4th Global Congress on Sickle Cell Disease

GLOBAL SICKLE CELL DISEASE NETWORK

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Haploidentical hematopoietic stem cell transplantation in sickle cell disease

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ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

No disclosure

Allogeneic hematopoietic stem cell transplantation (HSCT) in SCD

Curative option

BUT

- Transplant-related mortality - GVHD (graft versus host disease) - Infertility	Lack of donors

HSCT from HLA-matched related donor in SCD

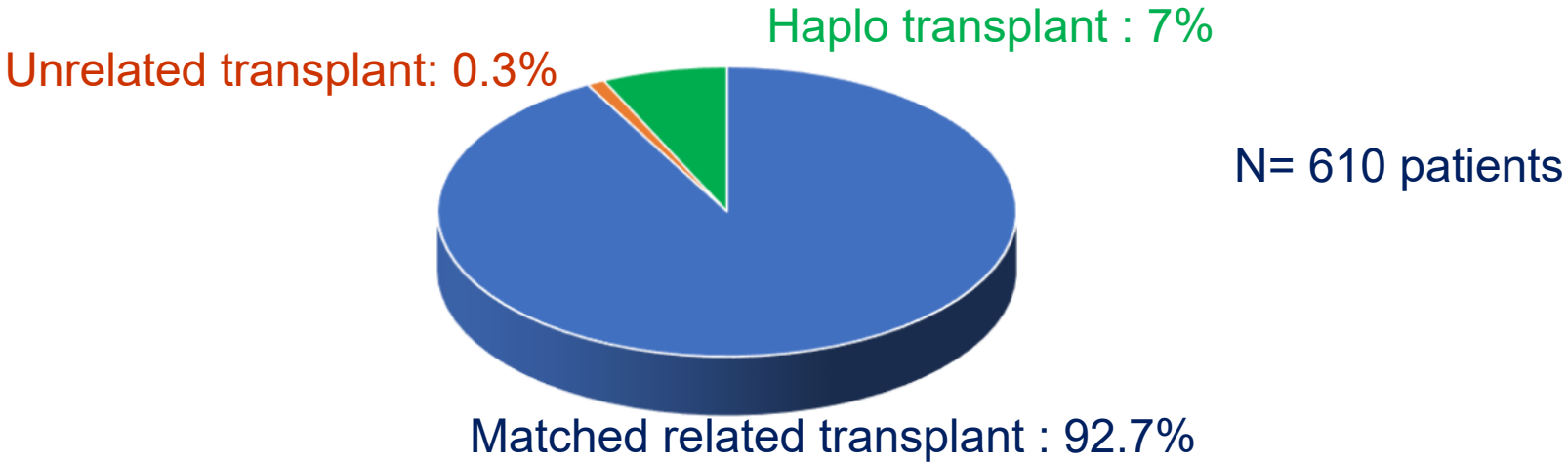
- In children : Myeloablative matched related transplant (MRT) : survival without SCD higher than 95% with low chronic GVHD
- In adults: more cGVHD and higher transplant mortality after myeloablative regimen
- In adults: promising results after reduced intensity conditioning regimens

Bernaudin Haematologica 2020, Iqbal Transplant and cellular thérapy 2021, Gluckman Blood 2017, Capelli Haematologica 2019, Hsieh NEJM 2009, Alzahrani BJH 2021

Matched related donor in only 15 à 30% of patients

Alternative transplant in SCD ?

Experience of the « Société Francophone de Greffe de Moelle et de Thérapie Cellulaire » (SFGM-TC)



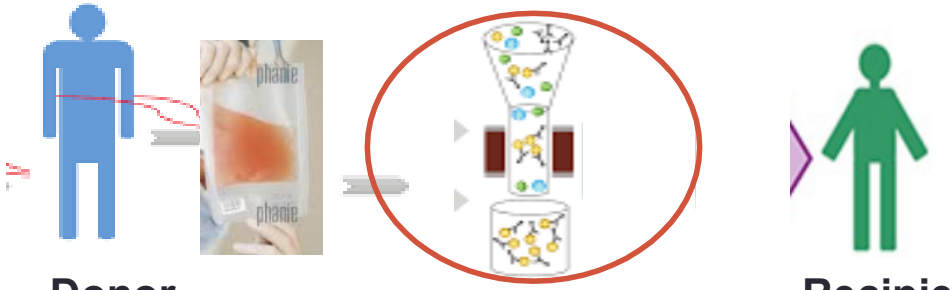
Haplo-identical transplant

Advantage	Inconvenient
Donor in ~ 90% of patients	Higher risk of graft failure
	Higher risk of GVHD

Specific modalities of transplant

Techniques of GVHD prophylaxis in haplo-transplant

***Ex vivo* T depletion**

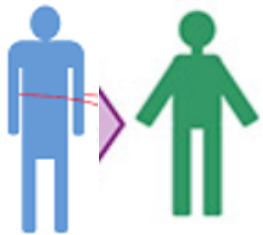


Donor

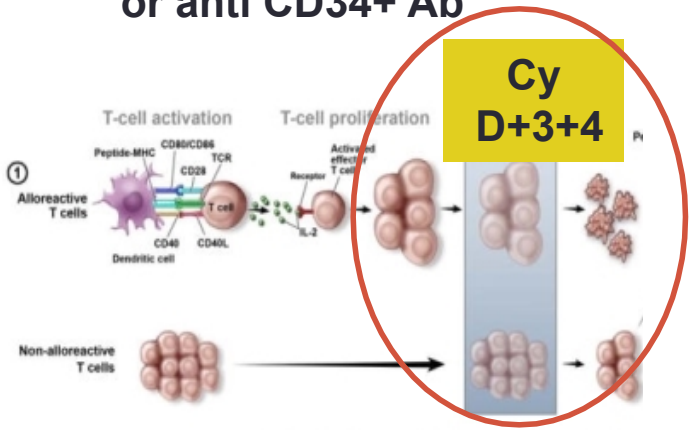
Anti T cell Ab*
or anti CD34+ Ab

Recipient
infusion

***In vivo* T cell depletion based on post-transplant high dose Cyclophosphamide (HDCy)**



Transplant



Allogeneic T cell
activation/proliferation

Depletion of
activated T cell

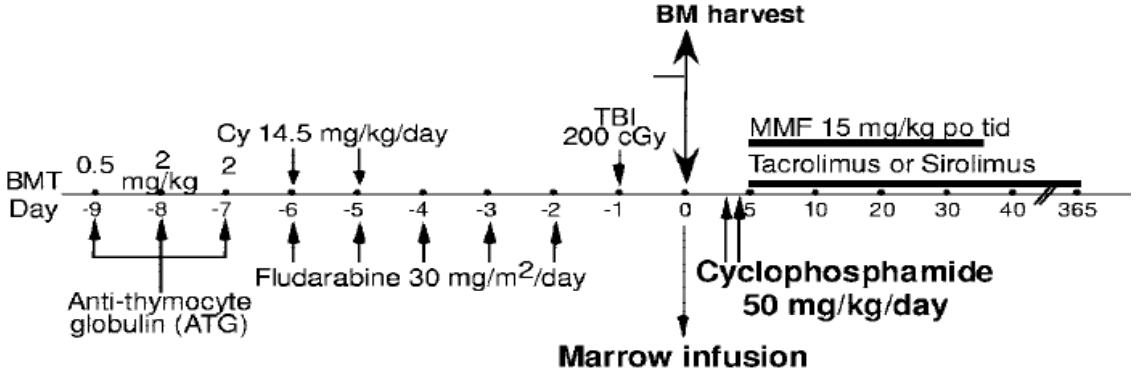
*Ab: antibodies

Haplo-transplant with *ex vivo* T cell depletion

	Foell HemOSCT 2020. N=25	Cairo Jama Ped 2020. N=19
Age	Median 13 (range 3-31)	Median 13 (range 3-20)
Type of T cell depletion	CD3/CD19=19. αβ T cell/CD19=6	CD34+ selection + add back of $2X10^5$ CD3+/Kg
Conditioning: MAC	ATG+ Treo+ Thio+ Fluda+	ATG+BU+ Thio+ Cy+TLI
Graft failure	4%	0%
GVHD acute : **chronic:**	Gr I-II: 28% Mild to moderate: 16%	Gr II-IV: 6.2% Moderate to severe: 6.7%
Transplant related mortality	12%	16 % at 2 years
Cause of death	Infection, graft failure, MAS	GVHD: N=2, SOS: N=1
Survival without SCD	88%	84% at 2 years

MAS: Macrophage activation syndrom, SOS: sinusoid obstruction syndrom, TLI: total lymphoid irradiation

Haplo-transplant with post-transplant HDCy
The Hopkins group approach



Results: N=14

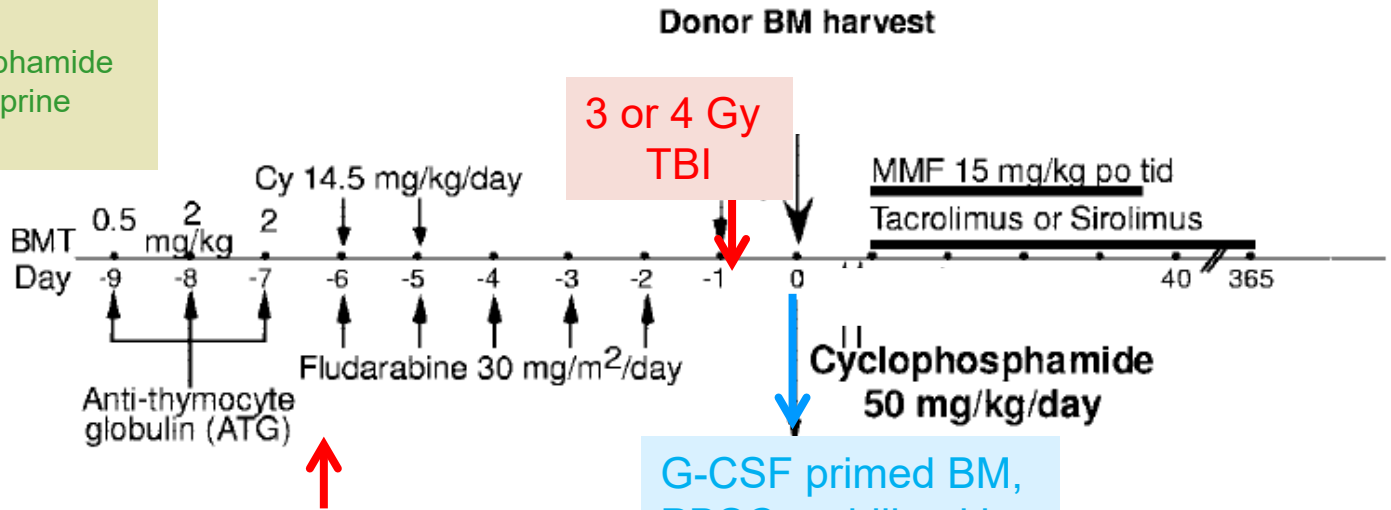
Age: 23 y (15 -42)
TRM:0
GvHD:0
Graft failure:7 (50%)
EFS:7 (50%)

RIC
- Decrease transplant toxicity
- Increase graft failure

Bolanos Blood 2012

Modifications of the Hopkins approach for improving engraftment

Pretransplant immune Suppression:
Fludarabine Cyclophosphamide
Dexamethasone Aziatioprine
Hydroxyurea



TBI: total body irradiation, G-CSF: granulocyte colony stimulating factor, PBSC: peripheral blood stem cells

Fuente BBMT 2018, Dhedin EBMT 2022, Kharya BMT 2021, Bolanos Lancet Haem 2019, Mallhi BBMT 2020, Saraf BBMT 2018

Hopkins' modified approaches

Study	De la Fuente BBMT 2018 N=15	Saraf BBMT 2018 N=8	Bolanos Lancet Haem 2019 N=12	Mallhi BBMT 2020 N=5	Kharya BMT 2021 N=25	Dhedin* Drep-Haplo EBMT 2022 N=19
Modifications Compared with Hopkins approach	**+ Thiotepa** GCSF primed BM	TBI **3GY** + **PBSC**	TBI **4GY** BM	TBI **4GY** **BM or PBSC**	**+ Thiotepa PTIS PBSC**	**+ Thiotepa (+/-GCSF primed) BM**
Median age	20 y (12-26)	28 y (20-38)	26 y (6- 31)	11y (13-47)	7y (1-27)	17y (13-39)
Median follow-up	13 m (6-30)	17m (12-30)	23 m (12-45)	30 m (18-41)	14 m (6-27)	18 m (2-50)
Transplant mortality	0%	12.5%	0%	0%	12% (**=1)	5% **
aGvHD cGvHD	III-IV 13.2% Mod: 6.6%	II-IV: 25% Mod: 12,5%	II-III 30% Mild+ mod:18%	II-IV: 80% 40%	II-IV: 20% Mod:12%	II-IV: 47% Mod + severe:22%
Graft failure	6.6%	12.5%	8%	0%	0%	5%
Survival	100%	87.5%	100%	100%	88%	95%
Survival without SCD	93.4%	75%	83%	100%	88%	89%

*preliminary results: drep-haplo trial **Related to GVHD, Mod: moderate, PTIS: pretransplant immune suppression, PBSC: peripheral blood stem cell, BM: bone marrow

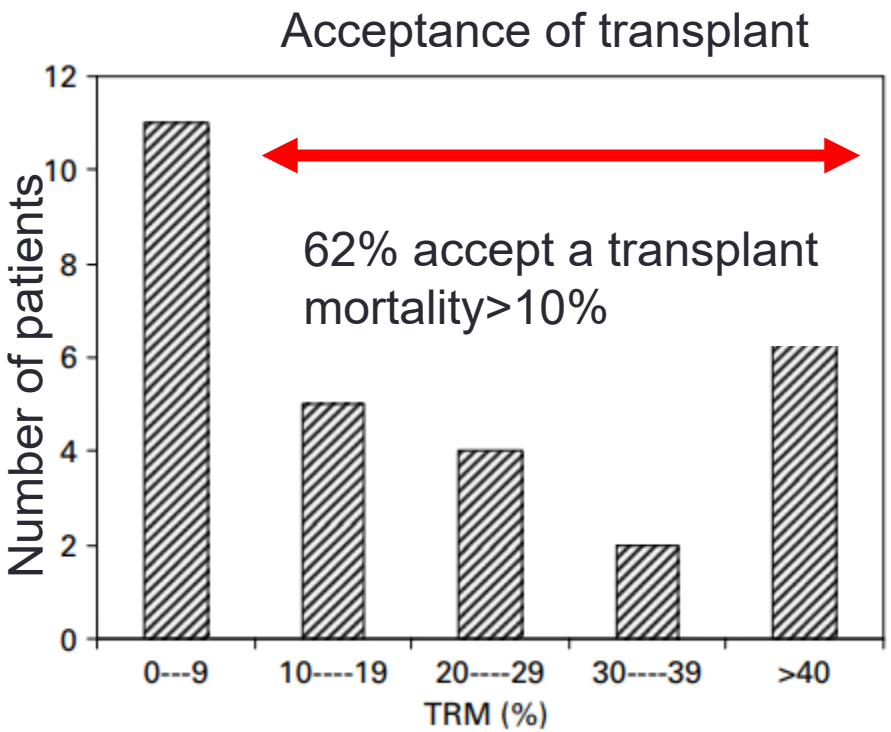
Indications for haploidentical transplant in SCD

	Indication	HLA-Matched Related Donor	Alternative Donor* Haploidentical donor
Predictors for Increased Mortality	≥2 VOC/year	X	X
	Recurrent acute chest syndrome	X	X
	Stroke	X	X
	Cognitive impairment + Abnormal cerebral MRI	X	X
	TRJV ≥ 2.7 m/s	X	X
	Sickle nephropathy	X	
Predictors for Increased Morbidity	Red blood cell alloimmunization	X	
	Recurrent priapism	X	
	Osteonecrosis of multiple joints	X	

HLA, human leukocyte antigen; VOC, vaso-occlusive crisis; MRI, magnetic resonance imaging: TRJV, tricuspid regurgitant jet velocity. * Despite hydroxyurea and/or chronic red blood cell transfusion therapy.

Saraf, Journal of clinical medicine 2019

Patients' perception of transplant risks



Population : N=30
Age : 29.5 y (r 18–56) 96% with QOL affected++

Results	**% of pts who accepted**
TRM> 10%	: 62%
Graft failure>10%	: 64%

cGVHD	: 20%
Infertility	: 50%

Chakrabarti BMT 2007

Haploidentical transplant versus gene therapy

	Haplo transplant advantages	Gene therapy advantages
Number of patients treated	+	
Documented cured patients	+	
Possibility of using RIC	+	
Absence of GVHD		+
Less myeloid maligancies	+	
Cost	+	

Conclusion

- Haplo-identical transplant is a feasible curative treatment for SCD with more than 200 patients reported
- Use of reduced intensity conditioning followed by post-transplant Cy has to be prefered in adults
- Current transplant modalities allow OS around 90% with less than 10% of graft failure leading a survival without SCD around 80%.
- Future challenges are to decrease GVHD, and if possible to preserve fertility by use of RIC
- Haploidentical transplant has to be discussed in patients with severe complications despite standard of care, before occurrence of terminal organ damages
- Gene therapy has also to be considered in patients with severe disease without matched donor

Thank you for your attention

- AYA Haematology unit.
Saint Louis. Paris
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And all the AYA team

- Centre intercommunal de Créteil
SCD referal center. C. Pondarre

- HEGP
SCD referal center; JB Arlet

- Patients and families