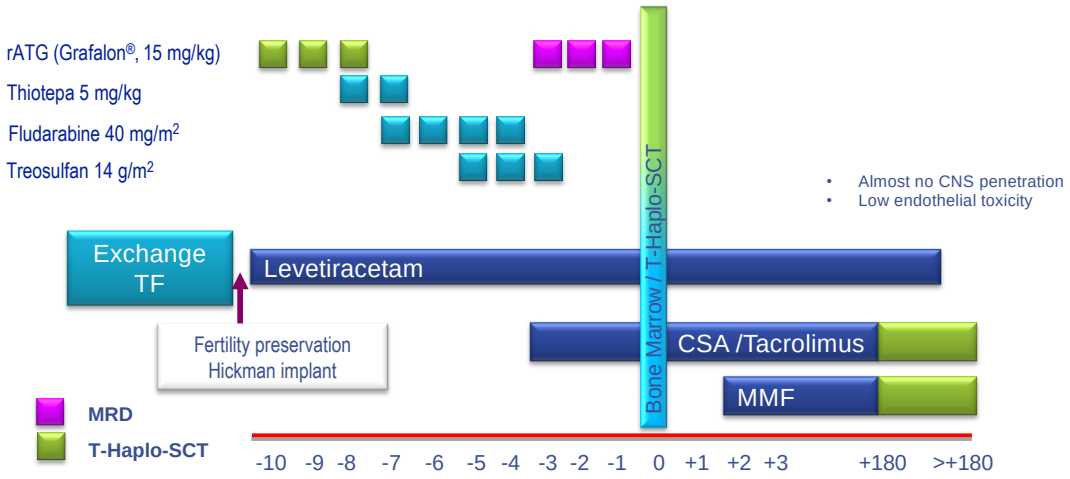
Kindly provided by J. de la Fuente

Haploidentical HSCT for SCD

In vitro TCR αß/CD19 Depletion

N=25

Conditioning Regimen



OS, DFS, TRM

T-Haplo-SCT	
OS	21/25 (88%)
DSF	21/25 (88%)
TRM	3/25 (12%)

T-Haplo-SCT		
Acute GvHD	Grade I-II	7/25 (28%)
	Grade III-IV	none
Chron. GvHD*	Mild - moderate	4/25 (16%)

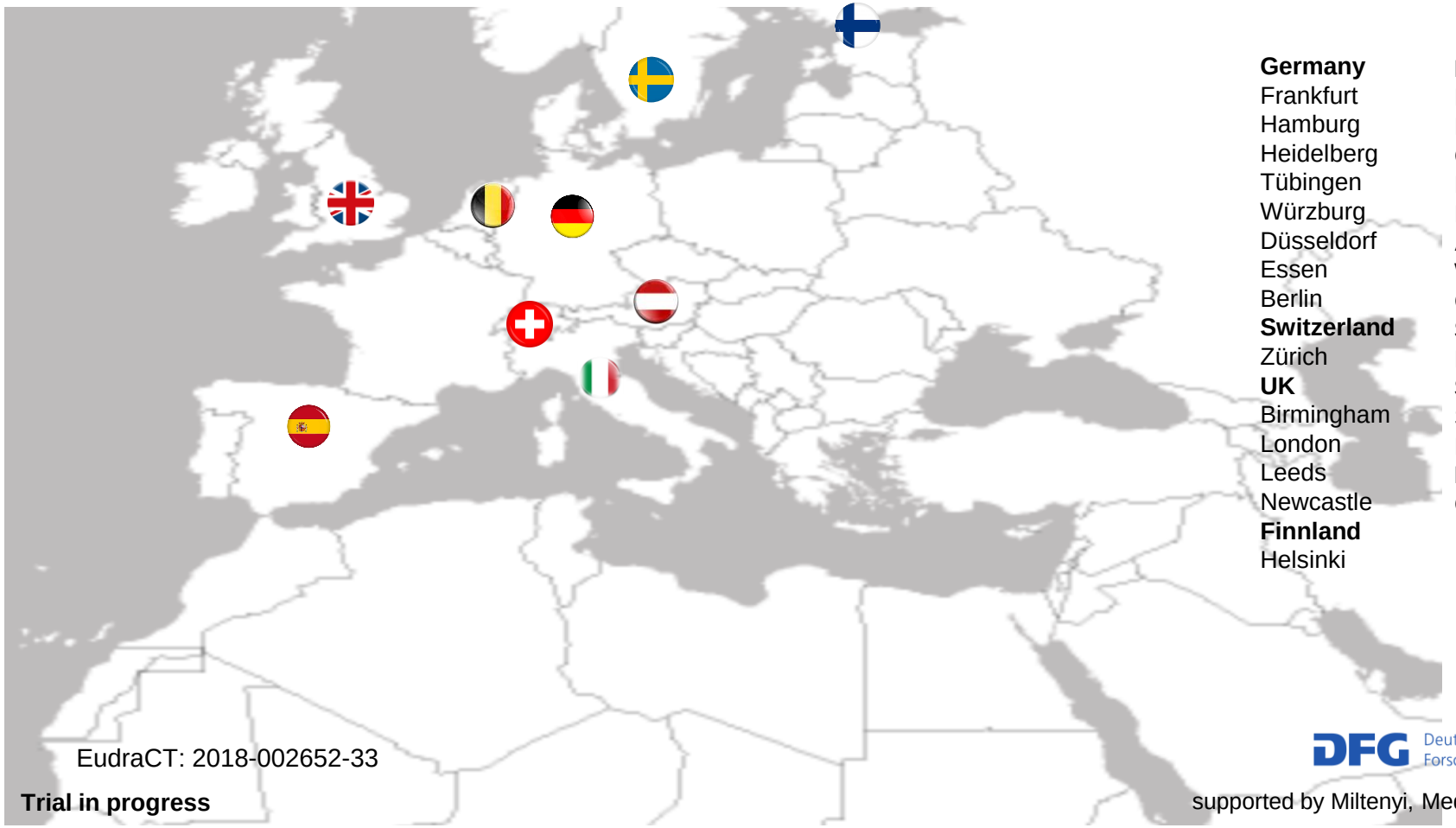
Chimerism off immunosuppression (median)

T-Haplo HSCT
99% (59,3% - 100%)

cGvHD was age dependent: 33% vs. 4% in patients above or below 18 years of age

Phase 2 trial to assess haploidentical a/ß T-depleted stem cell transplantation in patients with sickle cell disease with no available sibling donor

(T-Haplo-HSCT for SCD)



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Lund
Belgium
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EudraCT: 2018-002652-33

Trial in progress

DFG Deutsche Forschungsgemeinschaft

supported by Miltenyi, Medac and Neovii

Gene Therapy
Gene Editing
Gene Correction

?

- Succesful proof of concept
- Surogate therapy bypassing the problem with gene addition or HbF expression
- Potential risk for malignancy and off-target effects
- No long-term data available yet with regard to safety and efficacy
- Costs and availability in LMIC

Conclusion

Haploidentical HSCT is increasingly considered a valid alternative covering an unmet need!

Haploidentical HSCT

- is readily available and cost efficient compared to a MUD HSCT
- leads to an accelerated engraftment
- Safety is currently being evaluated in several ongoing trials
- can be advantageous even compared to MSD HSCT with regard to aGVHD & cGVHD and could outmatch overall outcome in AYA
- Prospective controlled trials are pivotal and underway

Gene therapy/gene editing

- Can potentially replace HSCT in developed countries
- Needs a longer track record with regard to efficacy, late effects and secondary malignancies
- Has similar drawbacks such a MAC and infertility
- Is less cost efficient than haploidentical HSCT

Thank you very much for your attention!