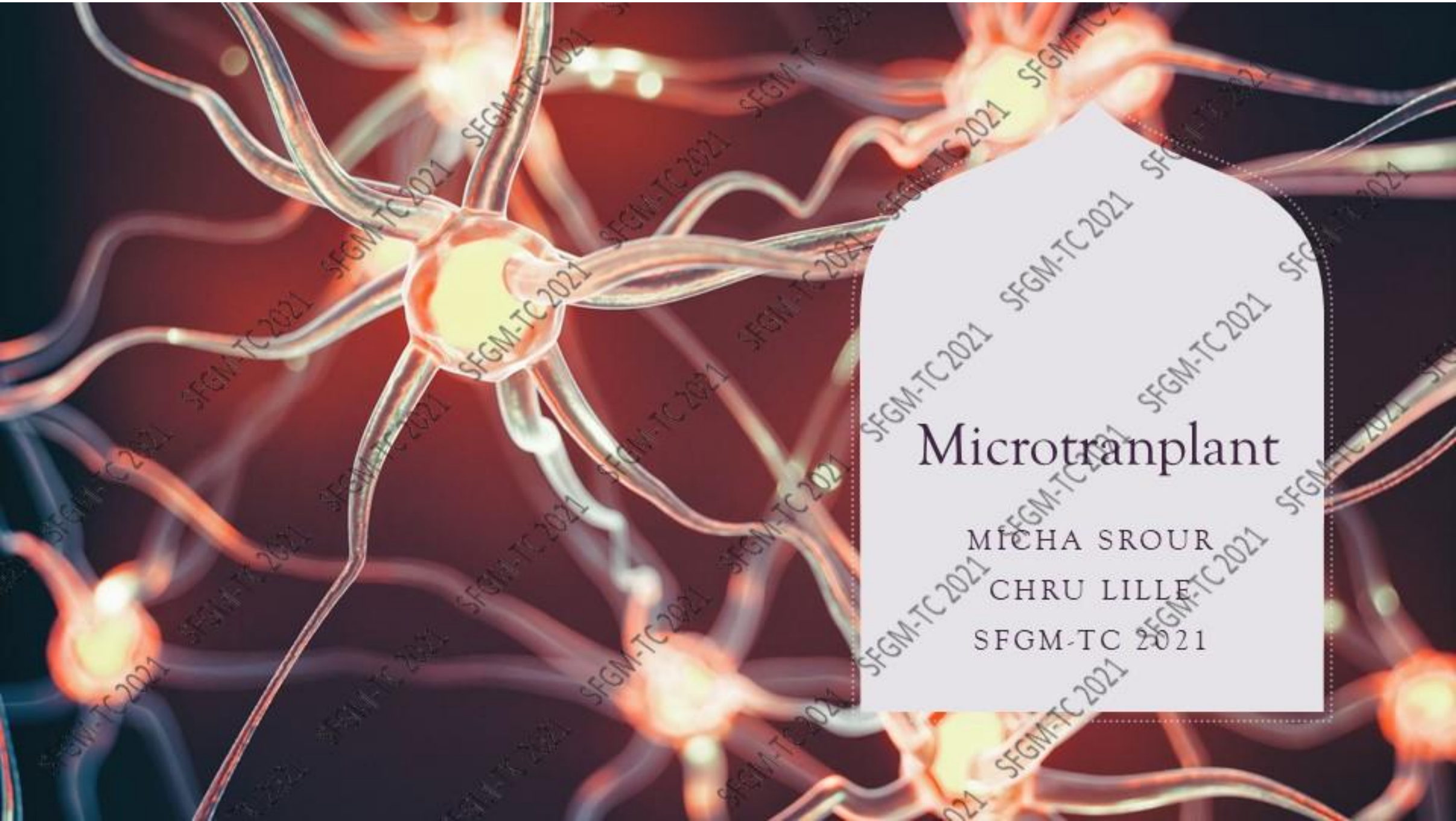

Microtranplant
MICHA SROUR
CHRU LILLE
SFGM-TC 2021

Le concept: *cell therapy has no limits*

Il y a plus de 50 ans on a commencé la greffe standard…

Depuis plus de 20 ans, on fait de la mini-allogreffe…

Depuis 10 ans, la première étude des premières microgreffes …

Et peut être dans 15 à 20 ans on fera de la nanogreffe…

1. Definition

une procédure particulière d'allogreffe de CSH où seul un **microchimérisme** transitoire est envisagé avec un objectif d'induire un effet immunologique anti tumoral tout en limitant l'effet GVHD.

Doit être réalisée dans les centres agrées pour la réalisation de l'allogreffe.

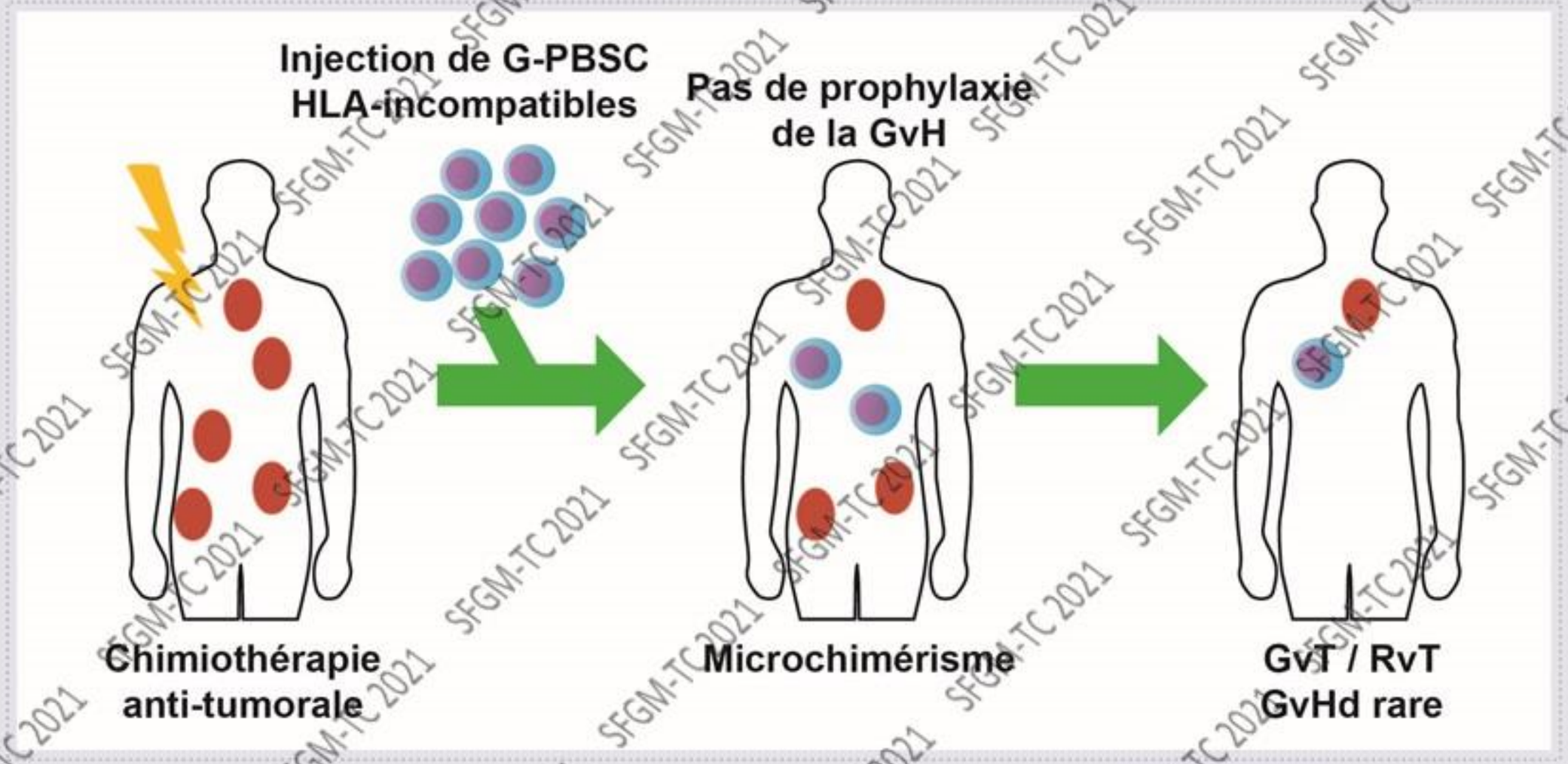
2. Procédure

INJECTION DE CSH ALLOGENIQUES MOBILISÉES PAR DU G-CSF,

HLA-MISMATCHÉES,

APRÈS UNE CHIMIOTHÉRAPIE CONVENTIONNELLE À VISÉE ANTI LEUCÉMIQUE NON IMMUNOSUPPRESSIVE.

SANS TRAITEMENT IS


Injection de G-PBSC
HLA-incompatibles
Pas de prophylaxie
de la GvH
Chimiothérapie
anti-tumorale
Microchimérisme
GvT / RvT
GvHd rare

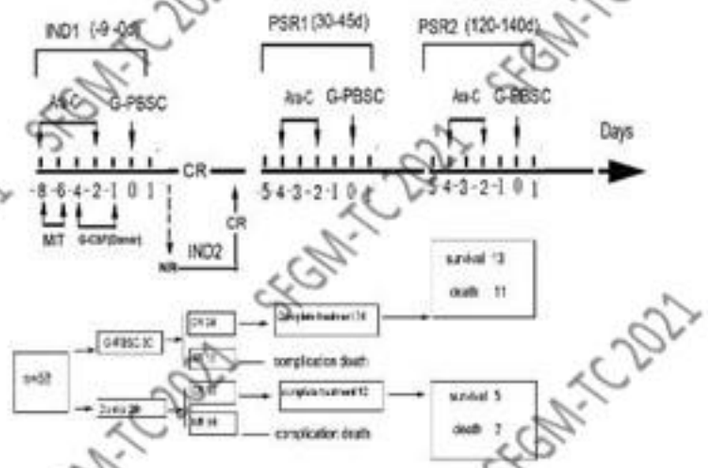
3. Concept

1. Effet **GVT** lié aux cellules immunocompétente de la MT (microchimerisme)

2. Effet **RVT**: réaction antitumorale immune de l'hôte: effet receveur versus tumeur (**RVT**), déclenché par la réaction immunologique associée au rejet du greffon

Infusion of HLA-mismatched peripheral blood stem cells improves the outcome of chemotherapy for acute myeloid leukemia in elderly patients

Guo M et al. Blood. 2011 Jan 20;117(3):936-41



- 58 patients (60-85y)
- AML at risk (APL excluded)
- Prospective, Randomised : MTX arm (30) vs Chemo (28)
- MTX= micro transplantation

Résultas

	Control group	G-PBSC group	*P*
Complete remission rates			
After the first induction, n/N	8/28	19/30	.006
After the second induction, n/N	12/28	24/30	.006
Patients >70 y, n/N	1/8	13/14	.0003
Patients <70 y, n/N	11/20	11/16	.4
In high-risk category, n/N	4/13	7/12	.23
In standard-risk category, n/N	8/15	17/18	.01
Disease resistance, n/N	11/28	3/30	.01
Early death rate, n/N	4/28	2/30	.69
Median time of ANC > 0.5 × 10⁹/L, d			
After the first induction	16	11	.02
After the post-remission	12.5	10	.06
Median time of platelet count > 30 × 10⁹/L, d			
After the first induction	20	14.5	.02
After the post-remission	17	14	.06
Severe infection			
After the first induction, n/N	16/28	8/30	.02
After the post-remission, n/N	10/24	5/24	.44

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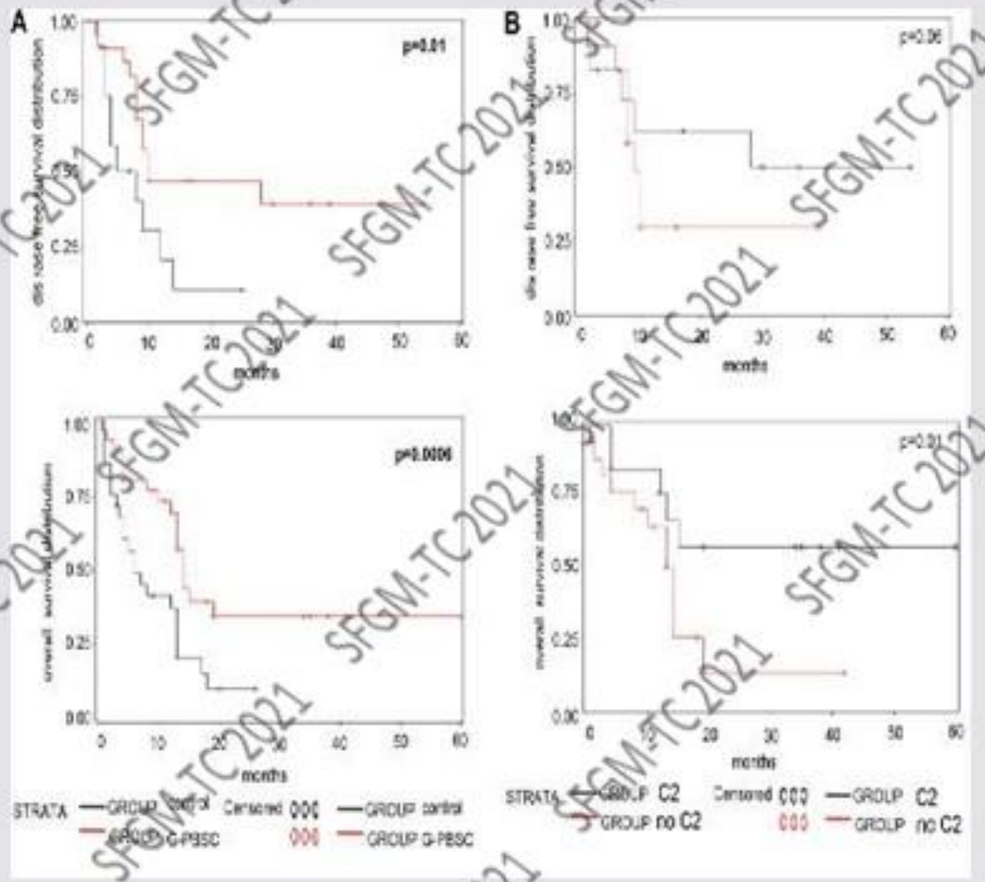
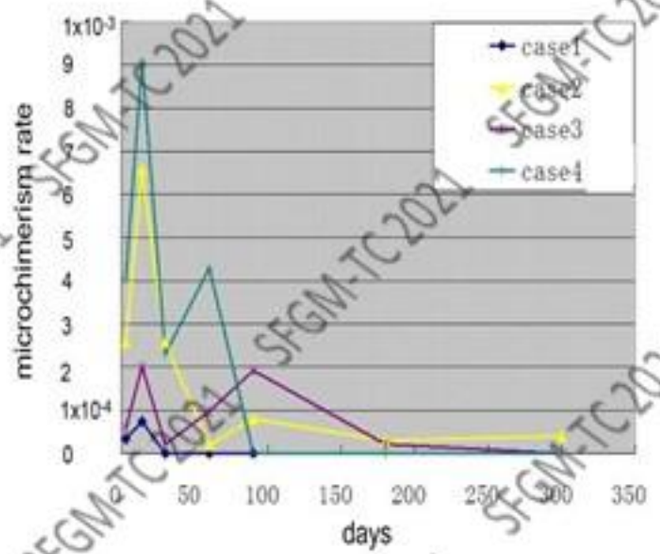
Résultas

(A)2-year DFS and OS were 38.9% and 39.3%, respectively, in the G-PBSC group. Vs 10.0% and 10.3%, respectively; P = .01 and P = .0006).

(B) HLA-C2 ligands (n = 13) had significantly higher OS compared with donor having no C2 ligands (n = 17) in the G-PBSC group (57.1% vs 12.5%; P = .01).





Résultas

The kinetics of donor microchimerism showed that microchimerism emerged on day 2 and reached its first peak on days 7-14 after the first G-PBSC treatment and its second peak after the second or third course of G-PBSC therapy, lasting 2 weeks to 10 months.

HLA-Mismatched Stem-Cell Microtransplantation As Postremission Therapy for Acute Myeloid Leukemia: Long-Term Follow-Up

Mei Guo et al, J Clin Oncol 30:4084-4090. © 2012 by American Society of Clinical Oncology

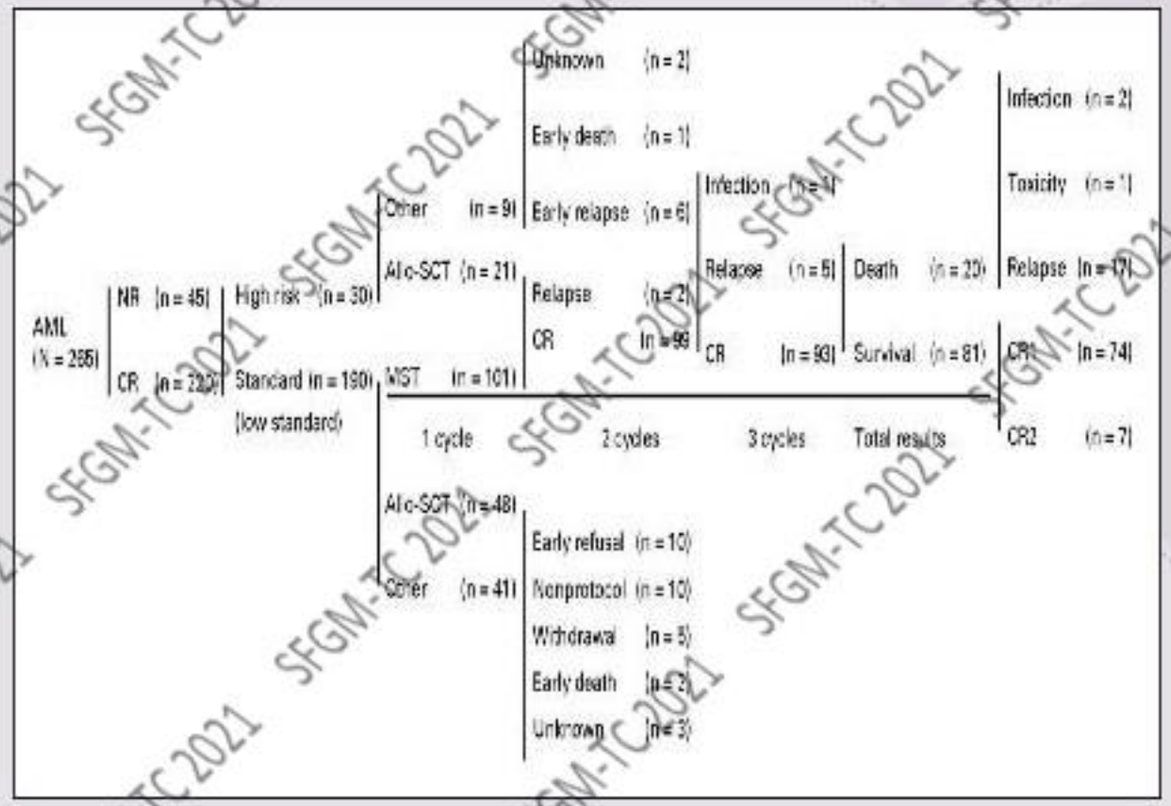
Eligibility: patients 9-65 years, de novo AML between May 2004 and February 2011 (APL excluded)

Induction chemotherapy (Ara-C 150 mg/m2, 7+ mitoxantrone (10 mg/m2) or daunorubicin (45 mg/m2), 3 d)

HR were excluded.

SR and LSR with HLA-matched related donor were excluded

3 cycles of HD Ara-C (2.5g/m2/12h days1,2, and 3) followed by infusion of GPBSCs 24 hours after Ara-C therapy with a 3-month interval between the courses

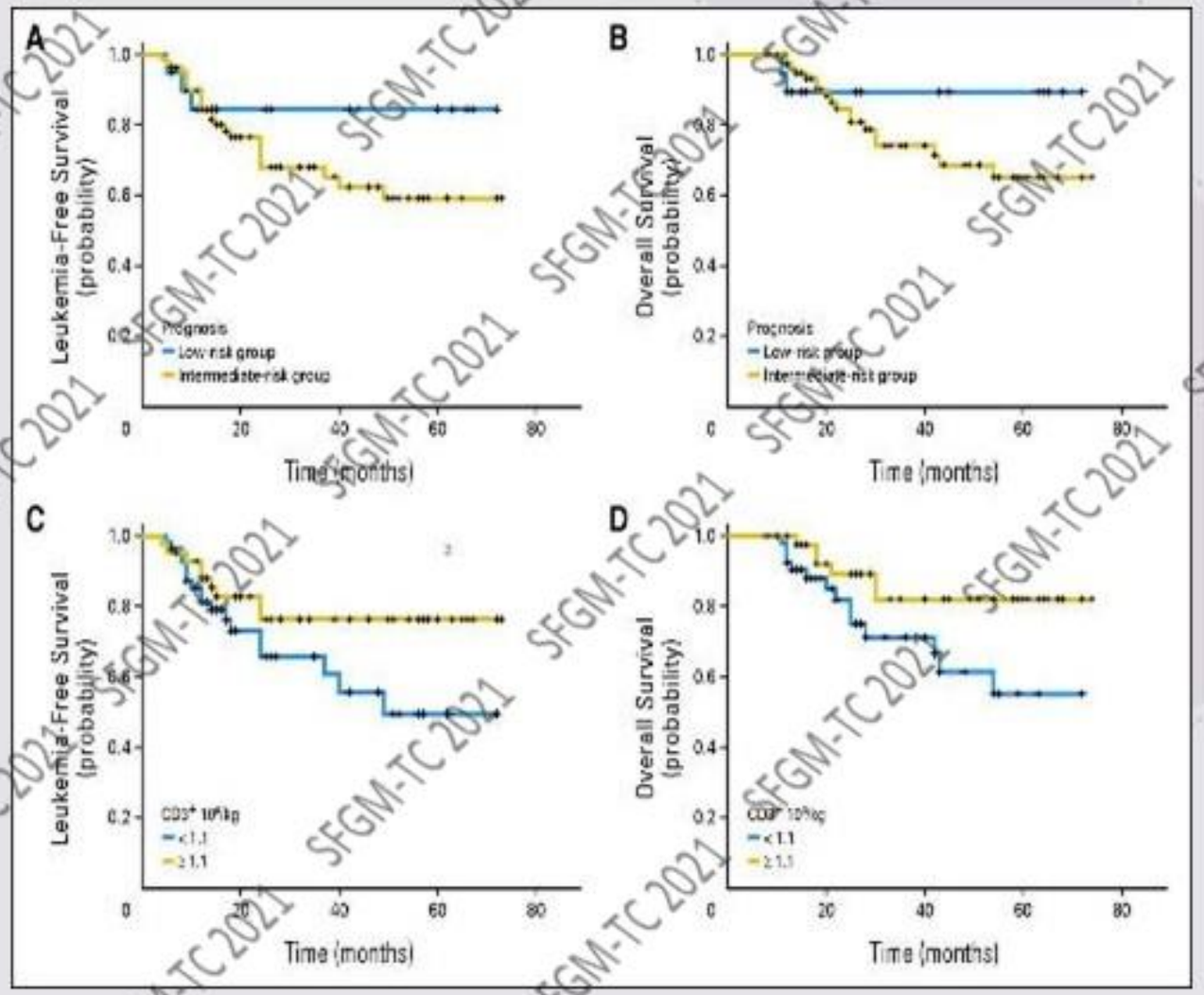


Results

(A)The 6-year LFS 84.4% Low risk vs 59.2% Inter risk (P = .272)

(B) The 6-year OS 89.5% Low risk vs 65.2 % Inter risk (P = .308)

The 6-year (C) LFS and (D) OS rates were 76.4% and 82.1%, respectively, in patients with a high dose of donor T cells (≥ 1.1 × 108/kg) for each course, vs lower dose of donor T cells (49.5% and 55.3%, respectively; P = .091 and P = .041).



HLA-Mismatched Microtransplant in Older Patients Newly Diagnosed With Acute Myeloid Leukemia Results From the Microtransplantation Interest Group

Mei Gu et al, JAMA Oncol. 2018;4(1):54-62.

Phase 2 prospective, patients from 60 to 85 y with de novo AML from 12 centers (China, USA, Spain), with all risk except APL.

Patients were divided 4 age groups: 60 to 64y, 65 to 69 y, 70 to 74 y, and 75 to 85 y.

Characteristics of Patients

	All patients (n=185	60-64 (n = 69)	65-69 (n = 47)	70-74 (n = 43)	75-85 (n = 26)	
Sex						P=0.764
Female	75	31	17	16	11	
Male	110	38	30	27	15	
FAB classification						P=0.986
M1 and M2	57	23	13	14	7	
M4 and M5	62	21	17	14	10	
M6 and other	66	25	17	15	9	
Disease risk group						P=0.483
Standard	95	36	28	19	12	
High	90	33	19	24	14	

Characteristics of Patients

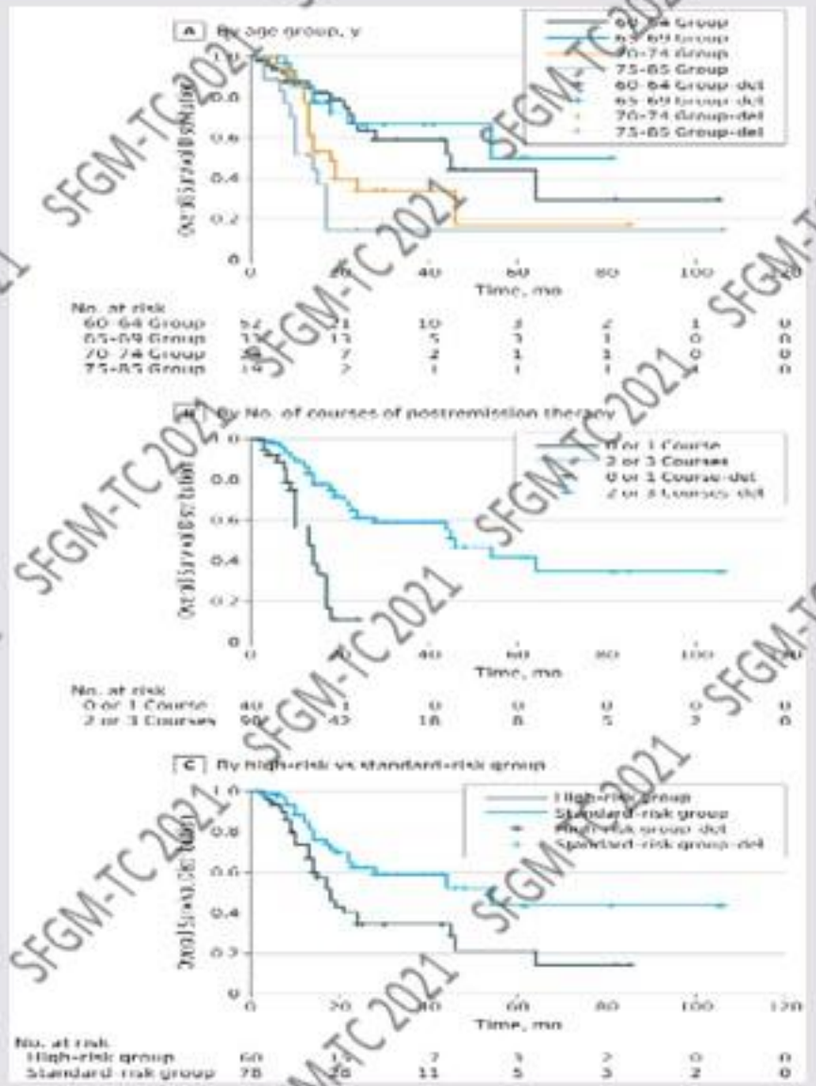
Donor/recipient with HLA mismatched loci						P=0.036
10/10	9	4	3	0	2	
9/10	4	2	1	1	0	
8/10	12	0	5	3	4	
7/10	3	0	1	1	1	
6/10	9	0	5	1	3	
5/10	133	55	31	34	13	
4/10	9	5	0	3	1	
3/10	6	3	1	0	2	
Donor selection						P=0.816
Related donor	166	62	43	39	22	
Unrelated donor	19	7	4	4	4	

Résultas, *overall survival*

A. The 2-year OS rate was 63.7% in the first age group, which was higher than the rates in the third (34.2%) (P=.02) and fourth (14.8%) (P<.001)groups

B. Patients who received 2 or 3 courses of post remission therapy higher 2-year overall survival, compared with those who received one course or none (61,3% vs 11,1%, p<0,001).

C. Patients in the high-risk group had a lower 2-year overall survival compared with the standard-risk group (34,3 vs 62,3 %).



Results, *Donor Chimerism and Microchimerism*

5/185 (2.7%): full or mixed chimerism.

➔ 2 patients full donor chimerism,

➔ 3 patients mixed chimerism.

Microchimerism emerged on day 2 and reached its peak on days 7 to 10

Till 10 months in 1 patient.

Results, *Graft-vs-Host Disease*

2 patients (1.1%) severe acute GVHD because of high fever, location of rash on the neck, and severe hyperbilirubinemia after neutrophil recovery and transient full donor engraftment

Failed to respond to anti-GVHD treatment and died of multiorgan failure at days 36 and 39, respectively, after MST

ref	Disease	age	Procedure	Donnor	Response rate	PFS	OS	GVH /CRS
Guo Blood 2011	N=58 AML all risk CR after Induction	60-88 With 22 >70 years	Induction + MTX vs induction Than 2 conso with ARAC +MTX vs ARAC alone	NA	80% vs 40% (p=0.006) (pts > 70 ans 92,8% vs 12,5%)	A 2 ans 38,9 vs 10,3%	OS (2 ans) 39,3% vs 10,3%	0%
Guo JCO 2012	N=101 AMLwith int or low risk CR after induction	9-65	2 conso ARAC +MTX	dose max 2,4 x10e8 CD3/kg) Dose CD3 (> 1,1 x10e8/kg) as prognostic response		LFS At 6 years Low risk = 84,4% Int risk =59,2%	OS (6 years) low risk 89,5% int risk 65,2%	0%
Zhao 2015	N=10 DLBCL (2), MCL (1), LLT (3), Burkitt (1), MDH (3)	20-69	Hyper CVAD x 4 +MT (Dexa10 +MT à 36-48 chimio)	5/10 dose CD3 >1,1x10e8 pronostique de la réponse	RC= 6/10 RP=1/10			CRS 58% GVH =0
Hu SCTM 2016	MDS , CMML et sAML	13-79	DECITABINE/ARAC Ou DEC/ARAC/Mitoxantrone + MTX If CR : 3 cycles conso+MTX	0/10 (4) 1-4/10 (12) 5/10 (22) 6-7/10 (5) dont 3 MMURD	MDS : 52,4% LAM : 36,4% (idem pour >60 et <60 ans)		OS (2 years) MDS :84,7% AML : 34,1%	0%
Li Leuk Ly 2017	N=42 (retrosp) LAM CR1	60-74	DAC/IDAC + MTX Vs IDAC			LFS (2years) 51,6% vs 27,1%	At 2 years 55,4 vs 34,2%	CRS 52% vs 3%
Zhu BBMT 2017	N=23 AML (phase 2)	60-87	DCAG +MTX x 1 to 8 cycle (continue if > PR on C2)	6/10 (n=2), 5/10 (n=12), <5/10 (9) âge 40 (26-46)	81,8% 80% in high risk	FUP 17 mo PFS med 13 month At 1 y : 46% At 2 y : 40%	OS med 17 mth At 1 y 56,5 At 2 y 34,8	0%
Guo JAMA 2018	N=185 AML	60-85 (4 groupes of age)	Induction +MTX than conso 1 et 2 +MTX	NA	74,6% (66,7% high risk 82% standard risk)	LFS 1 y 64,9-21,7% LFS 2 y 51%-14,5%	OS (1y) 79,9% (87-51%) OS (2y) 50,2 %(63,7-14,8%)	1,1% =100% death

Experience Lilloise

- 6 patients depuis 2017:

1 patient jeune en première ligne de LA de RI ➔ 8/10 avec son frère, 3 cures

1 patiente LA en rechute 15 ans post allogreffe 12/12 geno ➔ 5/10 avec son fils, 3 cures

1 patiente SMD acutisée ➔ 5/10 avec son fils, 2 cures

1 patient SMD ➔ 5/10 avec son fils, 1 cure ARC, 1 cure VIDAZA

1 patient LA de HR en Rechute ➔ 5/10 avec son fils, 2 cures

1 patient en rechute 2 ans post allogreffe 9/10 ➔ 5/10 avec son fils, en cours

Premiers résultats

- CRS 3/6, Pas de GVH
- Chimerisme: 1 patient 18% à J7
- Survie globale à 2 ans: 40%
- Nombre de patients trop faible pour conclure, population très hétérogène.