Surcharge en fer post transfusionnelle (syndrome myélodysplasiques) Traitements chélateurs du fer

C ROSE
Hôpital Saint Vincent de Paul
Université Catholique de Lille

Conflits d’ intérêts

- **Honoraires Board scientifiques : Celegene , Novartis, Genzyme-Sanofi**
- **Invitation congrès : Novartis**

Physiopathologie

Fe essentiel

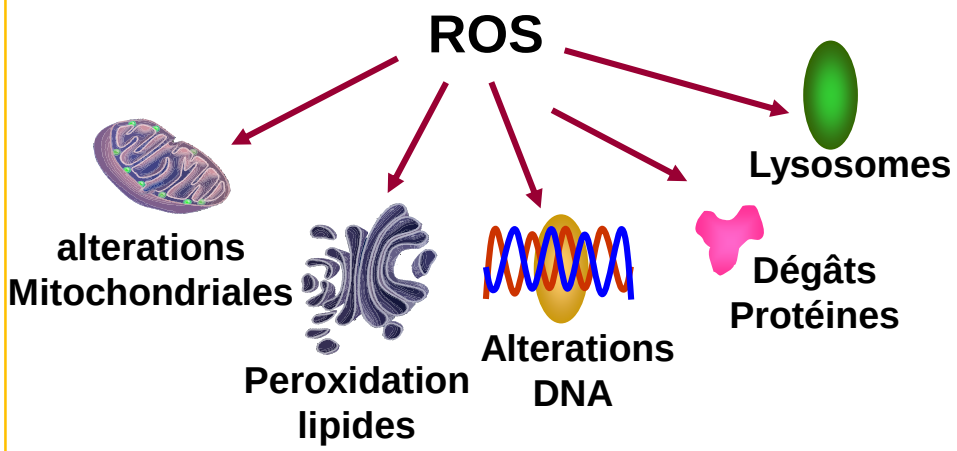
- O_2transport et échange
  - hemoglobine and myoglobin
- Chaine Respiratoire
  - complexe I and III
- Voies de Synthèse
  - hème
  - Fe/S cluster assemblage
- Reparation et synthèse DNA
  - ribonucleotide reductase
  - endonuclease III
- Croissance cellulaire et prolifération

Fer Toxique

- transfert electrons
- Production de radicaux libres

Fenton reaction:

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + \cdot OH$$

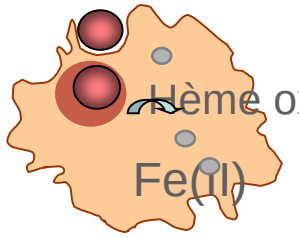


Physiopathologie surcharge post transfusionnelle

- 1 CE ou CGR (175ml, hte 65%) : 150 à 200 mg fer
- >20 CE saturation du système réticulo-endothélial

Transfusions

1 CE = 150- 200mg de fer

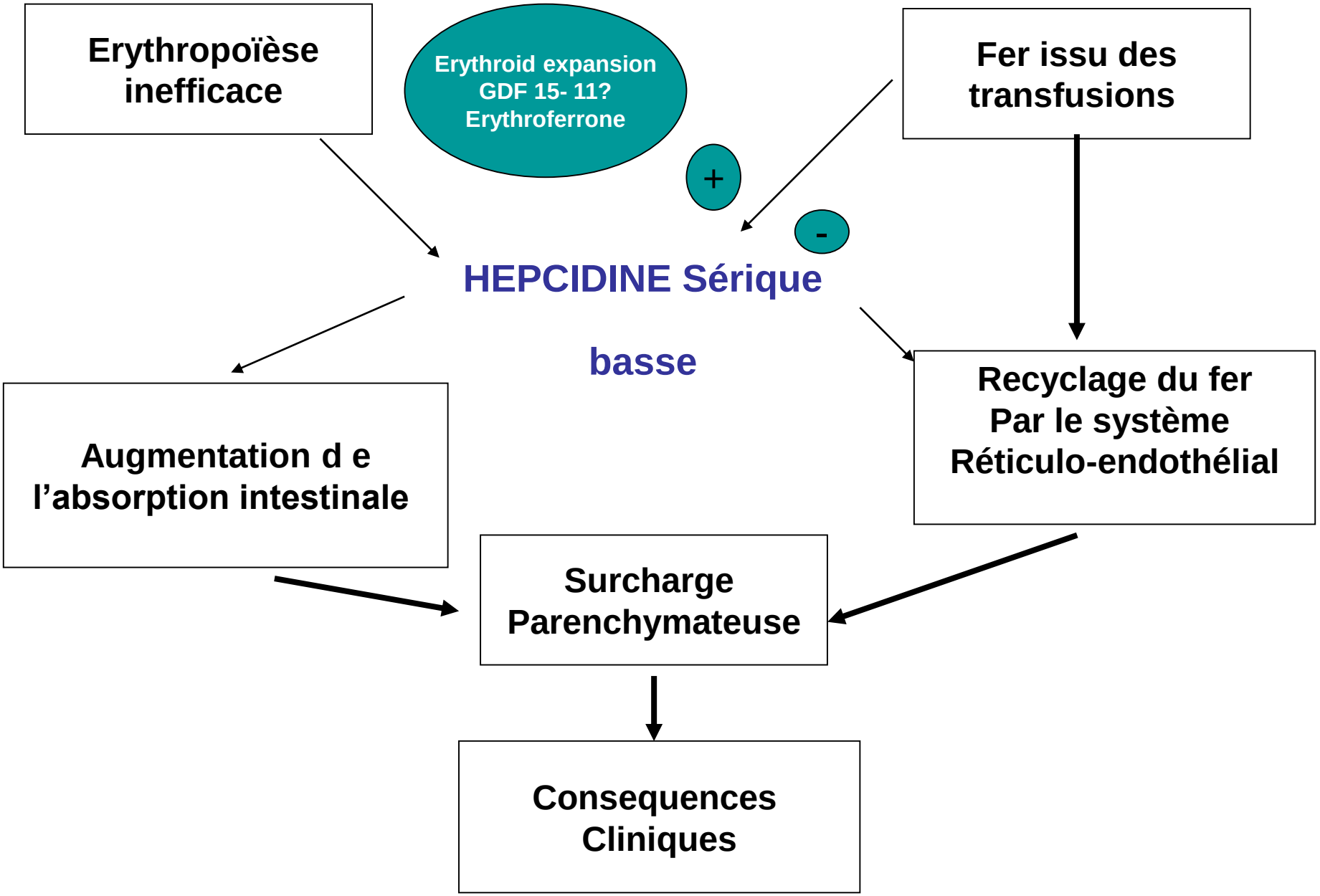


Surcharge en fer macrophagique

9% des patients transfuses ont reçu plus de 20CE

Leo-Kodeli S, 2014 Transf Clin Biol

Physiopathologie surcharge post transfusionnelle



Pathologies impliquées et Impact clinique

Diseases	Dyserythropoiesis Or ineffective E	Incidence (EU)	Clinical Impact
Congenital			
Thalassemia major and Int	++++	++	**major**
Blackfan Diamond D	+	+	+++
Congenital Dyserythropoiesis	++++	+	+++
Congenital sideroblastic anemia	++	+	++
Some cases of SCD, PK deficiency	0 to +	+++	**+ to ?**
Acquired			
Lowrisk Myelodysplastic syndromes	**+ to +++**	+++	**++ to?**
Aplastic anemia	**0**	+	+
Off-therapy leukemia, BMT recipients	**0**	++	**+ to?**

Conséquences : risque de lésions tissulaires

1.
Augmentation de la saturation de la transferrine

2.
Formation de fer libre plasmatique : NTBI, LPI*

3.
Pénétration du fer libre dans les organes
(non régulée)

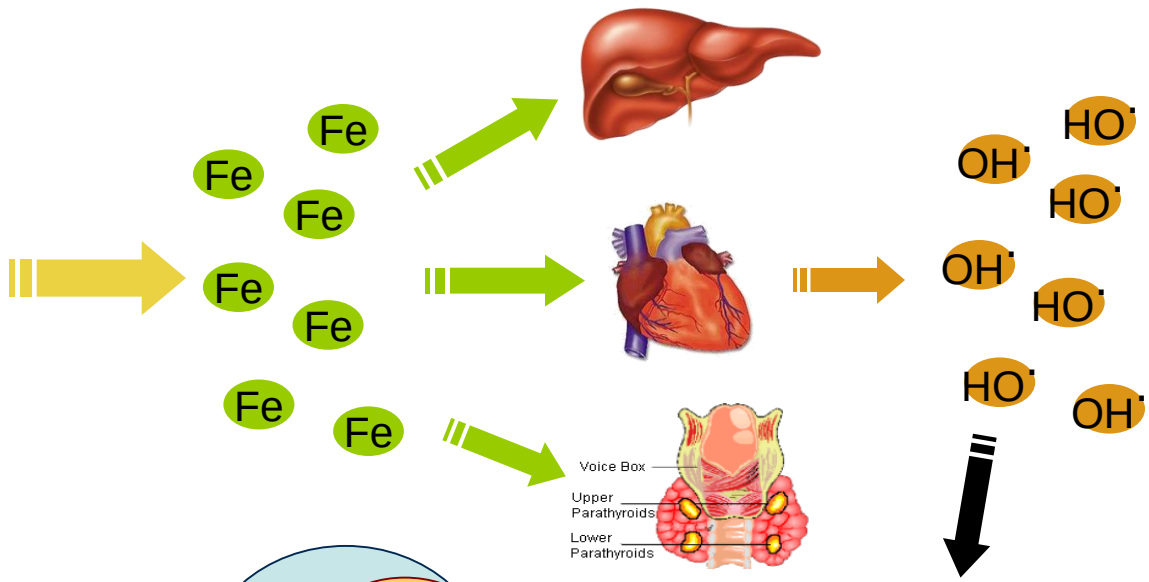
4.
Formation de radicaux libres

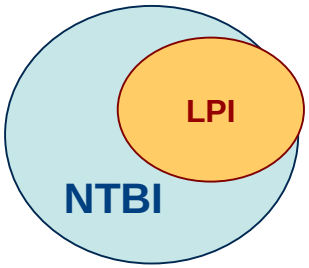
Saturation de la transferrine à l'état basal

100%

30%

Situation de surcharge en fer : saturation > 75%

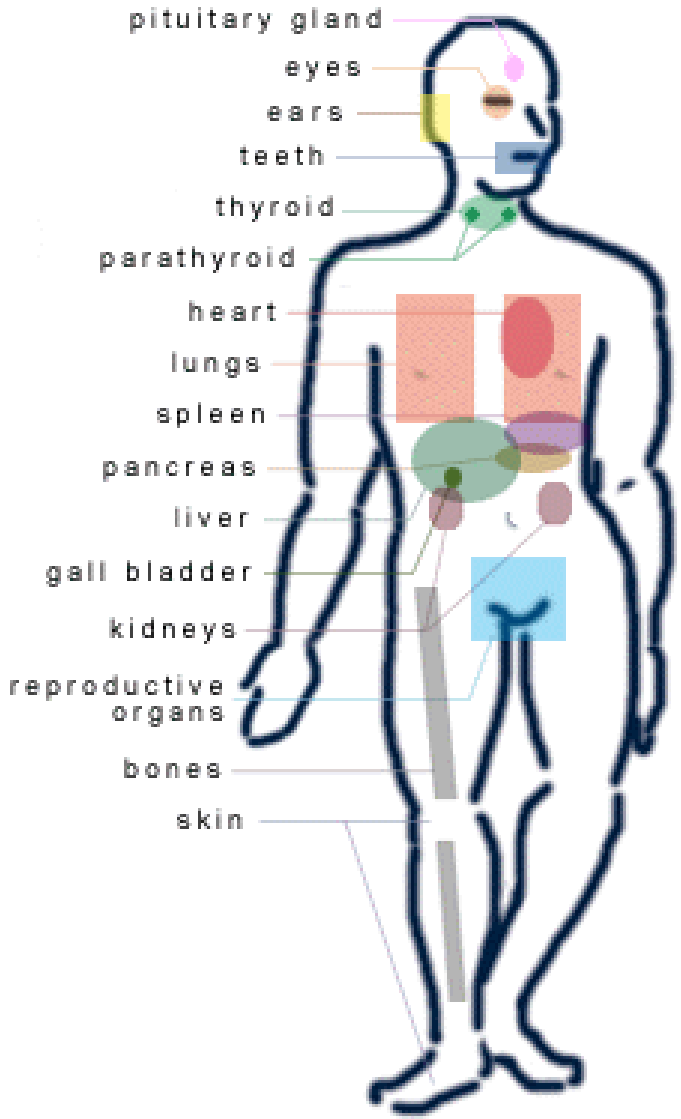




5.
Lésions tissulaires
(fibrose, mort cellulaire)
Foie , coeur , art, gldes endocrines

NTBI = non-transferrin-bound iron
LPI : Labile Plasma Iron

Retentissement organique de la surcharge en fer



Hypophyse → retard de croissance

Coeur → **cardiomyopathie**
insuffisance cardiaque

Foie → cirrhose hépatique

Pancréas → diabète

Gonades → hypogonadisme
infertilité

Un Impact clinique variable selon la Pathologie

- **Dysérythropoièse associée**
- **Nombre de CE transfusés**
- **Durée exposition à la surcharge en fer**
- **Quantité de fer en excès dans l'organisme (CSS , Ferritine ,IRM)**
- **Co morbidités**
- **Sensibilité des cellules au stress oxydatif**

- **Risque liés à pathologie associé**

Pathologies impliquées et Impact clinique

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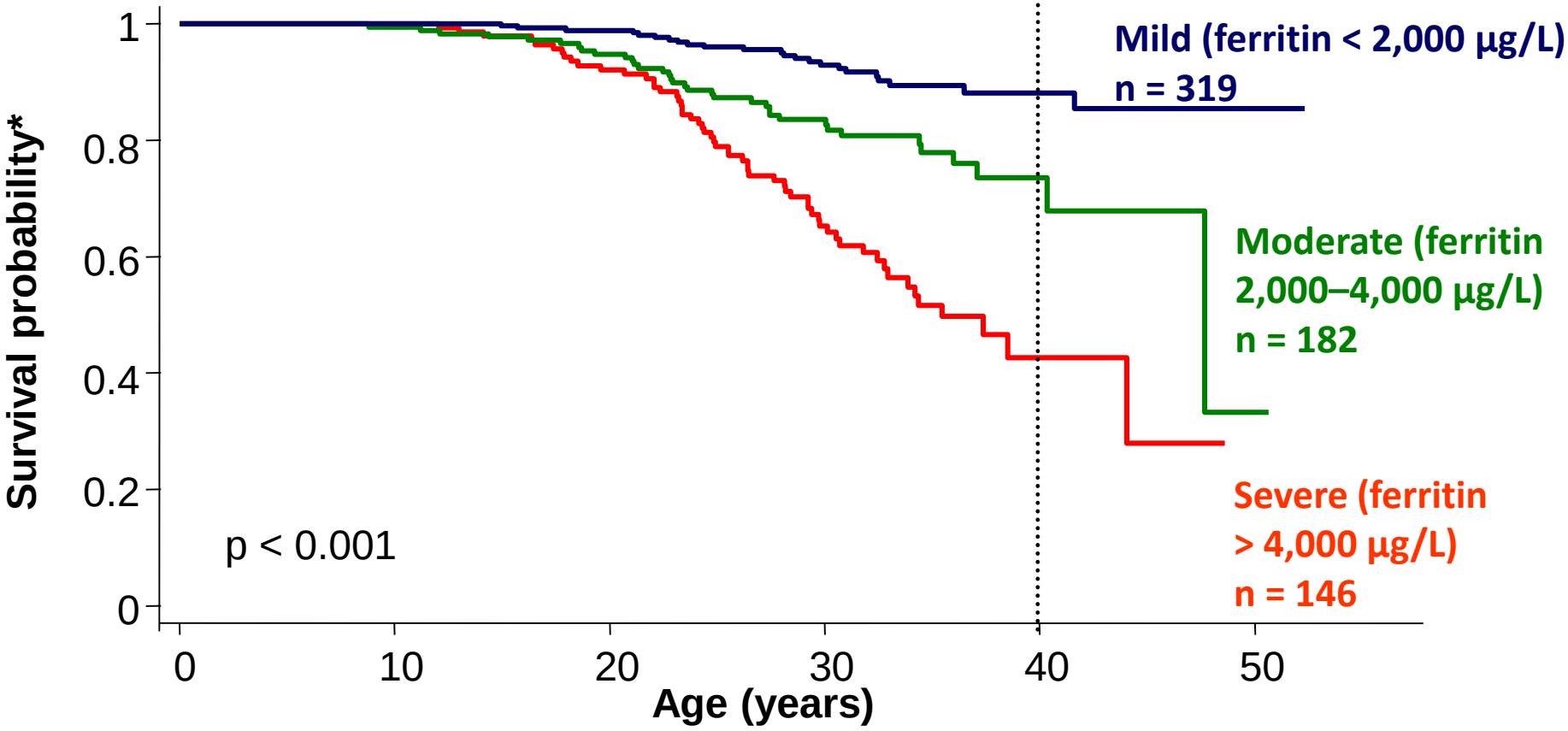
Acquired			
Lowrisk Myelodysplastic syndromes	**+ to +++**	+++	**++ to?**
Aplastic anemia	**0**	+	+
Off-therapy leukemia, BMT recipients	**0**	++	**+ to?**

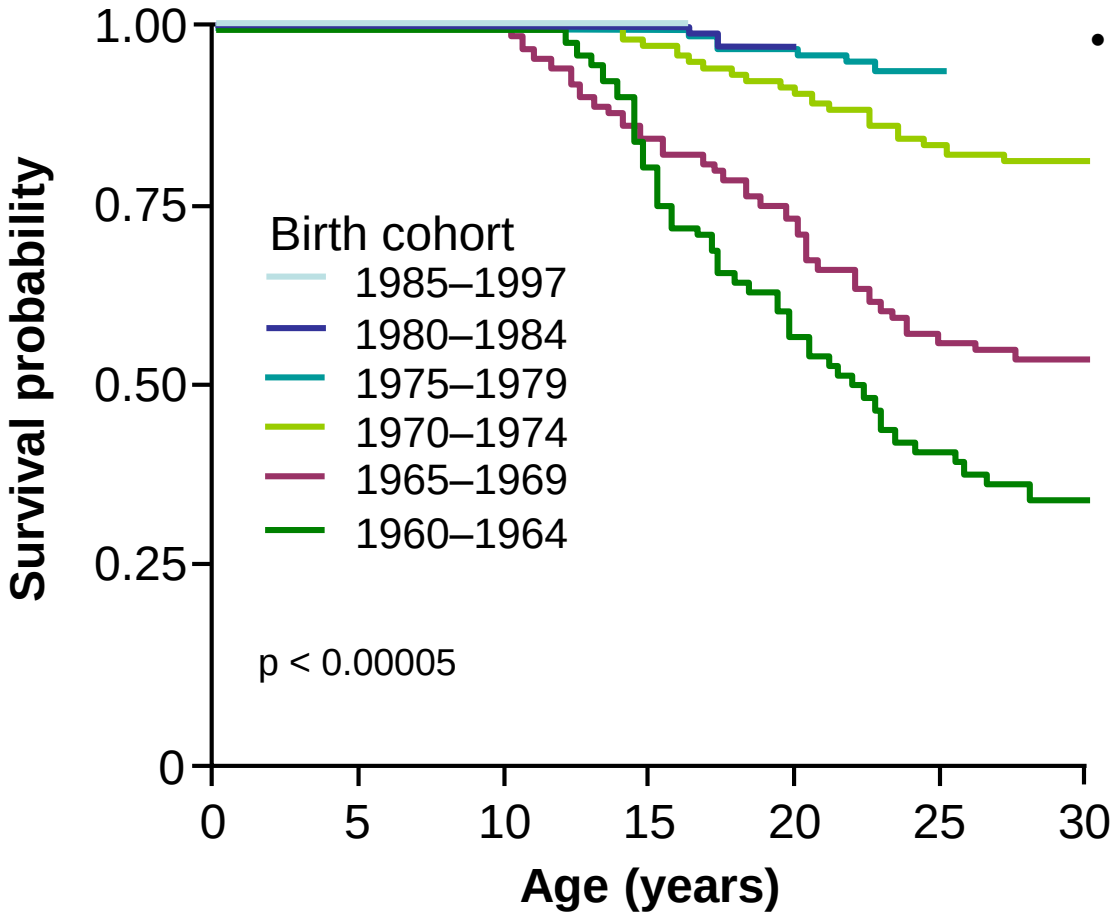
647 β-thalassaemia major patients divided in 3 groups based on last 5 years' mean serum ferritin level



*Estimated using Kaplan-Meier method.

Ladis V, et al. Ann N Y Acad Sci. 2005;1054:445-50.

Complication-free survival of Italian β-thalassaemia major patients



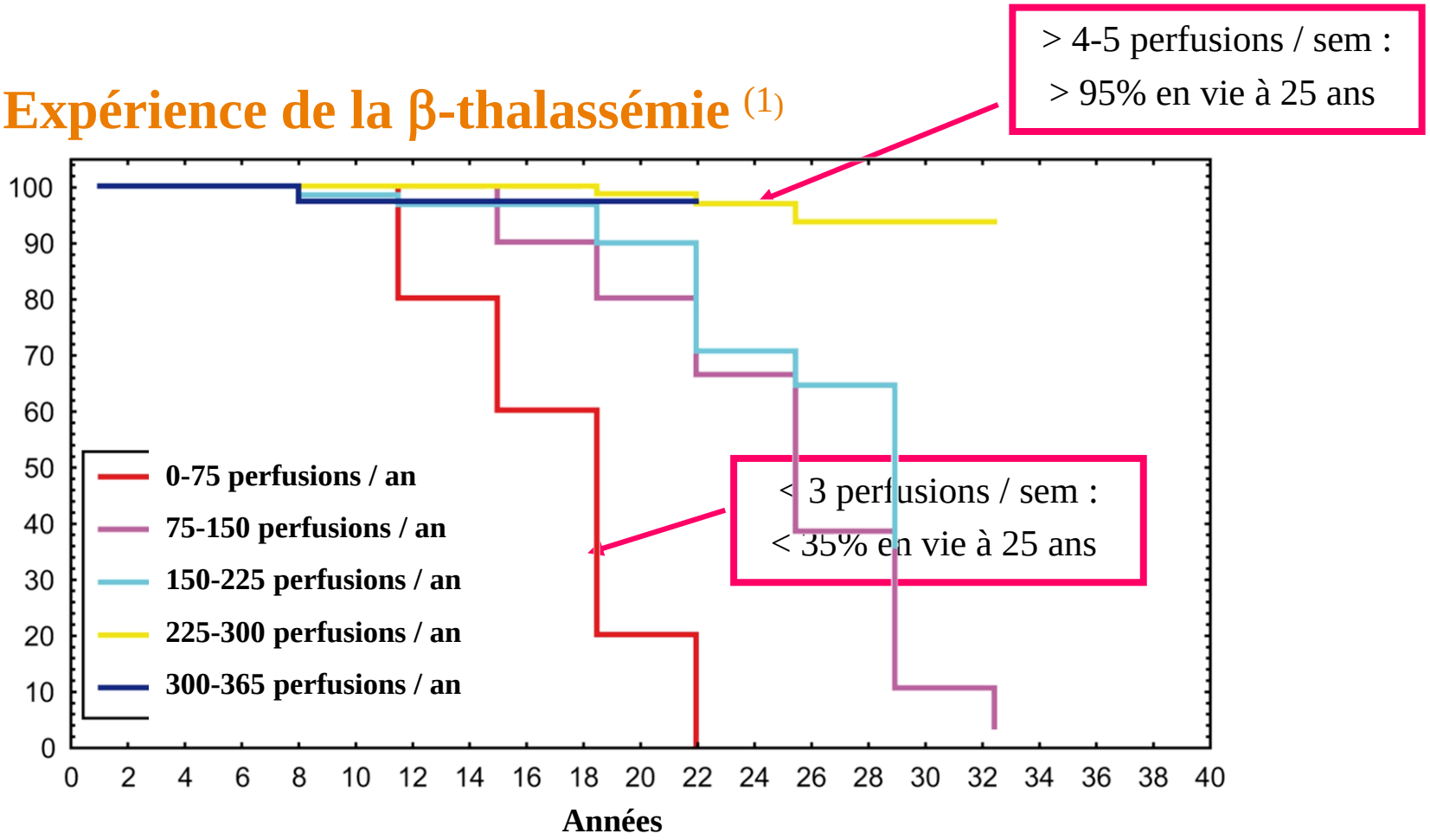
- Risk factors for mortality in β-thalassaemia major include
  - serum ferritin > 2,500 µg/L (HR 3.7)
  - arrhythmia (HR 2.4)
  - male sex (HR 1.9)
  - heart failure (HR 11.3)

HR = hazard ratio.

Borgna-Pignatti C, et al. Haematologica. 2004;89:1187-93.

Observance des patients au traitement chélateur par Desferal® et espérance de vie

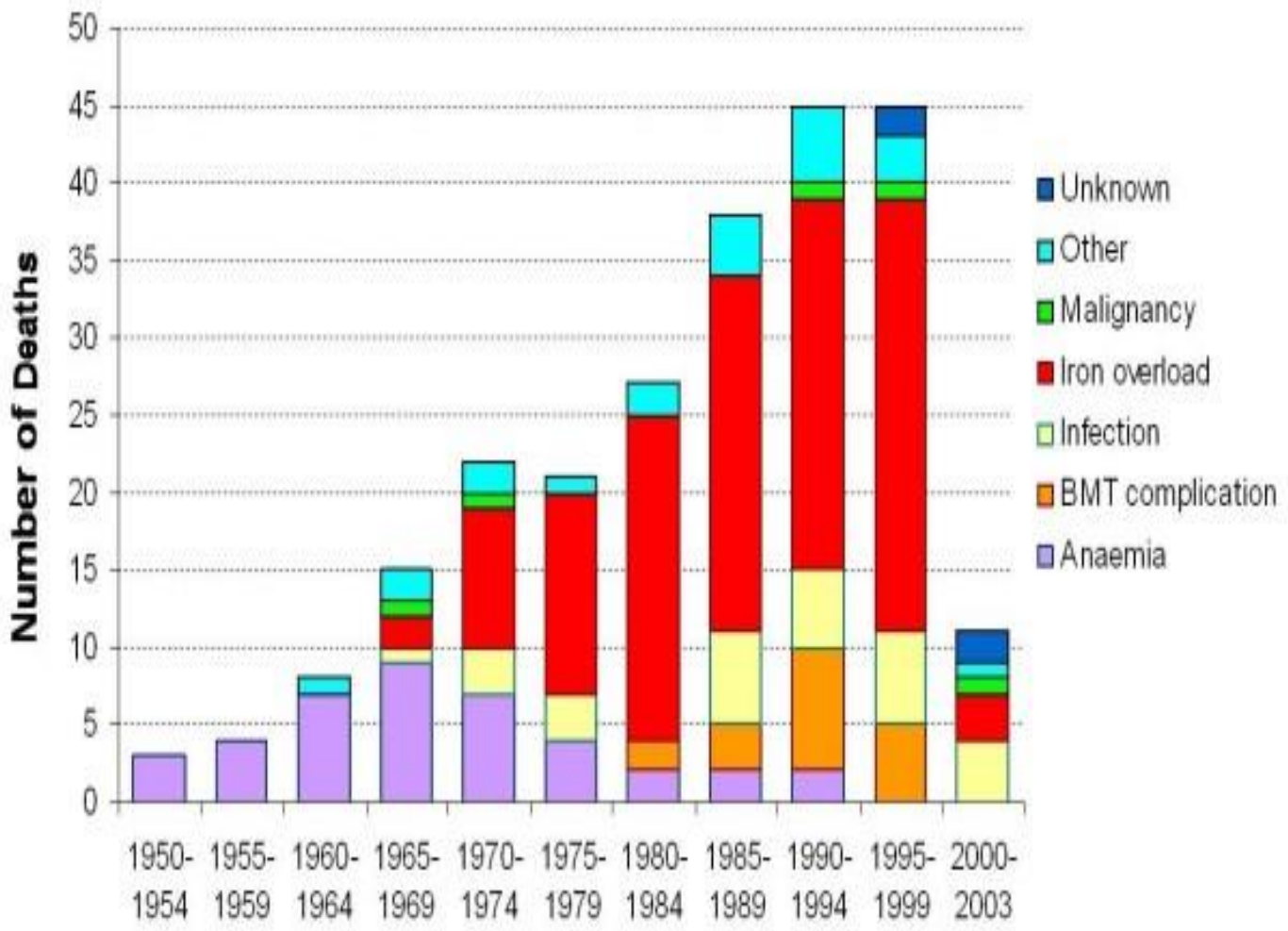
Expérience de la β-thalassémie (1)



Analyse Kaplan-Meier de la survie de 257 patients thalassémiques consécutifs selon leur niveau d'observance au traitement par Desferal SC

Brittenham GH, et al. N Engl J Med. 1994;331:567-73

Number of deaths by thalassemia major in the UK



Modell B, J Cardiovasc Magn Reson. 2008

Atteintes organiques: beta thalassémiques majeurs

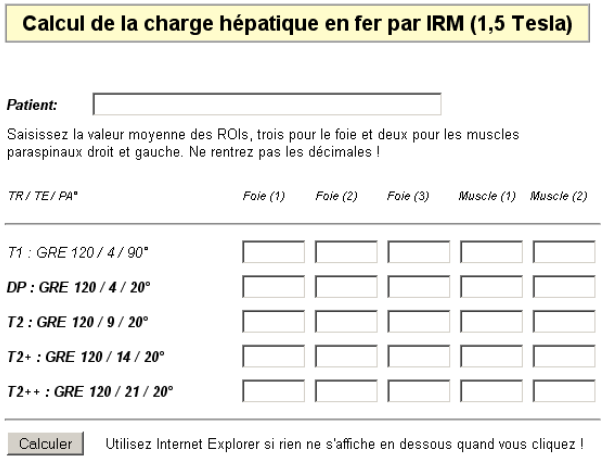
(Données issues du registre français chez les patients thalassémiques actualisées, 2016 I Thuret)

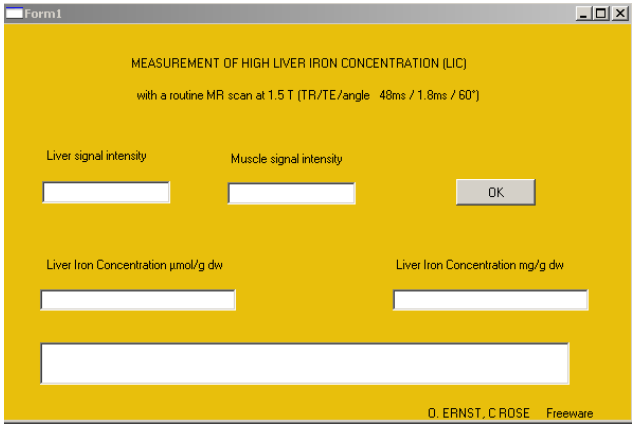
Registre Français	**319 thalassémiques Majeurs Age médian 24 (0,5-61 ans)**
Diabète	9%
Hypothyroïdie	12 %
Insf cardiaque	10%
Arythmie	9%
Hypogonadisme (Pts >13 ou14 ans)	48%
Parentalité (Pts>18 ans)	21% (14% H, 29% F)
Ferritine médiane ng/ml	1050

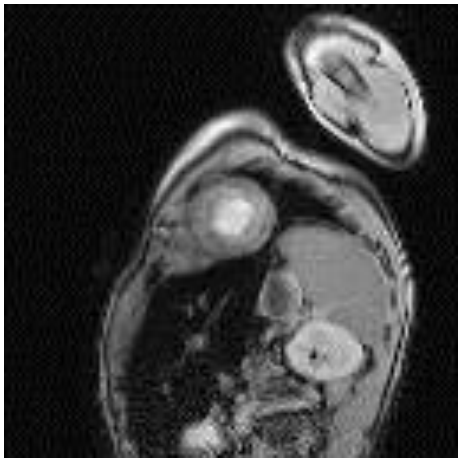
Importance IRM quantitative fer FOIE -COEUR

http://www.radio.univ-rennes1.fr/Sources/FR/HemoCalc15.html

http://oernst.f5lvg.free.fr/liver/iron.html







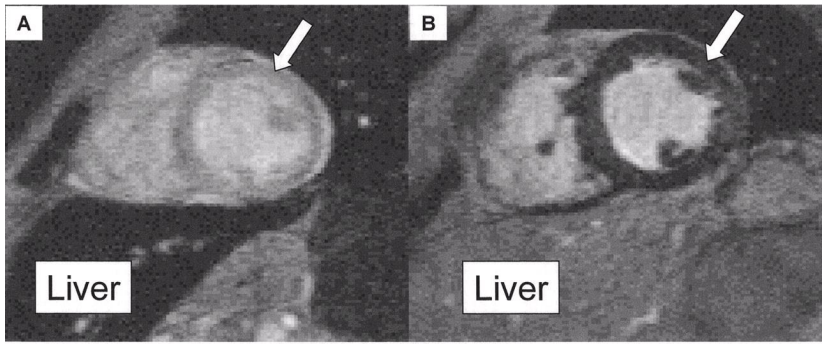
LIC< 300 µmol/g dw

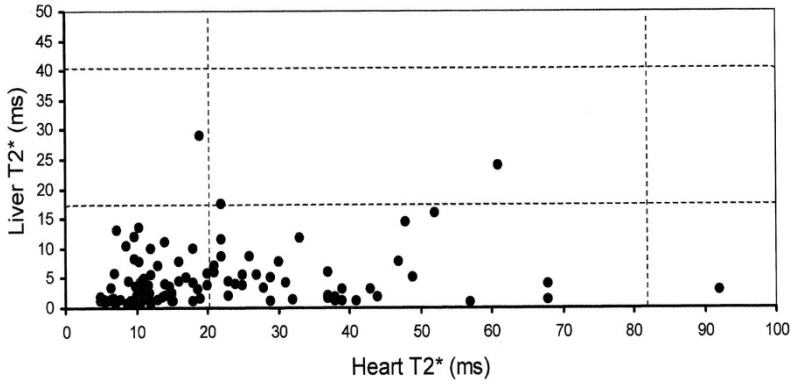
LIC >3OO µmol/g dw up to 800

Cardiac T2*

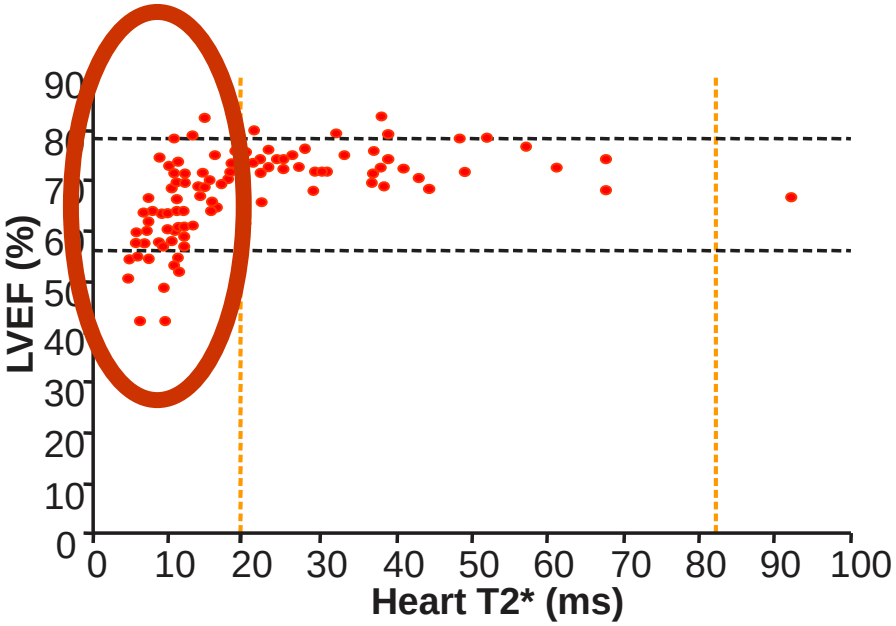
Verlhac, S Diag Interv Imaging 2015
Ernst O Diag Interv Imaging 2013
GandonY Lancet 2004

Cardiac MRI T2*





Pas de correlation entre LIC et T2* cardiaque



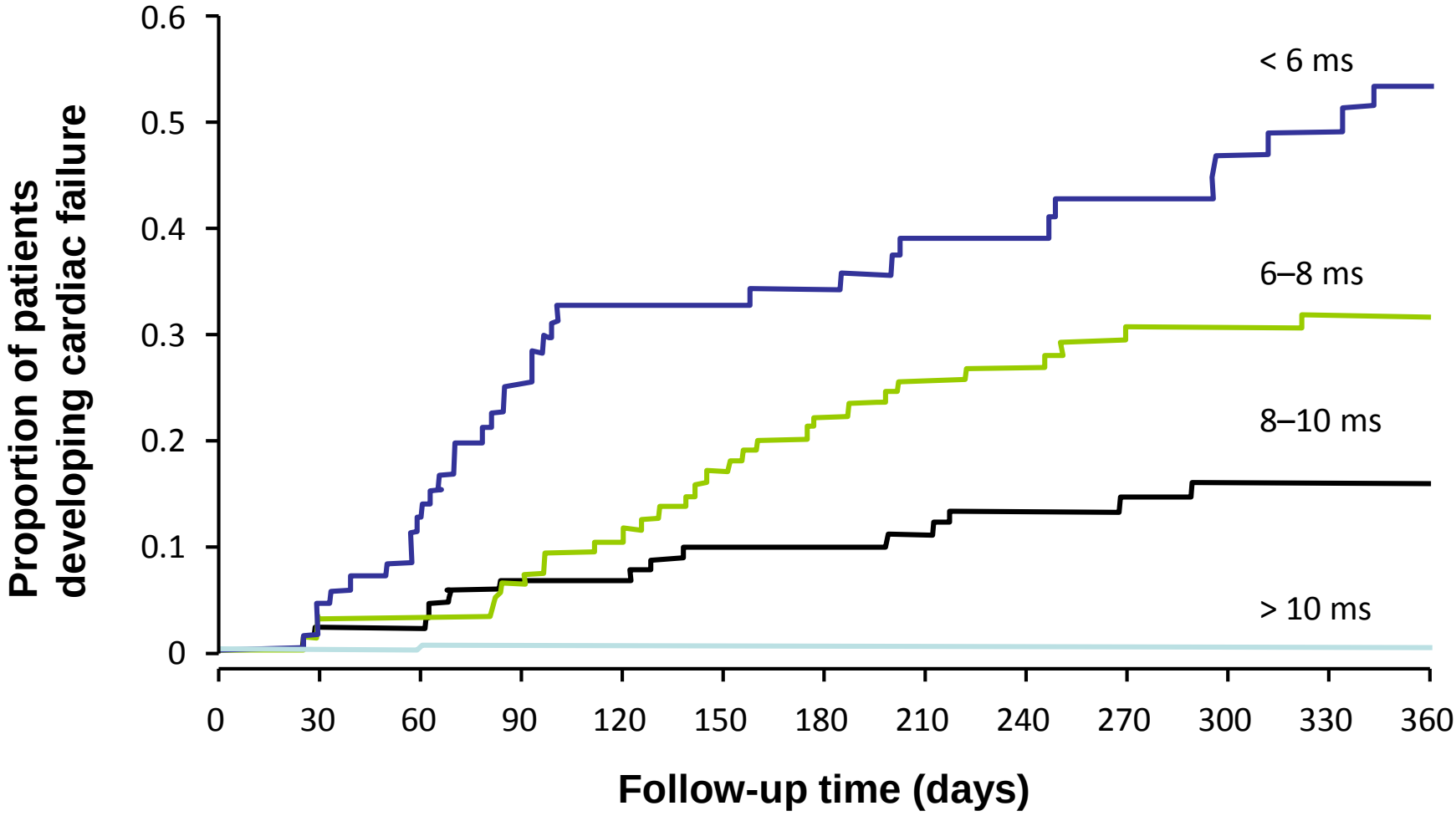
Pour un T2* myocardique < 20 ms, diminution progressive de la FES (r = 0.61, p < 0.0001)

Anderson L *Eur Heart J 2001*

Pennell D *Blood supp 2004*

Tanner M *Haematolgica 2006*

Relationship between cardiac T2* and cardiac failure

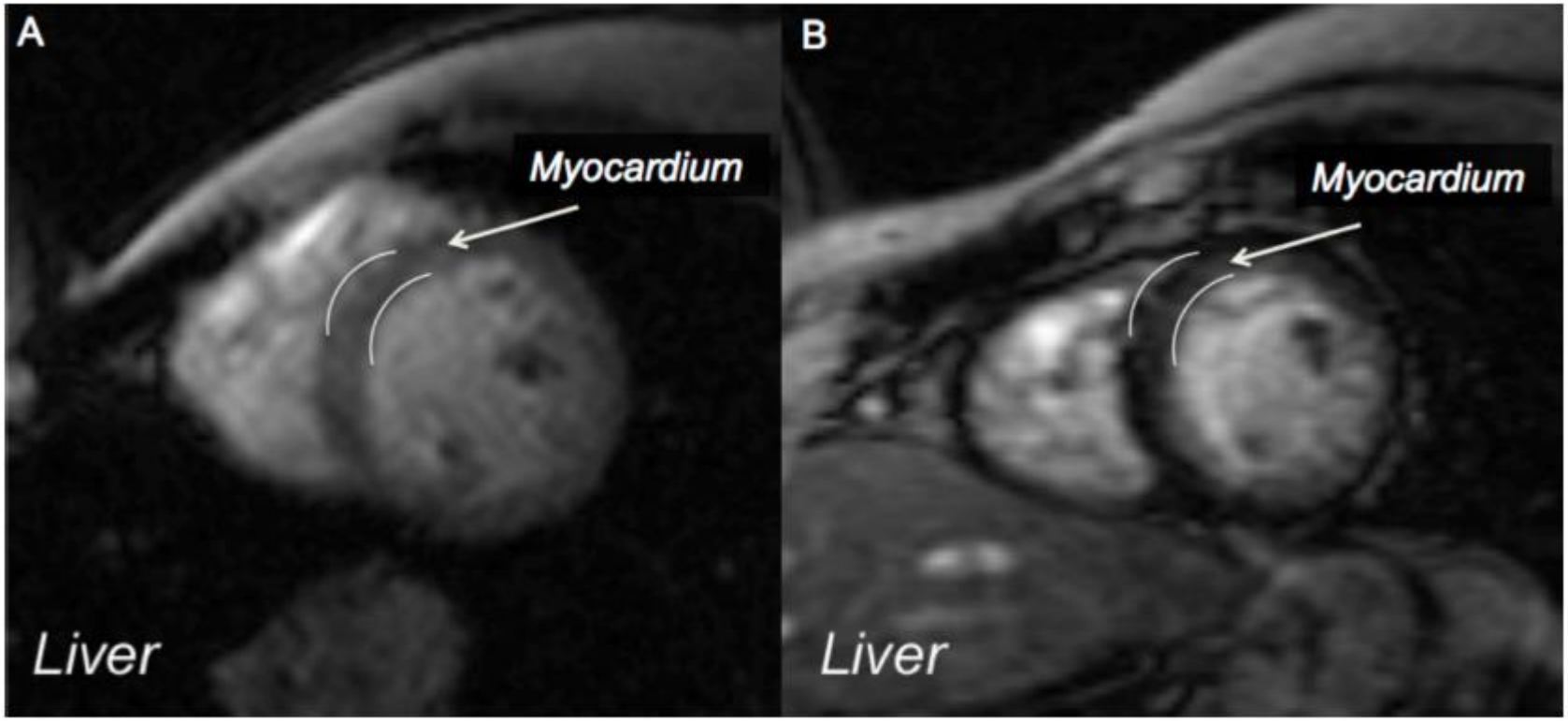


Kirk P, et al. Circulation. 2009;120:1961-8.

Kinetics of iron load differ in heart and liver

1st MRI
high iron in the liver
Low iron in the heart

2nd MRI (after chelation)
Less iron in the liver
But iron in the heart



Coates T, Free Radic Biol Med 2014

PLOS ONE

RESEARCH ARTICLE

Cardiac iron overload in chronically transfused patients with thalassemia, sickle cell anemia, or myelodysplastic syndrome

Mariane de Montalembert[1,2]*, Jean-Antoine Ribeil[3,4], Valentine Brousse[1,2], Agnes Guerci-Bresler[5], Aspasia Stamatoullas[6], Jean-Pierre Vannier[7], Cécile Dumesnil[7], Agnès Lahary[8], Mohamed Touati[9], Krimo Bouabdallah[10], Marina Cavazzana[3,4,11,12], Emmanuelle Chauzit[13], Amandine Baptiste[14], Thibaud Lefebvre[2,15,16], Hervé Puy[2,15,16], Caroline Elie[14], Zoubida Karim[2,15☯], Olivier Ernst[17☯], Christian Rose[18☯]

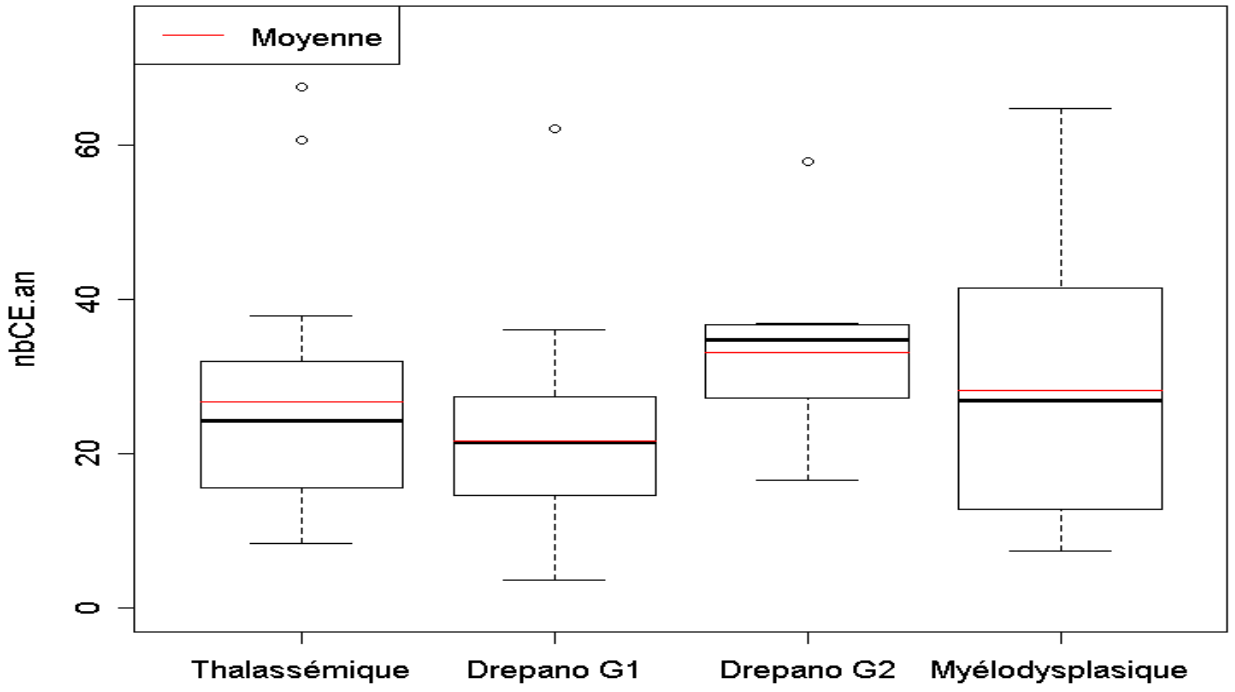
2017, doi: 10.1371

To assess the prevalence of cardiac iron overload defined as T2*<20 ms in patients with thalassemia major, SCA, and MDS

Transfusion and chelation data

	Thalassemia	non-E-SCA[a]	E-SCA[b]	MDS[c]	*P* value
	N = 20	N = 30	N = 11	N = 25	
Age at transfusion initiation (y)	8.5 [0-45]	7 [0-45]	16.5 [1-55]	66 [38-83]	<0.001
Time on chronic transfusion (y)	10 [1-39]]	7 [1-22]	10.5[0-25]	3 [1-10]	<0.001
Number of ECs[d] since diagnosis	359 [21-1360]	139 [24-791]	301 [14-888]	77 [16-544]	<0.001
Number of ECs[d]/y	24 [8-67]	21 [4-62]	35 [17-58]	27 [7-65]	0.09
					non-E-SCA
					vs. E-SCA
					= 0.03
Number of patients given chelation	19 (95%)	27 (90%)	8 (72.7%)	18 (72%)	0.10
Age at chelation initiation (y)	11 [1-48]	9 [2-47]	18 [6-31]	68 [38-84]	<0.001
Ferritin at	1148 [713-2400]	2075 [448	1500 [905-2804]	2398 [482	0.22
chelation initiation	(n = 8)	-3670]	(n = 5)	-5140]	
(ng/mL)		(n = 16)		(n = 12)	

N CE reçus/an



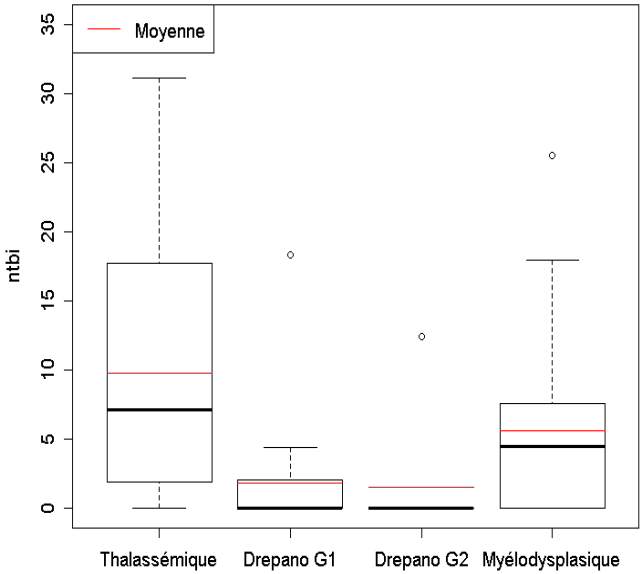
Médiane	24	21.5	34.7	26.9
Extrêmes	8-67.5	3.6-62	16.6-57.9	7.5-64.7

La seule différence significative est entre le groupe des drépanocytaires en échange manuel et ceux en érythraphérèse qui reçoivent plus de CE/an (p=0,03)

Blood iron variables, LIC and T2*

	Thalassemia N = 20	non-E-SCA[a] N = 30	E-SCA[b] N = 11	MDS[c] N = 25	*P* value
N with T2*<20 ms	3 (15%)	0 (0%)	0 (0%)	4 (16%)	0.047
LIC[d] (mg/g dry weight)	10.4 [0.8-20.2]	10.7 [0.8-37.1]	14 [0.8-19.7]	15.2[3.0-45.3]	0.29
Plasma iron	36.9 [31-57]	22.5 [6-45.2]	21 [13-46]	38.2 [11.9-72]	<0.001
(µmoL/L)					
NTBI[e] (µmoL/L)	7.1 [0-31.1]	0 [0-18.3]	0 [0-12.4]	4.45 [0-25.5]	<0.001
Ferritin (ng/mL)	870	2739	2404	1611	0.08
	[169-4339]	[393-5596]	[33-20 030]	[223-6813]	
Hepcidin (ng/mL)	1.35 [0-12.3]	9.95 [0-67.9]	2.10 [0-52.4]	36.35 [3-143.2]	<0.001
Ratio Hepcidin/LIC	0.10 [0-2.40]	1.19 [0-8.48]	0.17 [0-3.11]	2.77 [0.18-	<0.001
Median [range]				19.61]	
Ratio	0.15 [0-0.93]	0.58 [0-4.41]	0.04 [0-0.32]	1.78 [0.23-	<0.001
Hepcidin/Ferritinx10^2				10.22]	
Median [range]					
Deferasirox plasma level <0.5 µg/mL	3/8 (37.5%)	3/10 (30.0%)	3/5 (60.0%)	0/11 (0.0%)	0.03

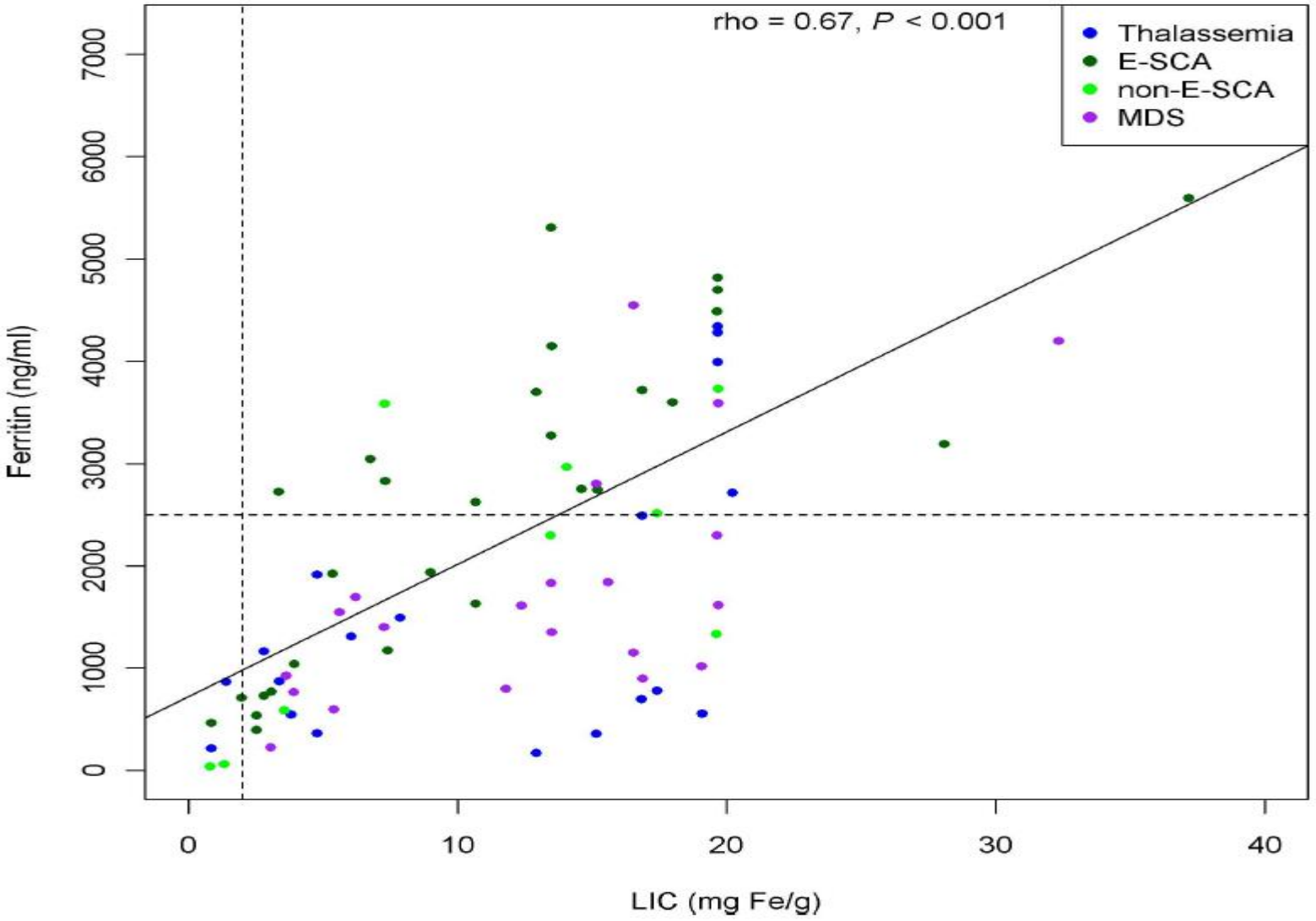
NTBI



Kruskal-Wallis Test global: **p = 0.0005297**
Test Wilcoxon 2 à 2:
Drepano G1 vs Drepano G2: p= NS;
thal vs MDS: NS ; Thal vs Drepano G1: **p= 0.0040** ;
Thal vs Drepano G2: **p= 0.0087** ;MDS vs Drepano G1: **p= 0.0363** ;
MDS vs Drepano G2: **p= 0.0436**

Les pts thalassémiques et MDS ont un NTBI comparable entre eux et très supérieur aux drépanocytaires

Association between ferritin level and LIC



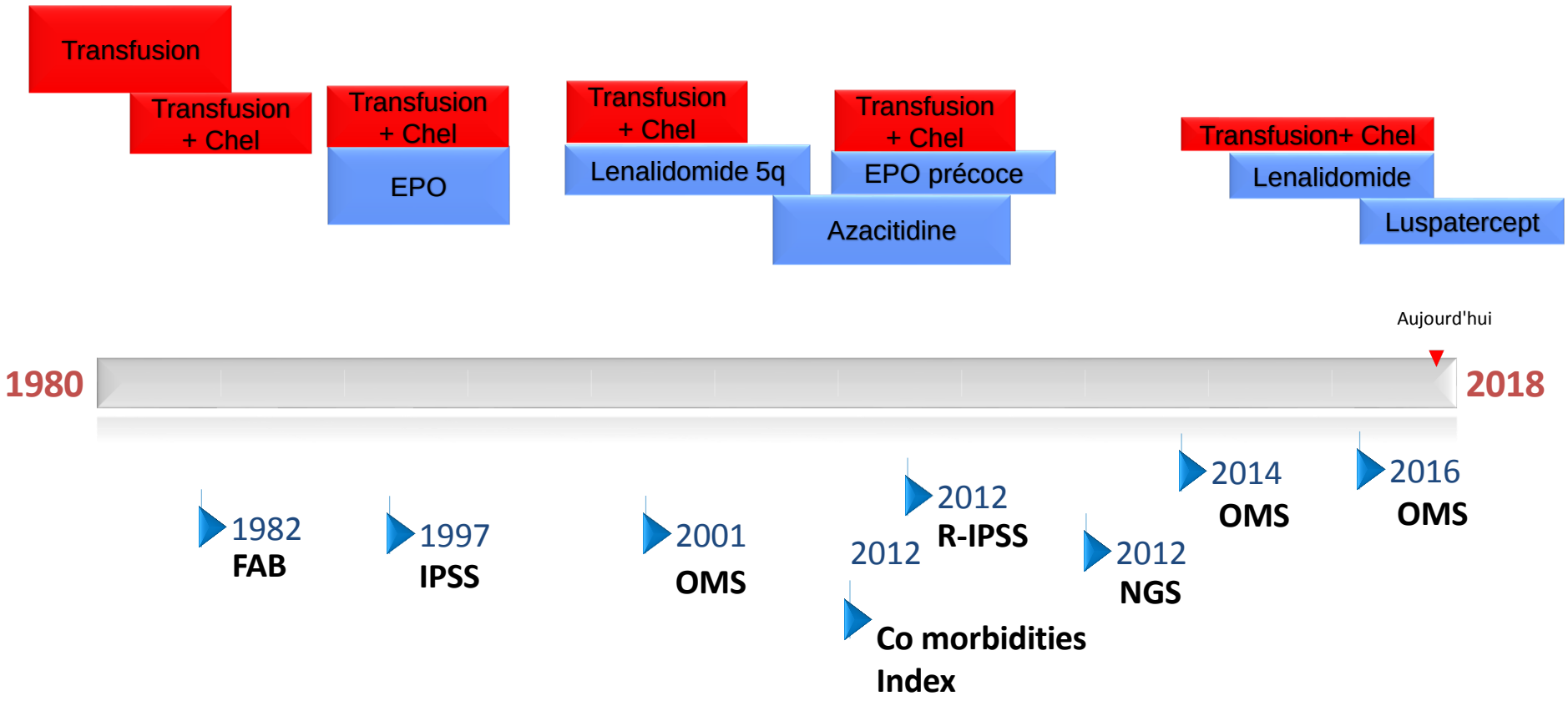
Main observations and conclusions

- ✓ Cardiac iron overload not associated with any of the transfusion or chelation parameters
- ✓ Observation of severe iron overload in SCA patients using erythrocytapheresis
- ✓ Liver in the main target of iron overload in SCA

  Heart is relatevely spared, most probably because of effective erythropoiesis

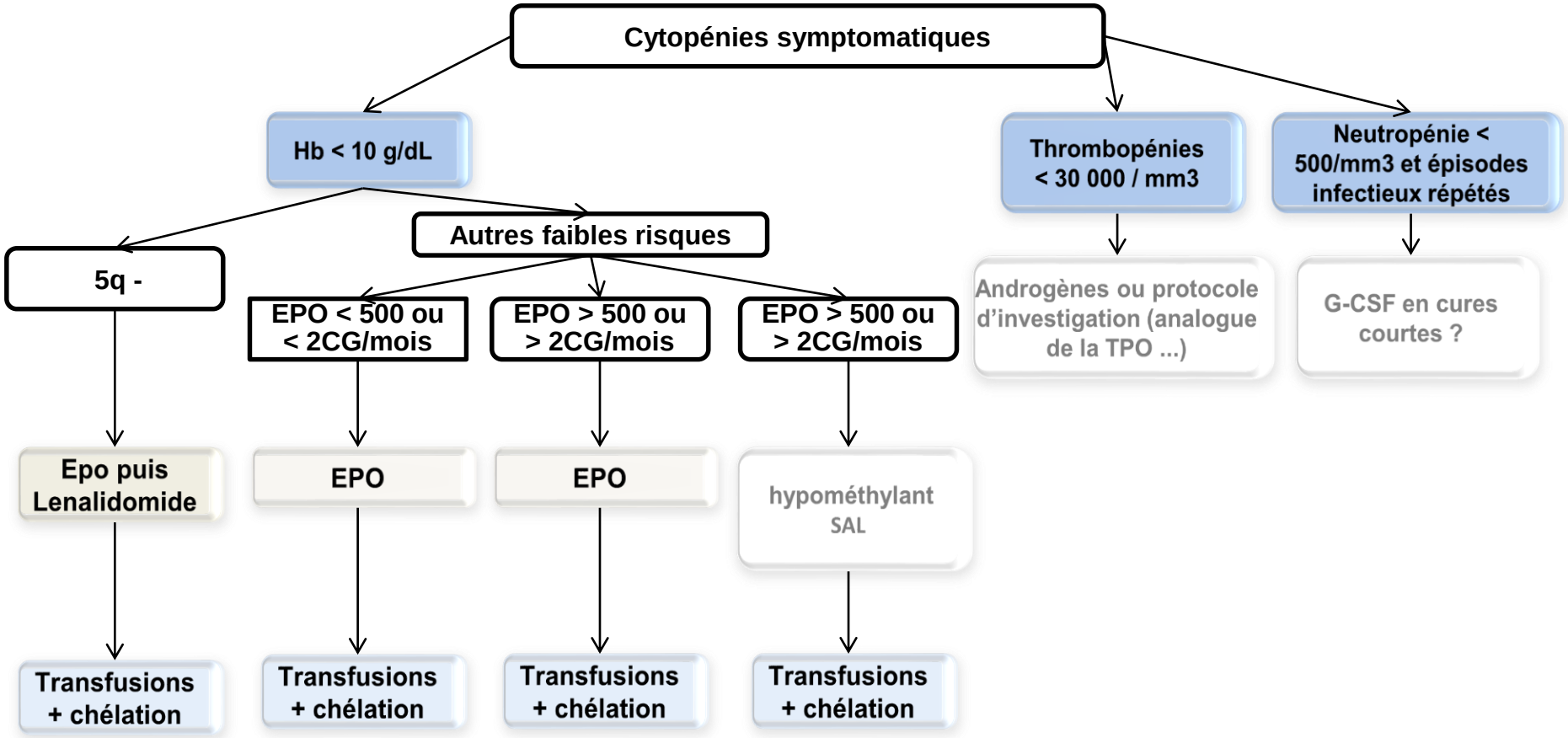
- ✓ In MDS, heterogeneity of the causative diseases and competing influence of abnormal erythropoiesis, inflamation and iron overload produce widely variable results

Syndromes Myélodysplasiques



HAS : Transfusions de globules rouges homologues : produits, indications, alternatives – Nov 2014
http://www.has-sante.fr/portail

Prise en charge des faibles risques



Groupe Francophone des Myélodysplasies

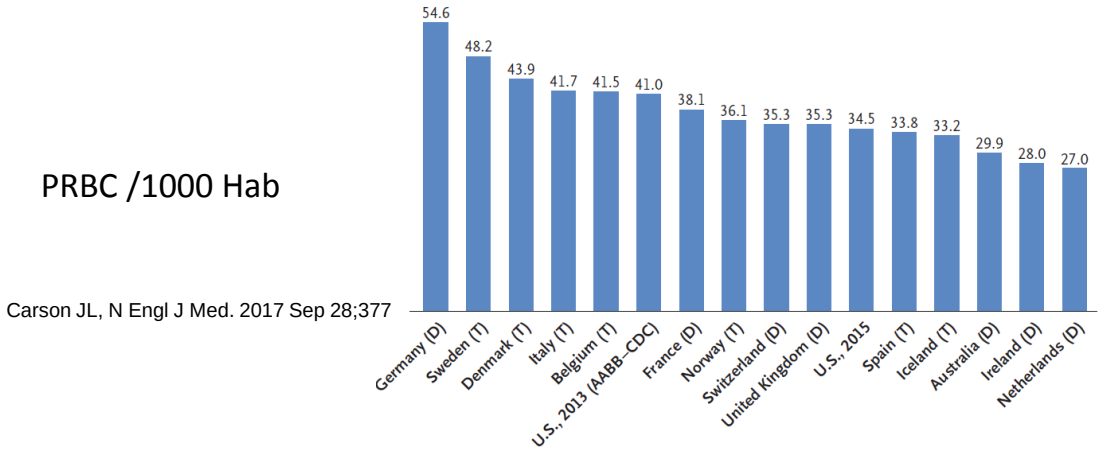
SMD Traitement de l'anémie faible risque

- 60 % répondeurs (Epo sérique < 500 UI/L, besoins transfusionnels limités)
  - pas de sur risque de transformation leucémique
  - études rétrospectives impact + sur la survie
  - Echappement médiane de 17 à 24 mois
- Devenir ; non répondeurs ou en échec EPO , la survie reste prolongée > 5 ans
  - Après EPO , 40 % TT second ligne, 60% transfusions
  - deuxième ligne: lenalidomide +-EPO 27% à 24%

Park S, J Clin Oncol 2017

SMD seuil transfu
Modalités transfusionnelles

- **Modalités transfusionnelles peu précises, HAS (entre 8 et 10 g/dl selon co morbidités)**
- organisation des hôpitaux de jour (places disponibles , report fréquent, chimiothérapie, transfusion de plaquettes)
- 110 hématologistes autrichiens 92% déclarent vouloir transfuser les patients atteints de SMD en dessous de 8g/dl
- Aucune étude dans la littérature , étude REDDS
- différences notables selon les pays (toutes indic confondues)

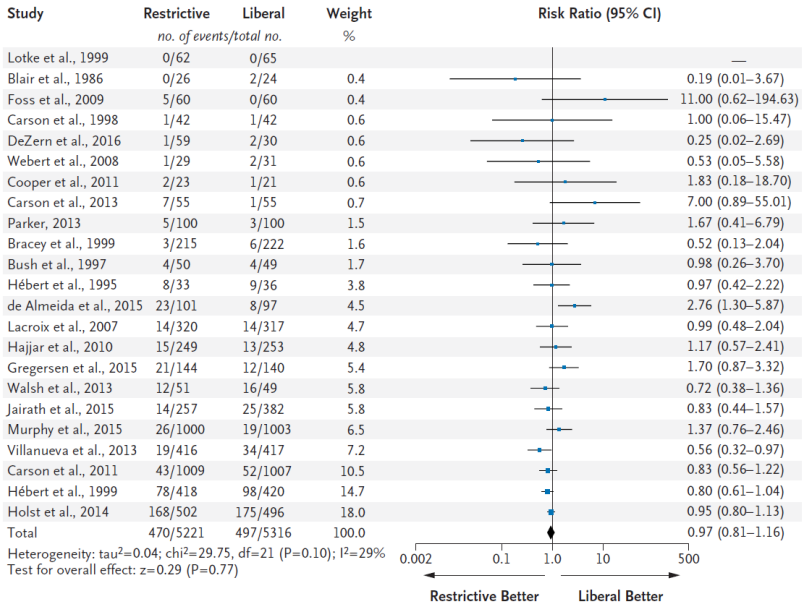


Carson JL, N Engl J Med. 2017 Sep 28;377

HAS : Transfusions de globules rouges homologues : produits, indications, alternatives – Nov 2014
http://www.has-sante.fr/portail

Seuil transfu :restrictif versus libéral hors SMD

- **Population gériatrique et <u>générale et anémie aigue</u> ; recommandation : régime transfusionnel <u>restrictif</u> (seuil 7g/dl)**



Study	Restrictive	Liberal	Weight	Risk Ratio (95% CI)
	no. of events/total no.		%	
Lotke et al., 1999	0/62	0/65		—
Blair et al., 1986	0/26	2/24	0.4	0.19 (0.01–3.67)
Foss et al., 2009	5/60	0/60	0.4	11.00 (0.62–194.63)
Carson et al., 1998	1/42	1/42	0.6	1.00 (0.06–15.47)
DeZern et al., 2016	1/59	2/30	0.6	0.25 (0.02–2.69)
Webert et al., 2008	1/29	2/31	0.6	0.53 (0.05–5.58)
Cooper et al., 2011	2/23	1/21	0.6	1.83 (0.18–18.70)
Carson et al., 2013	7/55	1/55	0.7	7.00 (0.89–55.01)
Parker, 2013	5/100	3/100	1.5	1.67 (0.41–6.79)
Bracey et al., 1999	3/215	6/222	1.6	0.52 (0.13–2.04)
Bush et al., 1997	4/50	4/49	1.7	0.98 (0.26–3.70)
Hébert et al., 1995	8/33	9/36	3.8	0.97 (0.42–2.22)
de Almeida et al., 2015	23/101	8/97	4.5	2.76 (1.30–5.87)
Lacroix et al., 2007	14/320	14/317	4.7	0.99 (0.48–2.04)
Hajjar et al., 2010	15/249	13/253	4.8	1.17 (0.57–2.41)
Gregersen et al., 2015	21/144	12/140	5.4	1.70 (0.87–3.32)
Walsh et al., 2013	12/51	16/49	5.8	0.72 (0.38–1.36)
Jairath et al., 2015	14/257	25/382	5.8	0.83 (0.44–1.57)
Murphy et al., 2015	26/1000	19/1003	6.5	1.37 (0.76–2.46)
Villanueva et al., 2013	19/416	34/417	7.2	0.56 (0.32–0.97)
Carson et al., 2011	43/1009	52/1007	10.5	0.83 (0.56–1.22)
Hébert et al., 1999	78/418	98/420	14.7	0.80 (0.61–1.04)
Holst et al., 2014	168/502	175/496	18.0	0.95 (0.80–1.13)
Total	470/5221	497/5316	100.0	0.97 (0.81–1.16)

Heterogeneity: tau^2=0.04; chi^2=29.75, df=21 (P=0.10); I^2=29%
Test for overall effect: z=0.29 (P=0.77)

Figure 1. Clinical Trials Comparing the Effect of Restrictive versus Liberal Transfusion on 30-Day Mortality.

Carson JL, N Engl J Med. 2017 Sep 28;377

ANEMIE pronostic

Anémie hospitalisés , mortalité , sujets âgés

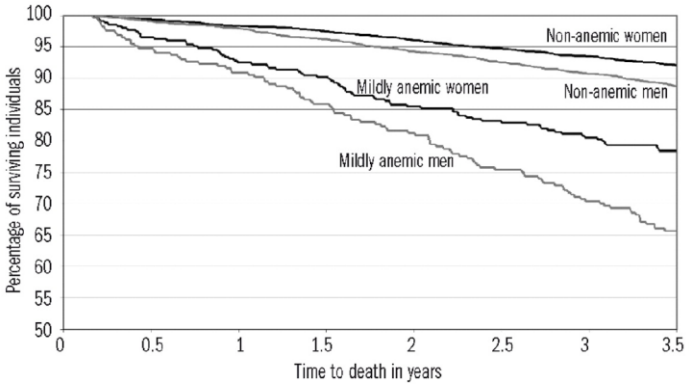
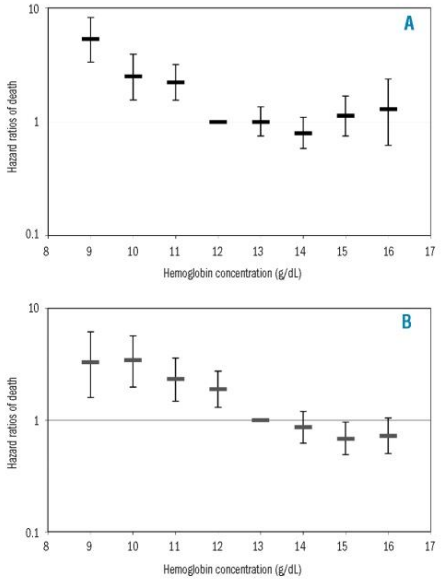


Figure 3. Time to death by sex and mild anemia status in the Health and Anemia population-based study (2003-2007). Kaplan-Meier curves for individuals aged 65-84 years (n = 7,406) from 60 days to 3.5 years after blood sampling. Mild anemia was defined as a hemoglobin concentration between 10.0 and 11.9 g/dL in women and between 10.0 and 12.9 g/dL in men.

Haematologica 2009 94-22-28

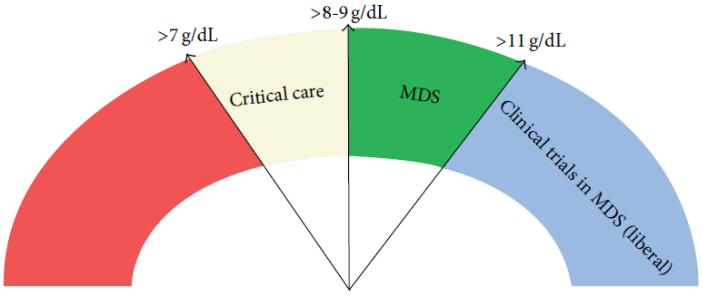


Chaves , J Am Geriatr Soc. 2004

SMD : qualité de vie et performance physique

- **Anémie : pronostic péjoratif; IPSS RIPSS**
  - **maladie clonale plus grave et/ou retentissement de l'anémie ?**
- **Population générale: impact négatif sur la survie et survie (cause ou conséquence)**
  - **Mécanismes; hypoxie , fragilité**
  - **Augmentation des Décès de cause cardiaque SMD transfusion dépendants**

- **Qualité de vie et anémie**
- **Expérience au cours des SMD avec les EPO**
  - **un impact positif : qualité de vie , performance physique**



Abel GA, (QUALMS). Haematologica. 2016
Kelaidi C, Ann Hematol. 2013

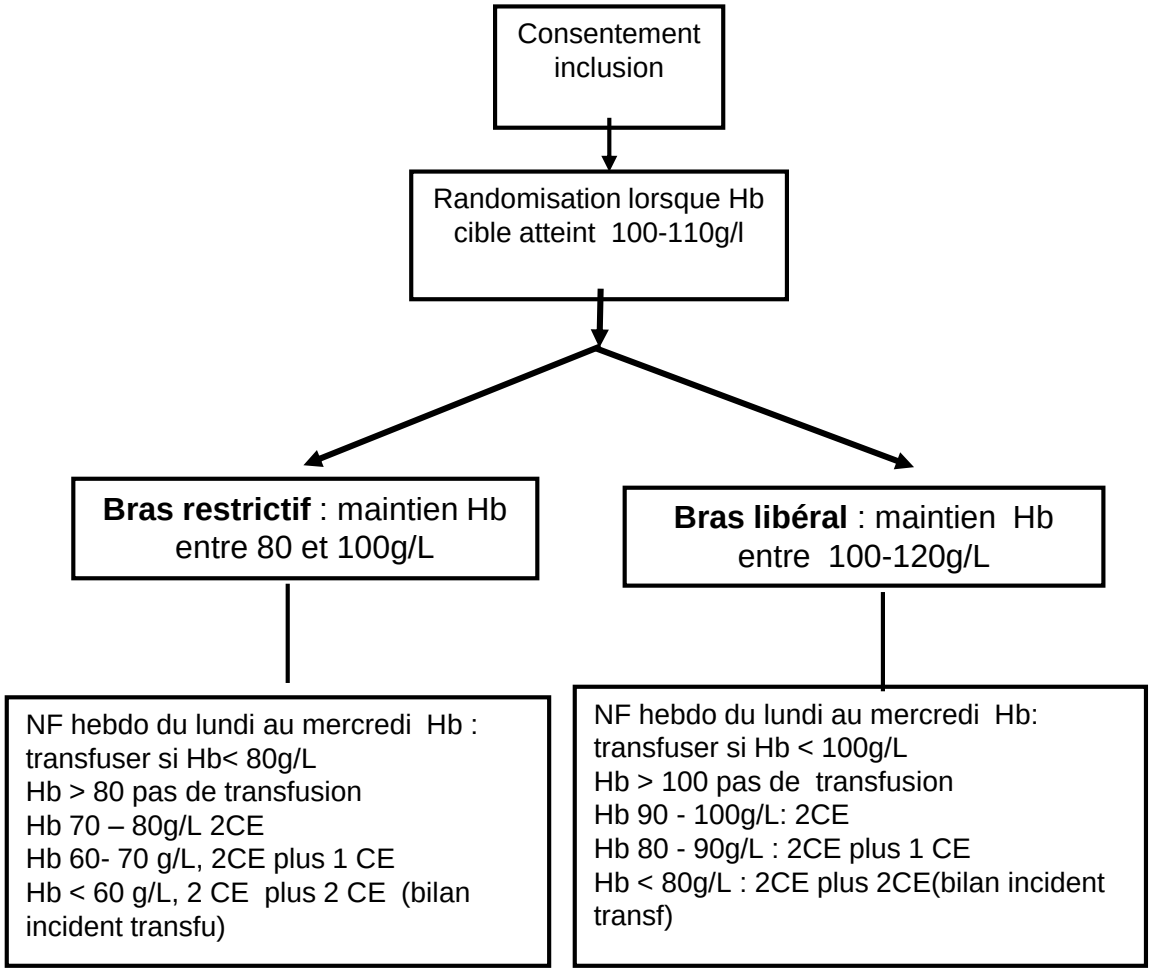
Groupe Francophone des Myélodysplasies

Protocole SMD Transfu

TITRE	**SMD TRANSFU - SMD faibles risques multi transfusés : étude randomisée multicentrique comparant un régime transfusionnel libéral versus restrictif**
POPULATION	**SMD faibles risques selon l'IPSS multi transfusés après échec ou réfractaire au traitement (Epo et ou autres traitements)**

Groupe Francophone des Myélodysplasies

Protocole SMD Transfu



Protocole SMD Transfu

OBJECTIF PRINCIPAL	Comparer l'impact de ces 2 stratégies transfusionnelles sur la **qualité de vie** des patients à moyen terme.
OBJECTIFS SECONDAIRES	1) Comparer l'impact de ces 2 stratégies transfusionnelles sur : a. **la qualité de vie** des patients à long terme b. la **performance physique** des patients 1) Comparer la survenue de complications transfusionnelles 2) Comparer les couts des 2 approches
CRITÈRE DE JUGEMENT PRINCIPAL	Echelle de qualité de vie **Qualms** (Quality of Life in Myelodysplasia Scale) à 6 mois post-randomisation. (évaluation a 3 , 6 , 12 ,18 24 mois
CRITÈRES DE JUGEMENT SECONDAIRES	1) a. Evolution de l'échelle de qualité de vie Qualms sur les 3 ans de suivi b. Evolution du temps requis au **Timed up and go test** à 6 mois post-randomisation et sur les 3 ans de suivi 2) Taux d'incidents transfusionnels parmi : - allo immunisation - hospitalisation pour surcharge pulmonaire - surcharge en fer (ferritine, CSS) 3) Cout des transfusions (nombre de concentrés érythrocytaires (CE) utilisés)

Use of red Cells : NHS ; North UK

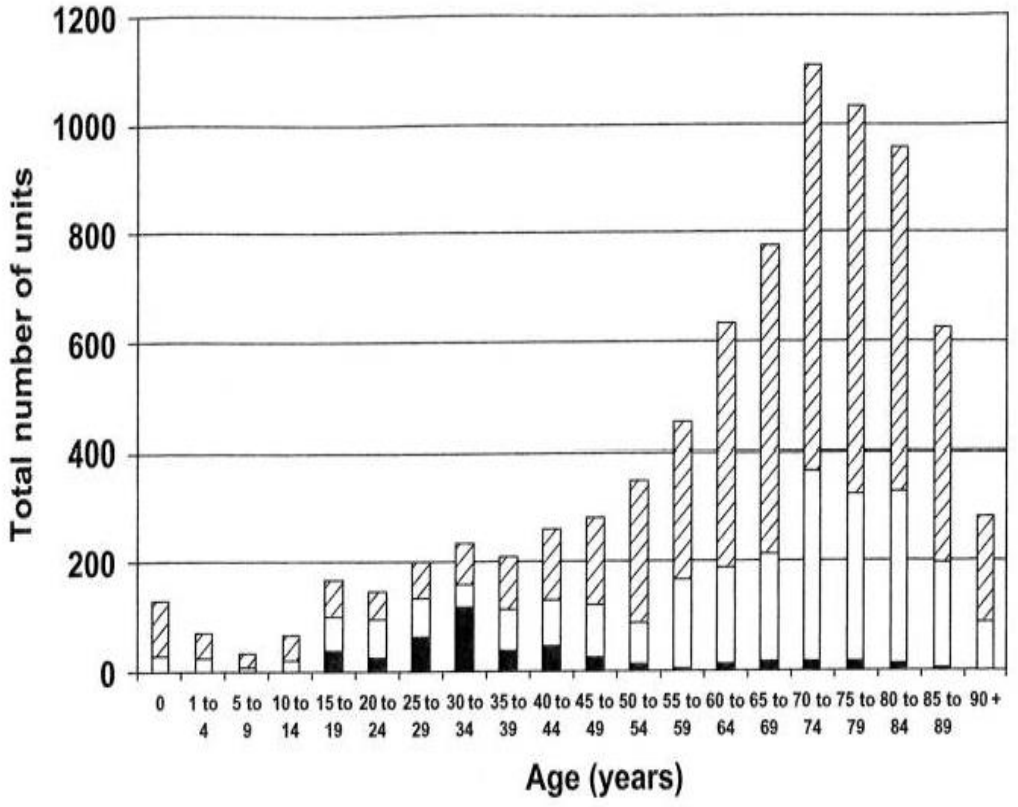


Fig. 1. RBC use by age and broad specialty in 2009. (■) Obstetrics/gynecology; (□) surgery; (▨) medicine.

TABLE 1. Medical indications for RBC use 2009

Hematology	1446
Myelodysplasia	449
Acute leukemia	238
Myeloma	110
Lymphoma (including HD and CLL)	254
Acquired hemolytic anemia	43
Inherited anemia (e.g., thalassemia)	15
Myelofibrosis	69
Other	268
Gastrointestinal bleeding	895
Renal failure	213
Cancer (nonhematologic)	772
Iron deficiency	127
B12/folate deficiency	13
Chronic disorders, e.g., rheumatoid arthritis	102
ITU/HDU admission	323
Pediatric/neonatal	122
Unknown cause	711
Other	432
Total	5156

CLL = chronic lymphocytic leukemia; HD = Hodgkin's disease; ITU/HDU = intensive care unit/high-dependency unit.

Tinegate H Transfusion 2013 and 2016

Syndromes Myélodysplasiques

Impact

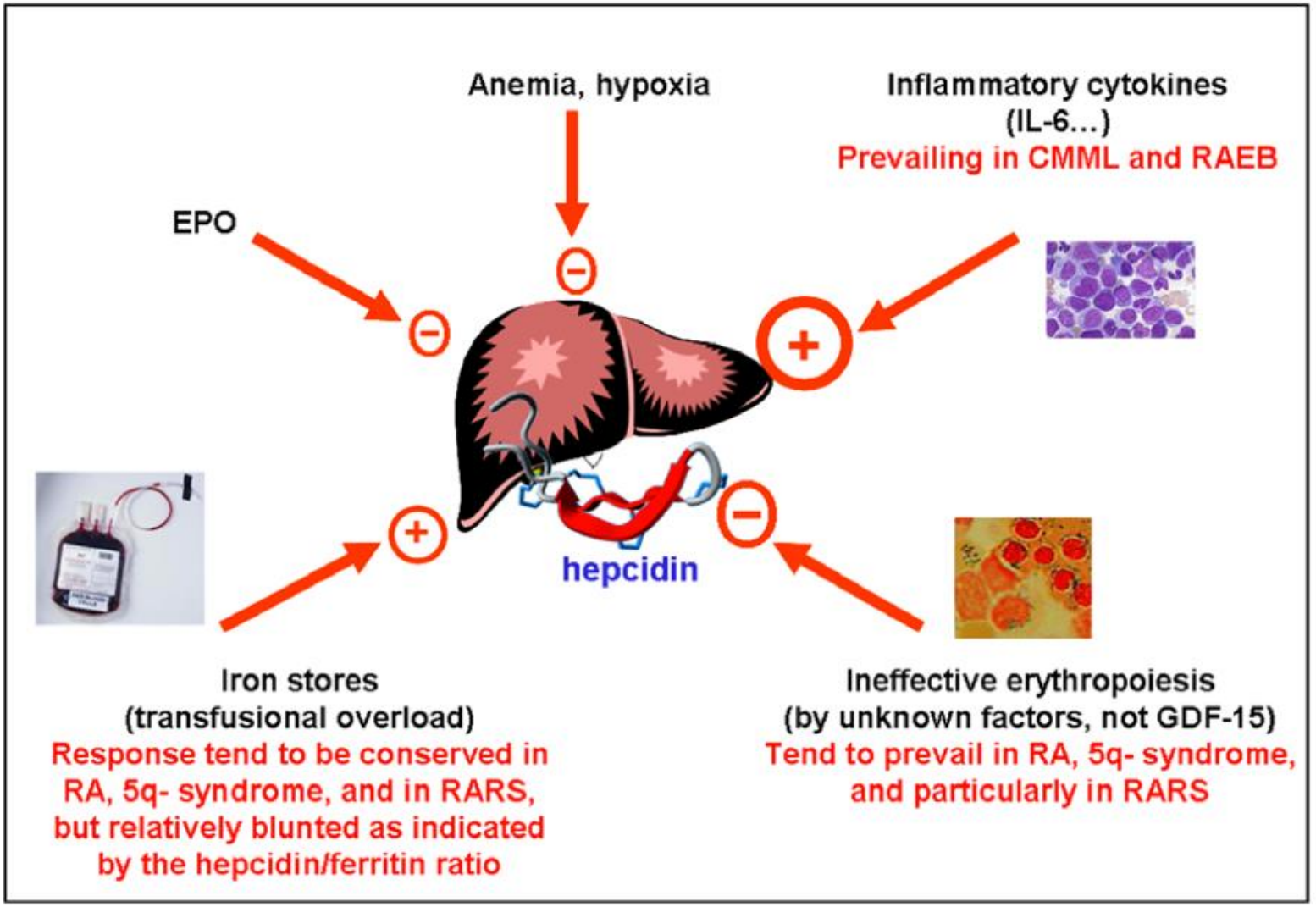
- **Etude rétrospectives ou prospectives non randomisées : chelation et survie**
  - **Vancouver study**
  - **GFM study**
  - **Lyon's Study**
- **pronostic: ferritine pré greffe**
- **IRM cardiaque: patho 15%**

Leitch HA, et al. Clin Leuk. 2008;2:205-11
Rose C, et al. Leuk Res. 2010;34:864-70
Lyons Leu Res 2017
Malcovati L, Haematologica. 2006;91:1588-90.
Armand P, et al. Blood. 2007;109:4586-8
de Swart L, et al. Blood. 2011;118:[abstract 2775
Pascal L GFM Brit J Haematol 2013
Roy N Brit J Haematol 2011

Impact Clinique

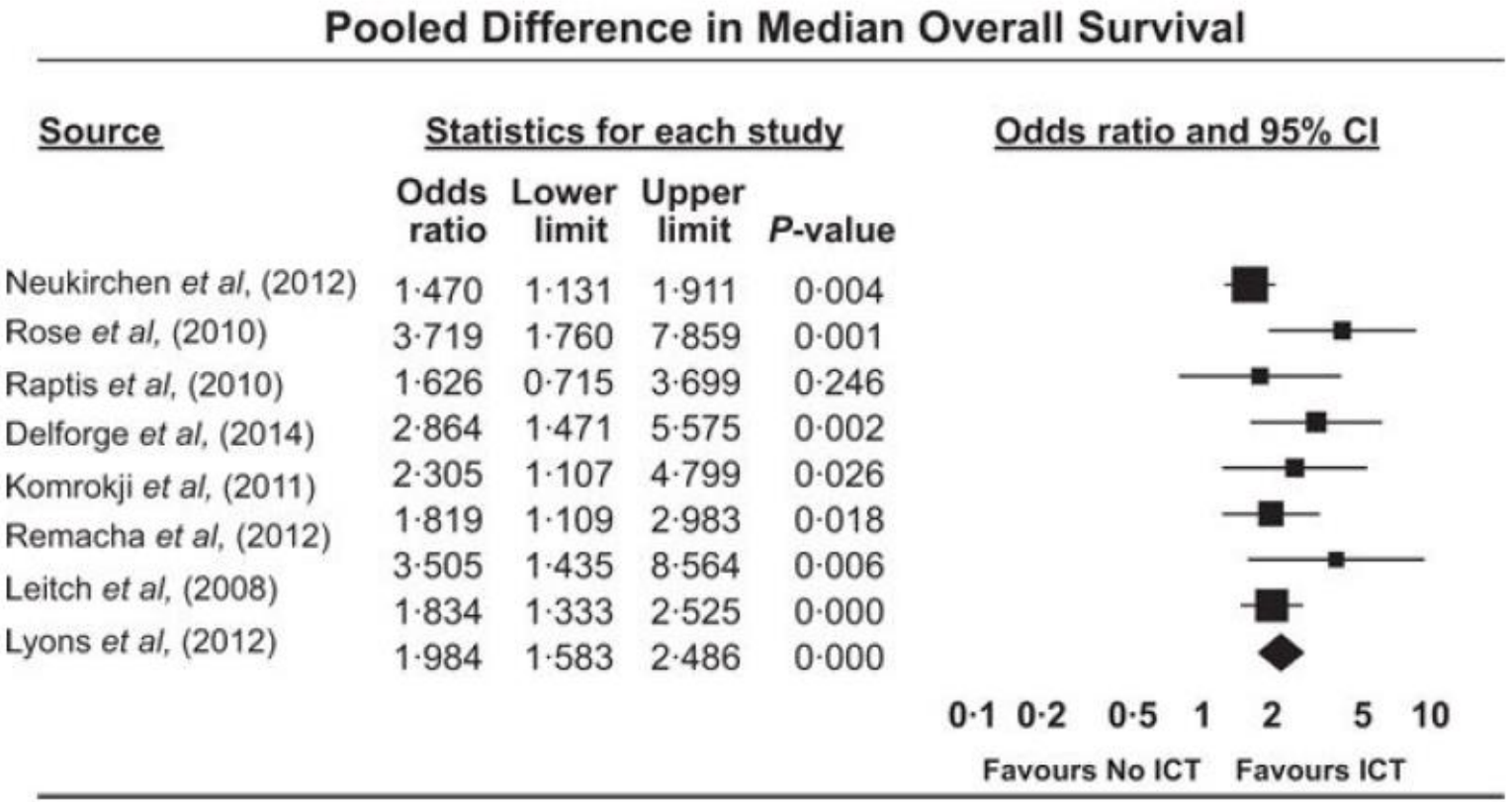
- **SMD**
  - **Dysérythropoièse associée**
  - **ARSI, AR , 5q-**
  - **allogreffe**
- **Lies au patient**
  - **Co morbidités**
  - **Sensibilité des cellules au stress oxydatif**
- **Lies à la transfusion**
  - **Nbre de CE , duree exposition**
  - **Qte de fer organisme IRM**

Proposed Mechanisms Controlling Hepcidin Production in Different MDS Types



Santini *et al. PLoS ONE* (2011) 6(8): e23109.

MDS : OS and chelation



SMD : En pratique QUI Chélaté?

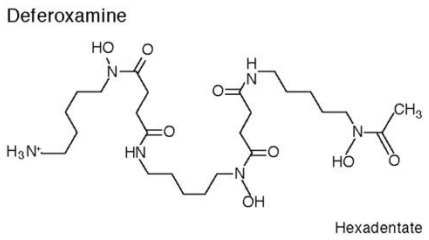
Consensus

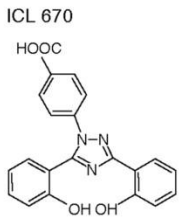
- **AR ARSI 5q-**
- **20 CE**
- **Candidat à une allogreffe++**
- IPSS faible ou int 1
- SMD non évolutifs sans co morbidité majeure limitant l' espérance de vie
- Ferritine supérieure à 1000 ng/ml ou présence de signes clinique de surcharge en fer
- Age ++

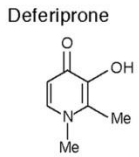
.Malcovati L 2013 , Blood; recommendations from the European LeukemiaNet:

Quel traitement chélateur ?

Major steps in Iron chelation Treatment







Deferasirox pelliculé

Deferasirox

Combined

Deferiprone

Desferal S.C bolus

Desferal I.V continuous

Desferal S.C slow infusion

Desferal I.V high dose

Desferal I.M

62 1967 1972 1977 1982 1987 1992 1997 2002 2007 2013 2018

Piga A, Rose C *ESH Book*

Caractéristiques des traitements chélateurs

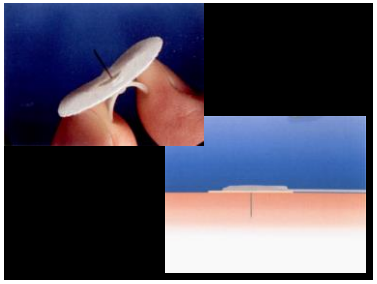
	Deferoxamine	Deferiprone	Deferasirox
Dose (mg/kg/j)	25-60	75	20-30
Voie d'administration	s.c., i.v. (8-12 heures, 5 j/sem)	Orale 3 prises par jour	Orale 1 prise par jour
Demi-vie	20-30 minutes	3-4 heures	8-16 heures
Excrétion	Urinaire, fécale	Urinaire	Fécale
Principaux Effets secondaires	Réactions locales, troubles ophtalmologiques et auditifs	agranulocytose/ neutropénie, arthralgie, augmentation des enzymes hépatiques	gastro-intestinaux, rash, augmentation de la créatinine
Indications	Hemosiderose II Seul (tolérance et observance?) Association DFP (coeur)	.CI DFO β-Thalassémie majeure .en cas d'atteinte cardiaque en association	• Transfusions chroniques Beta thal >6ans • CI DFO: SMD , autres anémies , B thal > 2 ans • NTD β-Thal >10ans

Hoffbrand V , Taher A Blood : How I treat

Desferoxamine : Desferal®

Historic Standard treatment

- Desferoxamine (DFO): 40 à 50 mg/kg/d 5-6 d a week sub cutaneously over night 8-12h
- Infusor or pump



High doses IV:

« symptomatic Cardiac iron overload »

Hoffbrand AV**.** *Lancet*. 1979

Davis BA *Blood 2000*

Deferiprone: a new story

1 Clinical Randomized trial 32DFO 29DFP

Inclusion criteria: LVEF >56%
T2*>8ms<20ms

Conclusion: Deferiprone was significantly more effective than deferoxamine over 1 year in improving asymptomatic myocardial siderosis

Pennell D *Blood 2006*

2 Retrospective studyObservation period from 1995 to 2003

- **DFO only or Deferiprone**

Results

- Group 359 DFO only, 157 deferiprone switched
- DFO :3610 patient-years Deferiprone : 750 patient-years

Cardiac event:

52 (10 deaths) in DFO group
0 in Deferiprone switched

Borgna-Pignatti C *Blood 2006*

Deferiprone studies : adverse effects

autorisé en Inde depuis 1994 et en Europe depuis 1999, pas d'AMM USA. En France, AMM limitée aux patients pour lesquels le ttt/DFO est inadéquat (intolérance/ non compliance) au DFO (TM). En association avec autre chélateur menace pronostic

Safety- tolerance

- **Agranulocytosis 0.5%**
- **Neutropenia 4.8%**
- **GI symptoms 24%**
- **Abdominal pain 14%**
- **Arthralgia 13%**
- **Liver fibrosis 0%**

Agranulocytosis

- **Transient**
- **Idiosynchratic**
- **Fatal**

Combined Therapy ++

Waneless A *Blood 2002*

Cohen A *Br J Hematol 2000*

Hoffbrand A *Blood 2003*

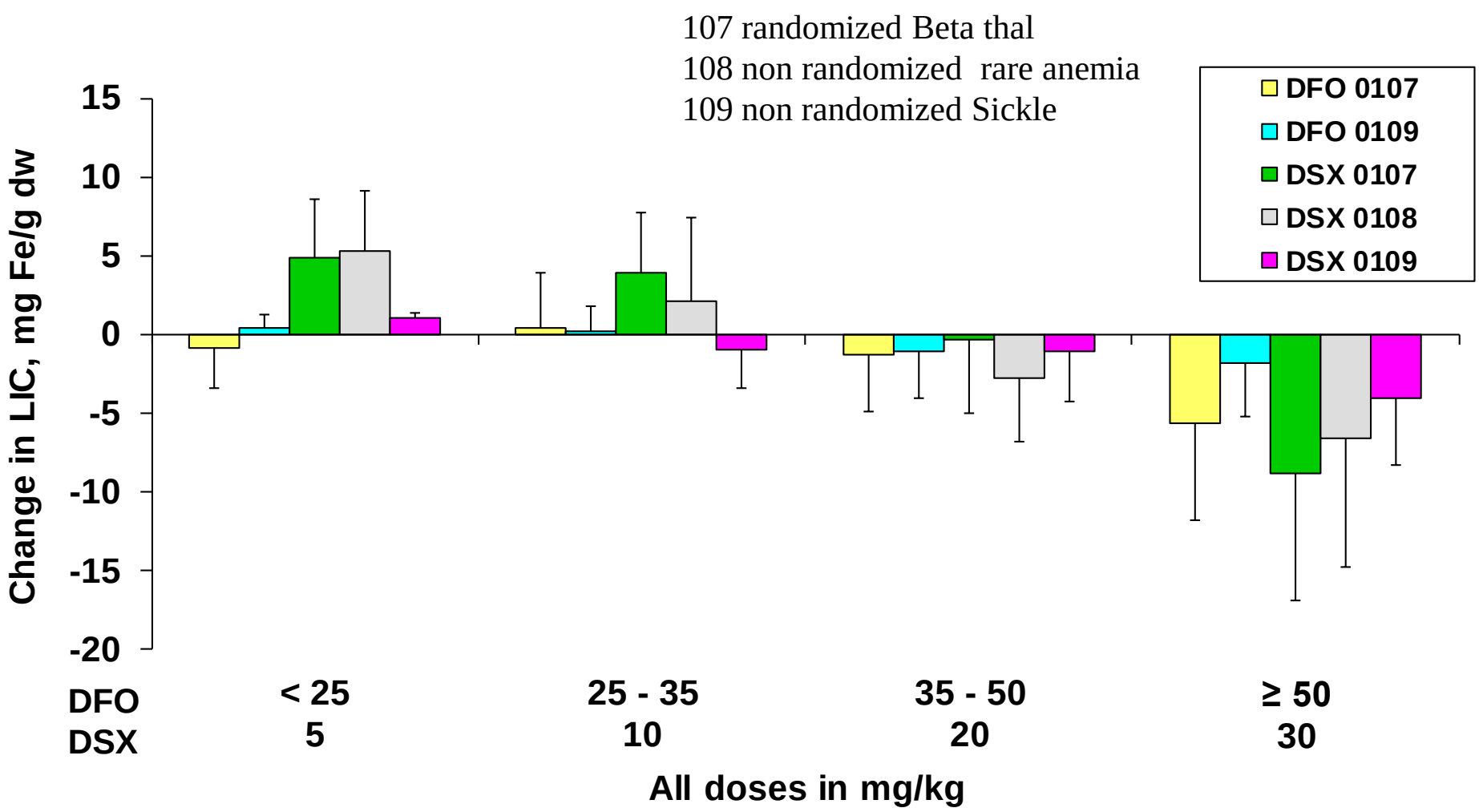
Hoyes K *Exp Hematol 1993*

Al-Refaie F *Eur J Haematol 1994*

Galanello R *Haematologica 2006*

Telfer P *Haematologica 2006*

Deferasirox :Efficacité sur la LIC selon les différentes études



DFO, deferoxamine; DSX, deferasirox.

Porter J European J Haematol 2008
Piga A Haematologica 2006
Vichinski Br J Haematol 2007

Tolérance et effets secondaires selon pathologies

Adverse events, n (%)	Thalassemia (n=1115)	MDS (n=341)	AA (n=116)	SCD (n=80)	Rare anemias (n=43)	Others (n=49)	All patients (n=1744)
	Most common (>3%) drug-related adverse events						
Diarrhea	87 (7.8)	111 (32.6)	18 (15.5)	9 (11.3)	13 (30.2)	13 (26.5)	251 (14.4)
Skin rash	129 (11.5)	23 (6.7)	13 (11.2)	3 (3.7)	4 (9.3)	2 (4.1)	174 (10.0)
Nausea	42 (3.8)	45 (13.2)	26 (22.4)	5 (6.3)	9 (20.9)	8 (16.3)	135 (7.7)
Abdominal pain	54 (4.8)	26 (7.6)	7 (6.0)	1 (1.3)	6 (14.0)	3 (6.1)	97 (5.6)
Upper abdominal pain	25 (2.2)	25 (7.3)	7 (6.0)	5 (6.3)	4 (9.3)	2 (4.1)	68 (3.9)
Vomiting	20 (1.8)	26 (7.6)	10 (8.6)	3 (3.7)	4 (9.3)	3 (6.1)	66 (3.8)

Baseline creatinine, n (%)*	Thalassemia (n=1115)	MDS (n=341)	AA (n=116)	SCD (n=80)	Rare anemias (n=43)	Others (n=49)	All patients (n=1744)
	Patients with two consecutive serum creatinine increases >33% above baseline and ULN						
Low	3	3	–	–	–	–	6
Normal	37	75	28	2	7	11	160
High	–	7	1	–	1	–	9
Total	40 (3.6)	85 (24.9)	29 (25.0)	2 (2.5)	8 (18.6)	11 (22.4)	175 (10.0)

Baseline ALT, n (%)	Thalassemia (n=1115)	MDS (n=341)	AA (n=116)	SCD (n=80)	Rare anemias (n=43)	Others (n=49)	All patients (n=1744)
	Patients with two consecutive increases in ALT >10 x ULN						
Normal (<45 U/L)	1	1	–	–	–	–	2
High (>45 U/L)	6	–	2	1	1	1	11
Total	7 (0.6)	1 (0.3)	2 (1.7)	1 (1.3)	1 (2.3)	1 (2.0)	13 (0.7)

*Baseline creatinine levels were considered low, normal and high compared with the normal age- and gender-dependent range.

Cappelini MD Haematologica 2009.

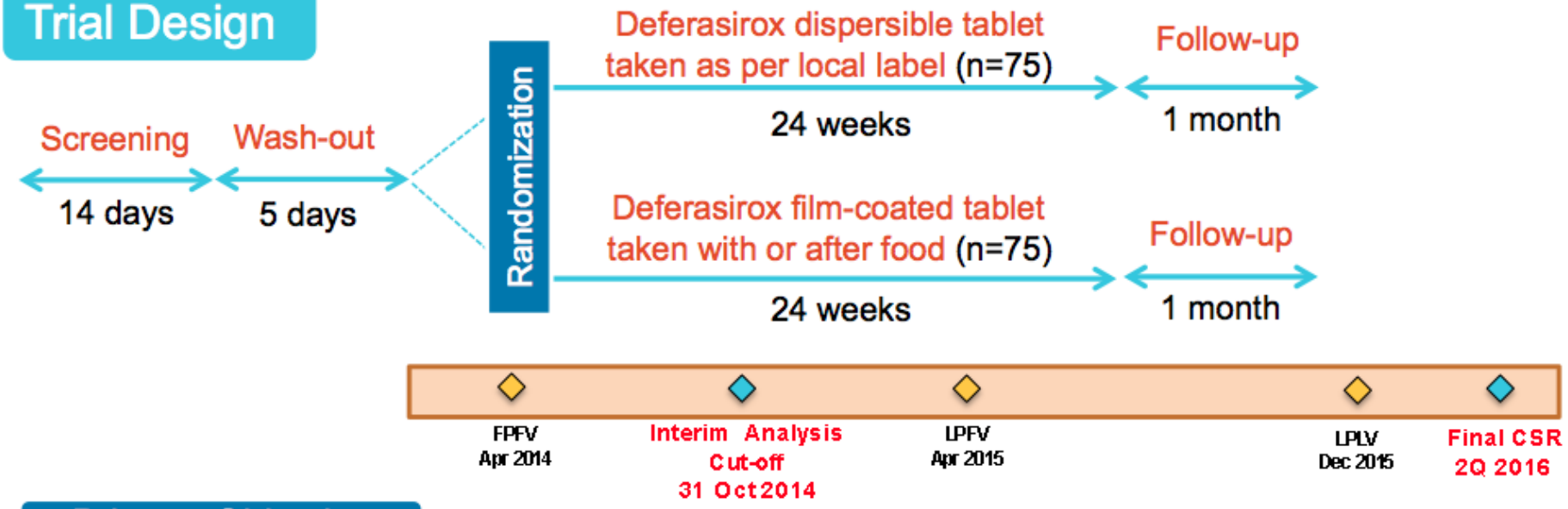
Tolérance et effets secondaires selon pathologies

	Thalassemia (n=1115)	MDS (n-=341)	AA (n=116)	SCD (n=80)	Rare anemias (n=43)	Others (n=49)	All Patients (n=1744)
Discontinued treatment, n	105	166	28	17	13	26	355
Adverse event, n	39	78	13	2	8	13	153
Consent withdrawn, n	28	33	6	7	1	2	77
Unsatisfactory Therapeutic Effect, n	13	6	0	0	1	0	20
Lost to follow-up, n	6	2	1	1	0	0	10
Death*, n	4	26	5	0	2	5	42
No longer requires study drug	2	8	2	1	0	2	15
Other, n	13	13	1	6	1	4	38
Patients completed, n	1010	175	88	63	30	23	1389

Cappelinin MD Haematologica 2009.

ECLIPSE Study: Meilleure Formulation: film-coated T

Trial Design



Primary Objective

To evaluate the overall safety, as measured by frequency and severity of adverse events and changes in laboratory values, of deferasirox FCT and deferasirox DT formulations in patients with transfusion-dependent thalassaemia or myelodysplastic syndrome at low or intermediate-I risk

Secondary Objectives

- To evaluate both formulations on selected GI AEs.
- To evaluate pharmacokinetics of both formulations.
- To evaluate both formulations on patient satisfaction, palatability and GI symptoms using Patient Reported Outcomes (PRO) tools.
- To evaluate both formulations on patient compliance using pill count and a daily dairy

Taher , Am J Hematol 2017

Results : ECLIPSE study

n= 173 : DT (n = 86) or FCT (n = 87)

- Adverse events (overall): consistent with the known deferasirox safety profile with Similar proportions of patients for each formulation (DT89.5%; FCT 89.7%),

- lower frequency of severe events observed in patients receiving FCT (19.5% vs. 25.6% DT).
- Greater adherence and satisfaction, better palatability
- Higher compliance compliance (92.9%) versus (85.3%).

New Formulation enhanced patient satisfaction, which may improve adherence, thereby reducing frequency and severity of iron overload-related complications.

Taher , Am J Hematol 2017

Deferasirox dosing and administration

Deferasirox

Once-daily oral suspension
Starting dose 20 mg/kg/day (thalassemia)

Multistep preparation may conflict with daily activities

Restrictions on taking with food

Palatability issues can make administration a challenge

Deferasirox pelliculé

Once-daily film-coated tablets
Starting dose 14 mg/kg/day (thalassemia)

No preparation or mixing required
For pts who are unable to swallow a whole tablet, it may be crushed and sprinkled on soft food

May be taken with a light meal

Does not contain lactose and sodium lauryl sulfate

Deferasirox FCT dose is ~30% lower than DT, due to higher bioavailability

Surveillance patients chélatés: en pratique

Suivi de la surcharge en fer

Au diagnostic, puis à intervalle régulier, selon le rythme transfusionnel

En pratique :

- Rythme transfusionnel , nbre total CE
- **CSS**, Ferritinémie tous les 3 mois pour les patients régulièrement transfusés
- Evaluation de la surcharge organique par IRM cardiaque (>50CE) et hépatique annuel
- Evaluation des fonctions cardiaques et hépatiques , glycémie semestrielle
- Endocrinien

Suivi traitement chélateur

- **Deferasirox**
- (NF, urée , creat, ferritine , TGO, TGP, gamma GT, bil, protéinurie) (iono)
- Prévention des effets secondaires +++
- **Deferiprone** NF bilan hépatique
- **Deferoxamine DFO**

Chelating Agents:Other potential advantages

- Improvement in Neuro Degenerative diseases
  - Parkinson, Friedrach , ferritinopathy , acreuloplasminemia
- Improvement hematopoisesis
  - In vitro studies (deferoxamine)
  - Hematolgical improvement in 5% of cases in US 03 trial –(IWG2000 criteria)
- Lowering infection risk
  - Mainly anti fungi activity (deferasirox, ciclopiroxolamine)
- Improving outcome after allo HSCT
  - Reduction of infections
  - Lowering rate of sinusoidal obstruction syndrome
  - Reduction iron overload complications
- Delaying leukemic transformation
  - Anti proliferative activity in various cell lines
  - High ferritin associated to LFS
  - Differentiation of primary progenitors into monocytes

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Groupe Francophone des Myélodysplasies

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Home > Find Studies > Search Results > Study Record Detail

Trial record **47 of 74** for: deferasirox

◂ Previous Study | Return to List | Next Study ▸

A Study of Combined Deferasirox, Vitamin D and Azacytidine in High Risk MDS (GFM-EXVD-AZA)

This study is not yet open for participant recruitment.

Verified October 2012 by Groupe Francophone des Myelodysplasies

Sponsor:
Groupe Francophone des Myelodysplasies

Collaborator:
Novartis

Information provided by (Responsible Party):
Groupe Francophone des Myelodysplasies

ClinicalTrials.gov Identifier:
NCT01718366

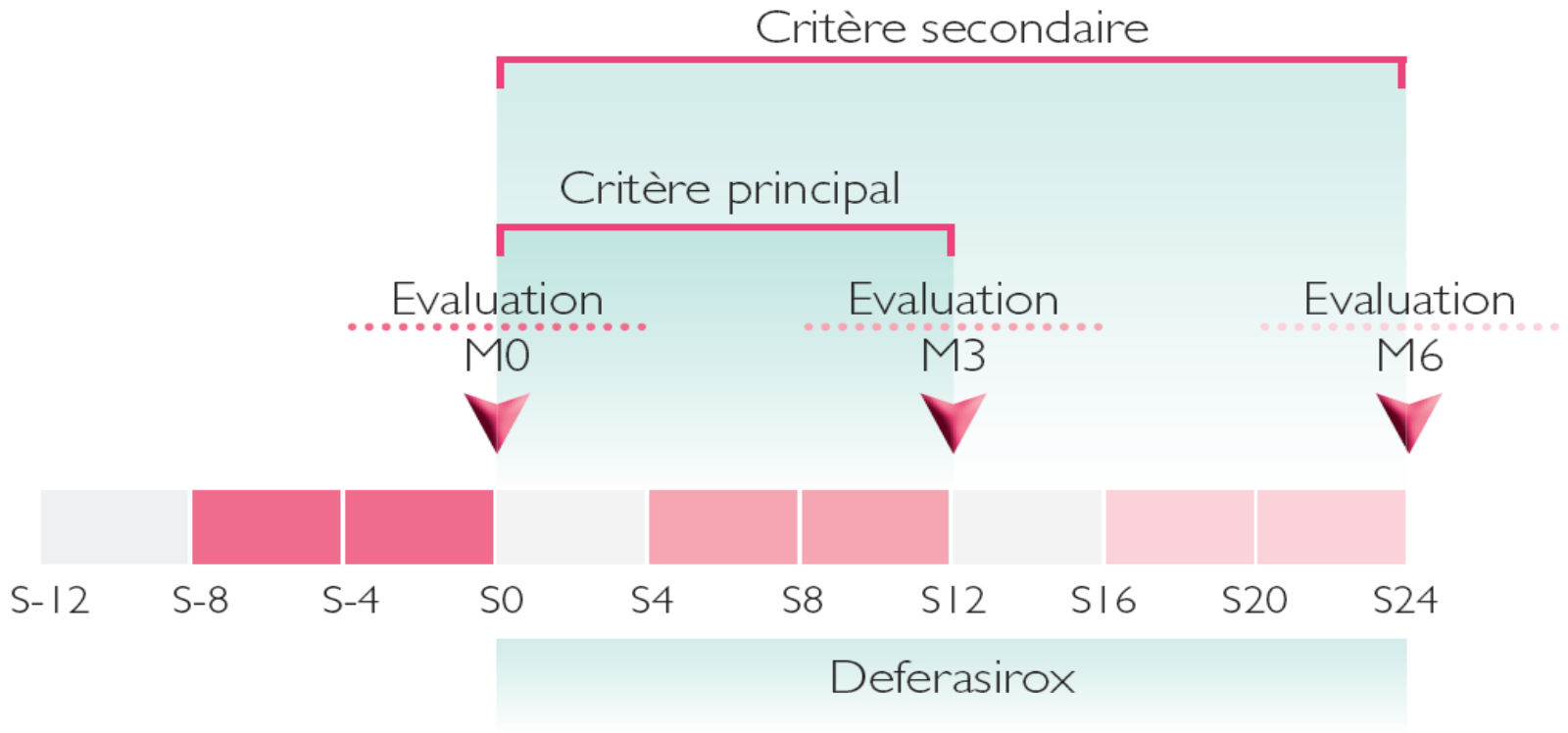
First received: October 24, 2012
Last updated: October 30, 2012
Last verified: October 2012
History of Changes

- Deferasirox dose escalation during phase I. MTD will be used during phase II.
- Deferasirox will be administrated once daily during all the study period.
- Uvedose will be administrated once weekly during all the study period (100.000 UI P.O).
- Azacitidine will be administrated 75 mg/m²/d, during 7 days, J1 to J7 of each 28-day cycle

ACTION SUR HEMATOPOIESE faible risques : ETUDE RYTHMEX

Groupe Francophone des Myélodysplasies

Etude observationnelle, prospective multicentrique évaluant le **RYTHMe** transfusionnel des patients atteints d'un syndrome myélodysplasique de faible risque présentant une surcharge en fer



In press, European J Hematol 2018

ACTION SUR HEMATOPOIESE faible risques : ETUDE RYTHMEX

Results

57 patients were evaluable.

3 **months: no effect was seen on transfusion requirement** (5.9 PRBC versus 5.8)

However, during the 12-month follow-up after deferasirox

initiation, 17 patients (31.5%) achieved minor erythroid response [HI-E] according to IWG criteria, 10of whom having achieved Hb improvement at month 12.

Co nc l us i o n

After 3 months of treatment, deferasirox had **no impact on transfusion requirement in regularly** transfused low risk MDS patients. However, deferasirox could **induce31% of erythroid responseduring the 12-month** follow-up period thus suggesting that iron chelation therapy with deferasirox may

induce an effect on hematopoiesis in a subset of patients with MDS and iron overload.

In press, European J Hematol 2018

NFKB ACTIVATION WITH DFX 3µM modeles murins

M. Meunier, S. Park , ASH 2016, abs 3152

TRANSLATIONAL APPLICATION: CLINICAL TRIAL IN GRENOBLE WITH LOW DOSE OF DFX

- Patients:
  - **Anemic Low risk MDS**
  - ESA refractory or low need of red blood cell transfusions,
- **Low dose of DFX 5mg/kg/d**
- 11 patients included; 6 patients with analyzable data: stable Hb

LODEFI trial in France:

- Phase II trial, 15 centers, 42 patients
- Dose of DFX: 3,5mg/Kg corresponding to 3µM in vitro
- Inclusion criteria: low risk MDS pts refractory to ESA
- Primary endpoint: transfusion independency at 12 months

Chelating Agents:Other potential advantages

- Improvement in Neuro Degenerative diseases
  - Parkinson, Friedrach , ferritinopathy , acreuloplasminemia
- Improvement hematopoisesis
  - In vitro studies (deferoxamine)
  - Hematolgical improvement in 5% of cases in US 03 trial –(IWG2000 criteria)
- Lowering infection risk
  - Mainly anti fungi activity (deferasirox, ciclopiroxolamine)
- Improving outcome after allo HSCT
  - Reduction of infections
  - Lowering rate of sinusoidal obstruction syndrome
  - Reduction iron overload complications
- Delaying leukemic transformation
  - Anti proliferative activity in various cell lines
  - High ferritin associated to LFS
  - Differentiation of primary progenitors into monocytes

CONCLUSIONS

- **Le Traitement chélateur du fer préventif est indiqué pour tous les patients présentant une hémochromatose post transfusionnelle**
- **Le bénéfice attendu est variable selon la pathologie sous jacente**
- **Un Amélioration de l'observance par les chélateurs oraux**

  Nouvelle forme deferasirox

- **Un traitement étiologique limitant les transfusions**
  - Thérapie génique et hémoglobinopathie
  - Luspatercept et dysérythropoïèse (ARSI , Bthal)
  - Epo , Revlimid , Luspatercept et MDS
- **Mieux explorer les modalités transfusionnelles (SMF)**

Remerciements

- **Hôpital C Huriez**

Service maladies du sang

B Quesnel , C Berthon

Service d'Imagerie

O Ernst

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- **Groupe Français des Myélodysplasies**

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  - **B Carpentier**
  - **B Hivert**
  - **L Pascal**
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