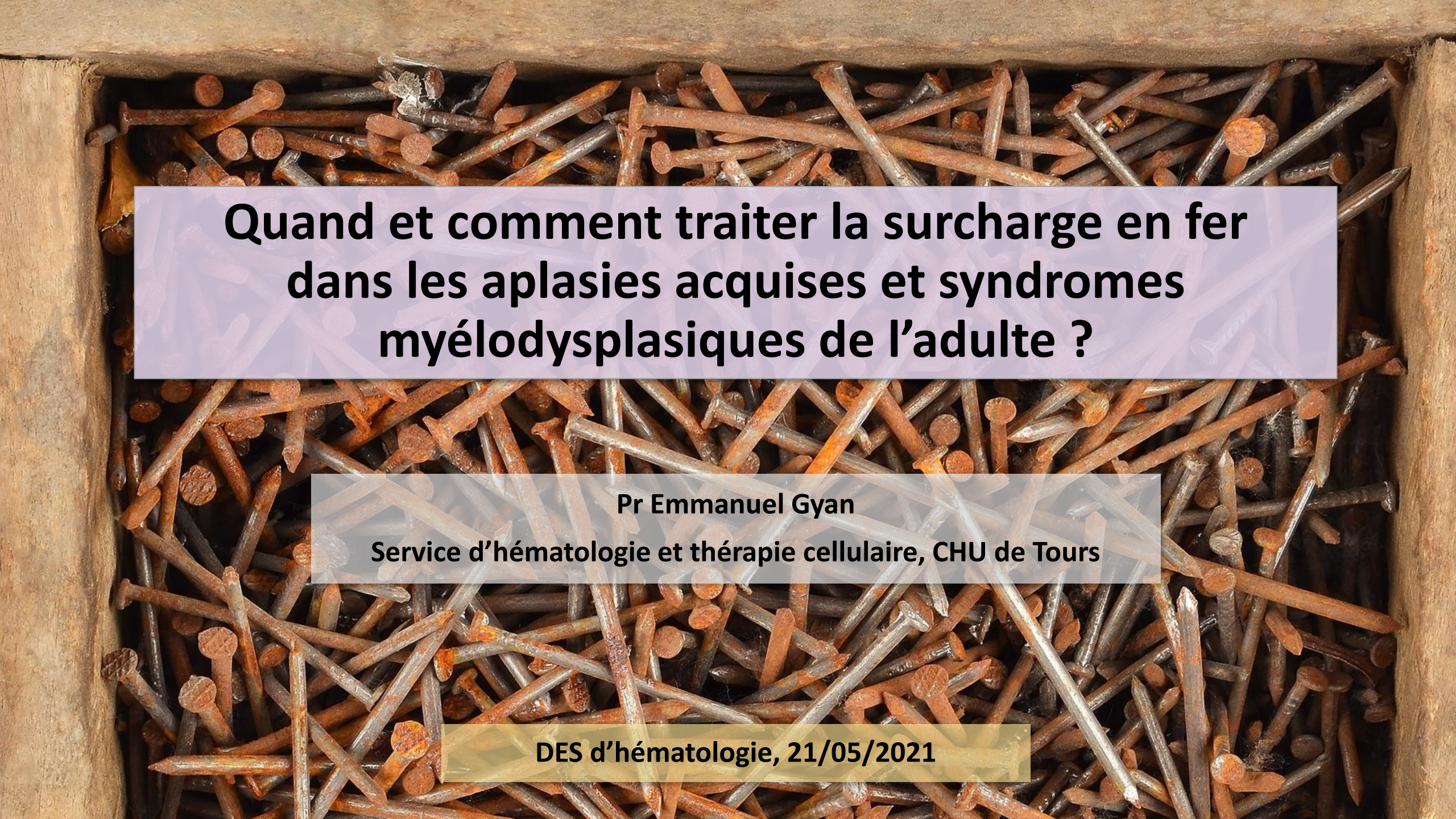


Quand et comment traiter la surcharge en fer dans les aplasies acquises et syndromes myélodysplasiques de l'adulte ?

Pr Emmanuel Gyan

Service d'hématologie et thérapie cellulaire, CHU de Tours

DES d'hématologie, 21/05/2021

Objectifs

- Rappels sur la physiopathologie de la surcharge martiale dans les insuffisances médullaires
- Options thérapeutiques et impact biologique
- Indications thérapeutiques de la chélation
- Synthèse

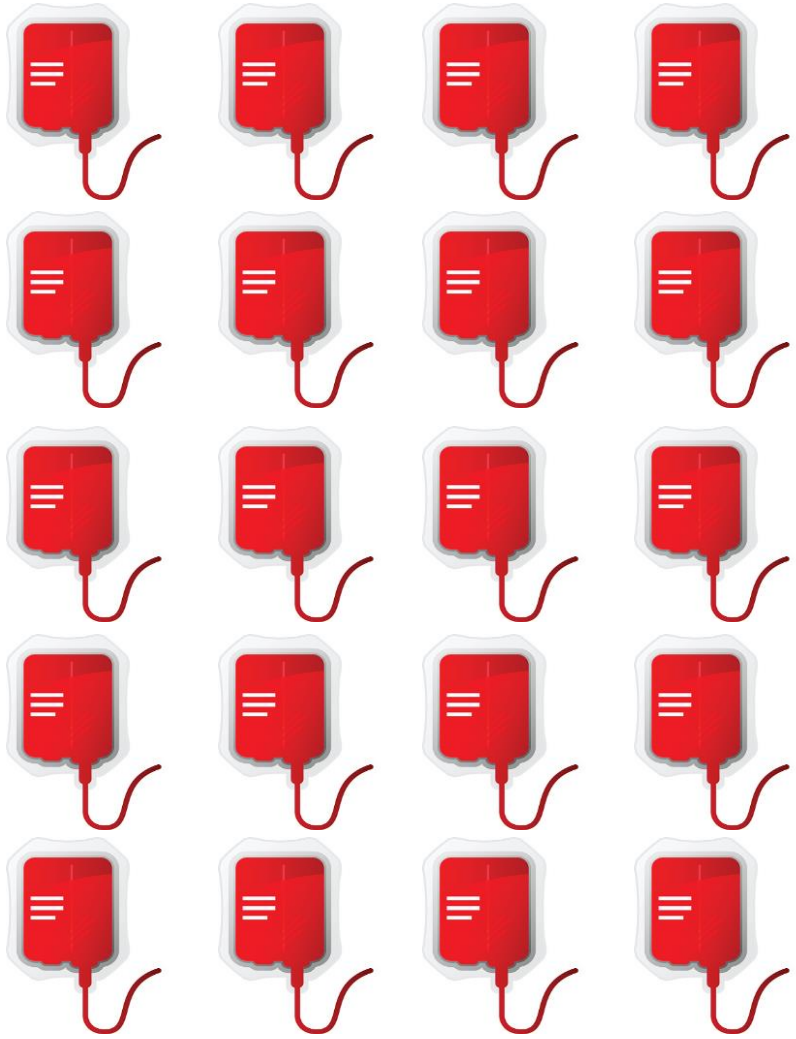
Pourquoi y a-t-il une surcharge en fer dans les insuffisances médullaires ?

Question 1

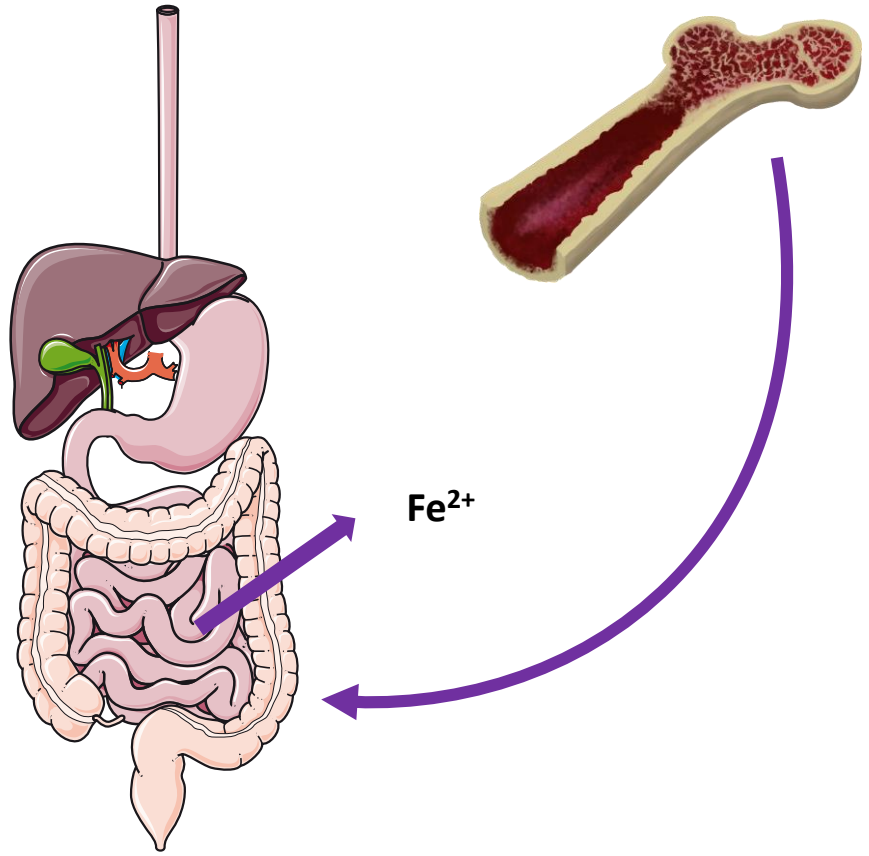
Quelle(s) peu(ven)t être l’ (les) origine(s) de la surcharge martiale dans les insuffisances médullaires ?

A. l’apport de fer de la transfusion érythrocytaire
B. l’excès d’apport de fer dans l’alimentation
C. l’augmentation de l’absorption intestinale du fer
D. la supplémentation en fer devant l’anémie
E. le syndrome inflammatoire associé

Deux grands mécanismes

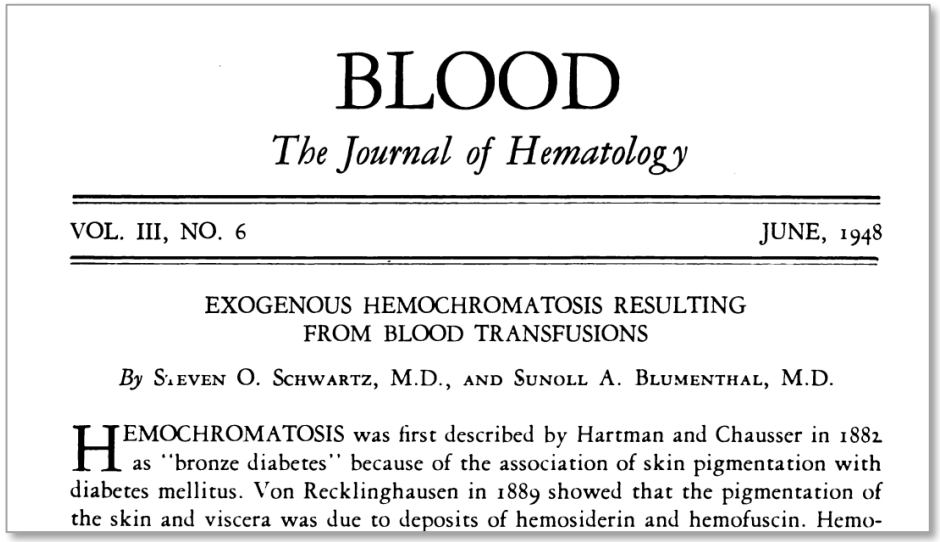


Transfusion chronique



Erythropoïse inefficace
Augmentation de l'absorption intestinale du fer

Surcharge martiale post-transfusionnelle



BLOOD

The Journal of Hematology

VOL. III, NO. 6 JUNE, 1948

EXOGENOUS HEMOCHROMATOSIS RESULTING FROM BLOOD TRANSFUSIONS

By Steven O. Schwartz, M.D., and Sunoll A. Blumenthal, M.D.

HEMOCHROMATOSIS was first described by Hartman and Chausser in 1882 as "bronze diabetes" because of the association of skin pigmentation with diabetes mellitus. Von Recklinghausen in 1889 showed that the pigmentation of the skin and viscera was due to deposits of hemosiderin and hemofuscin. Hemo-

- Apport de fer par voie parentérale
- Une poche de CGR contient 250 mg de fer
- L'élimination du fer n'est possible chez l'humain qu'à hauteur de 1 à 2 mg/j (sécrétions, desquamation, menstruations)
- Tout programme transfusionnel au long cours entraîne une surcharge martiale dépendante du nombre de transfusions

Schwartz & Blumental, Blood 1948;3:617-40

Surcharge martiale chez les patients MDS non transfusés

- 107 patients MDS non transfusés
- Comparaison à des sujets sains
- Mesure de l'hepcidine, et de GDF-15

Erythropoïèse inefficace

↓

↑ GDF-15

↓

↓ hepcidine hépatique

↓

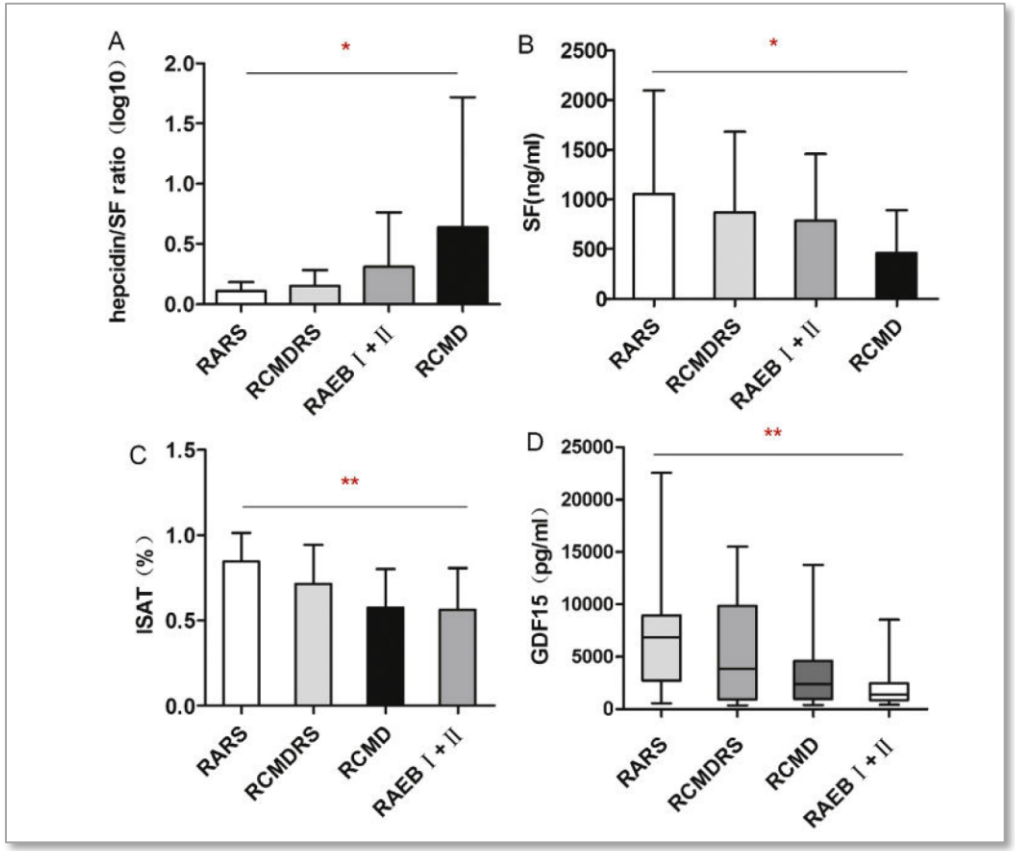
↑absorption intestinale de fer

↓

↑ coefficient de saturation de la transferrine

↓

↑ ferritine



Cui et al., Leuk Res. 2014;38:545–550.

Des avancées dans la compréhension du mécanisme de suppression de l'hepcidine dans les MDS

Blood Cells, Molecules and Diseases 78 (2019) 1–8

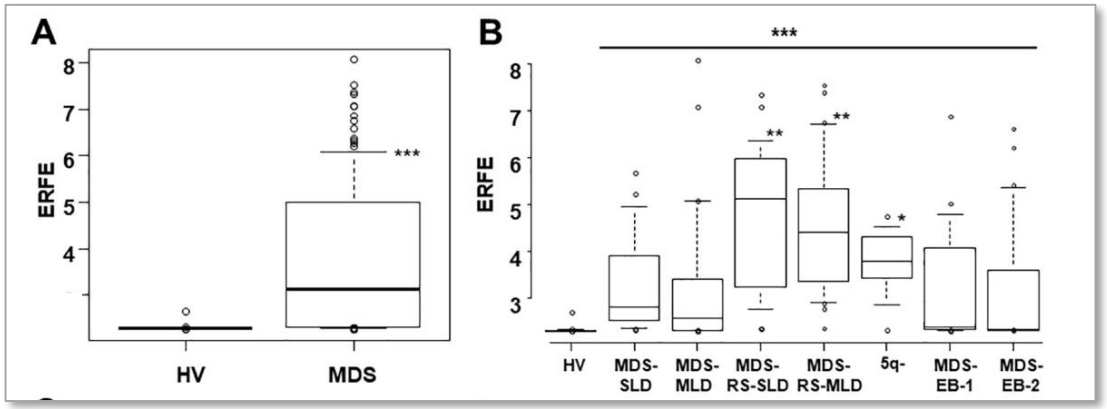
Contents lists available at ScienceDirect

Blood Cells, Molecules and Diseases

journal homepage: www.elsevier.com/locate/bcmd

EPO-R+ myelodysplastic cells with ring sideroblasts produce high erythroferrone levels to reduce hepcidin expression in hepatic cells

Shogo Miura[a,b], Masayoshi Kobune[a,*], Hiroto Horiguchi[a], Shohei Kikuchi[a,b], Satoshi Iyama[a], Kazuyuki Murase[a,b], Akari Goto[a], Hiroshi Ikeda[a], Kohichi Takada[a,b], Koji Miyanishi[b,**], Junji Kato[b]



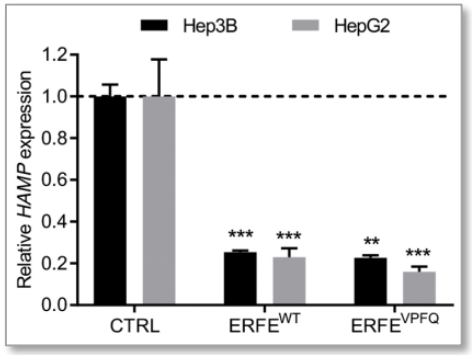
Miura et al., Blood Cell Mol Dis 2019;78:1-8

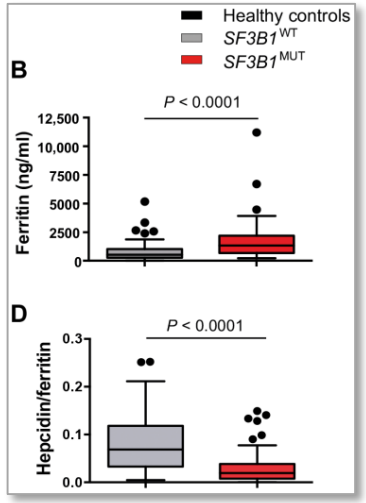
SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

MYELODYSPLASTIC SYNDROME

A variant erythroferrone disrupts iron homeostasis in *SF3B1*-mutated myelodysplastic syndrome

Sabrina Bondu[1,2,3,4]*, Anne-Sophie Alary[1,2,3,4,5]*, Carine Lefèvre[1,2,3,4,6], Alexandre Houy[7], Grace Jung[8], Thibaud Lefebvre[1,6,9], David Rombaut[1,2,3,4], Ismael Boussaid[1,2,3,4], Abderrahmane Bousta[1,2,3,4], François Guillonneau[1,2,3,4,10], Prunelle Perrier[11], Samar Alsafadi[12], Michel Wassef[13], Raphaël Margueron[13], Alice Rousseau[1,2,3,4], Nathalie Droin[14], Nicolas Cagnard[1,15], Sophie Kaltenbach[1,16], Susann Winter[17], Anne-Sophie Kubasch[18], Didier Bouscary[1,2,3,4,19], Valeria Santini[20], Andrea Toma[21], Mathilde Hunault[22], Aspasia Stamatoullas[23], Emmanuel Gyan[24], Thomas Cluzeau[25], Uwe Platzbecker[18], Lionel Adès[1,26], Hervé Puy[1,6,9], Marc-Henri Stern[27], Zoubida Karim[1,6,9], Patrick Mayeux[1,2,3,4,6,10], Elizabeta Nemeth[8], Sophie Park[28], Tomas Ganz[8], Léon Kautz[11], Olivier Kosmider[1,2,3,4,5,6†], Michaëla Fontenay[1,2,3,4,5,6†]





Bondu et al., Sci Transl Med 2019;11:5467

Comment identifier la surcharge en fer ?

Question 2

Quel(s) examen(s) demandez-vous en routine pour poser le diagnostic d'une surcharge martiale post-transfusionnelle ?

A. IRM cardiaque T2*
B. dosage de la ferritinémie
C. biopsie hépatique
D. dosage de l'hepcidine
E. nombre de concentrés érythrocytaires transfusés

Examens diagnostiques

- Biologie :
  - Ferritinémie +/- coefficient de saturation de la transferrine
- Imagerie :
  - SQUIDD
  - T2*

  Plus difficiles d'accès
- Anapath
  - Biopsie hépatique : non pratiqué dans les insuffisances médullaires (risque de saignement)

Zeidan & Griffiths, Blood Reviews 2018;32:368-77.

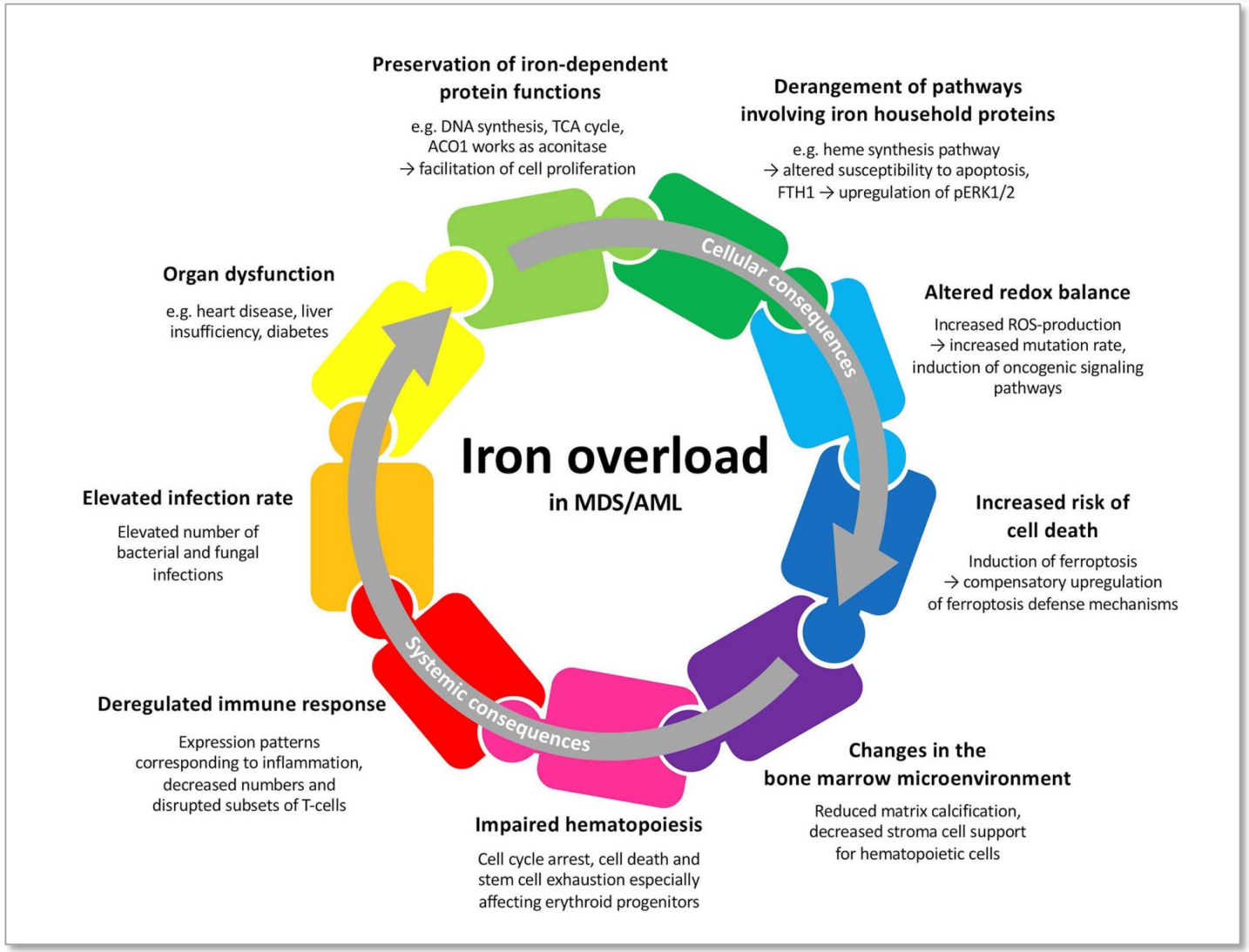
Quelles conséquences de la surcharge en fer ?

Question 3

Quelle(s) complication(s) faut-il craindre chez un patient atteint de MDS transfusé au long cours et porteur d'une surcharge martiale post-transfusionnelle ?

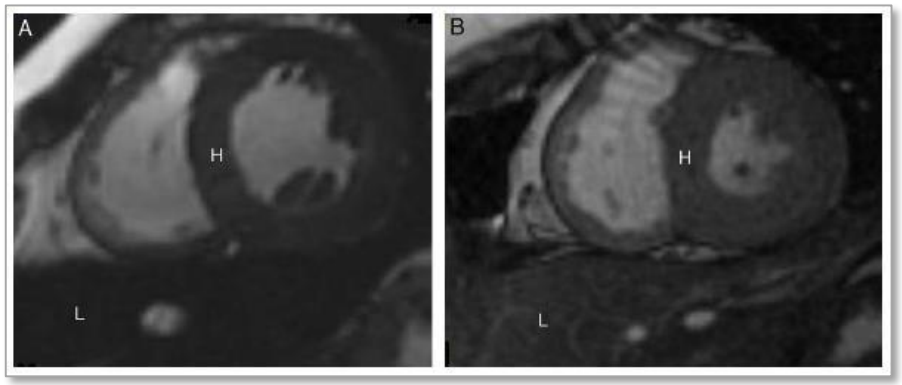
A. insuffisance cardiaque
B. diabète
C. infections
D. insuffisance hépatique
E. évolution vers une leucémie aiguë

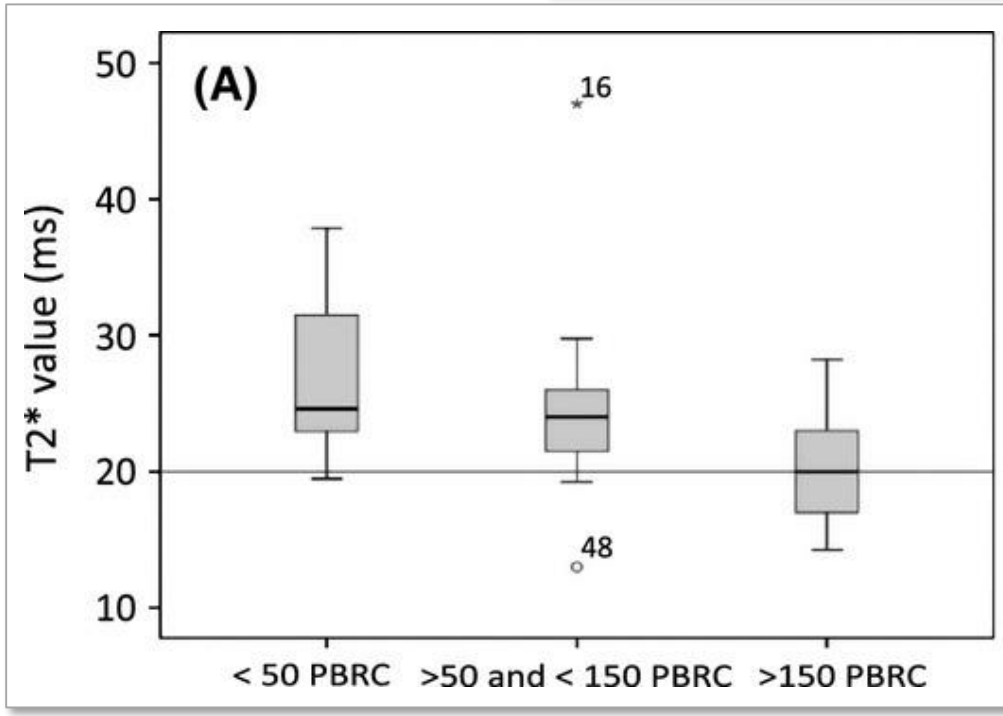
Les conséquences de la surcharge en fer



Weber et al., Front Immunol 11:627662.

IRM T2*





(B)

		Myocardial Iron Overload (Cardiac T2*≤20ms)		Total
		Yes	No	
Severe cardiac dysfunction (LVEF ≤35%)	Yes	3	8	
	No	1	45	
Total		4	53	57

Fisher's test p = 0·002

Pascal et al., Br J Haematol 2013;162:413-5.

Association ferritinémie – évolution leucémique (MDS)

Table 2
Iron overload was an independent predictor of overall survival and leukaemia-free survival in a multivariate analysis of data from 2241 patients with MDS[a].

	Iron overload		WPSS	
	HR	p value	HR	p value
Overall survival	4.34	<0.001	1.60	<0.001
Leukaemia-free survival	2.13	<0.001	2.24	<0.001

HR = hazard ratio; WPSS = WHO Prognostic Scoring System.

[a] Reproduced with permission from Sanz G, et al.[29] *Blood* 2008;**112**: abstract 640. © the American Society of Hematology.

Fenaux & Rose. Blood Reviews 2009;23:S15-19.

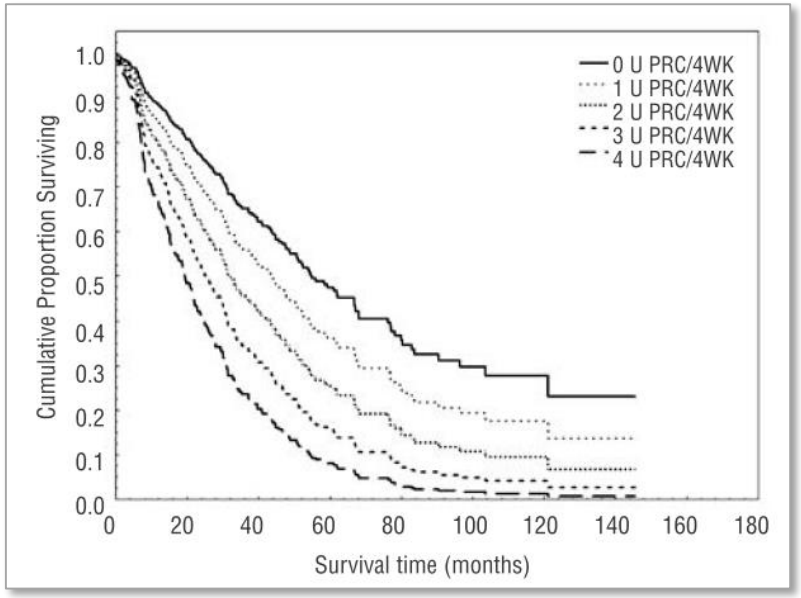
Association ferritinémie – survie

EDITORIALS & PERSPECTIVES

Predicting survival and leukemic evolution in patients with myelodysplastic syndrome

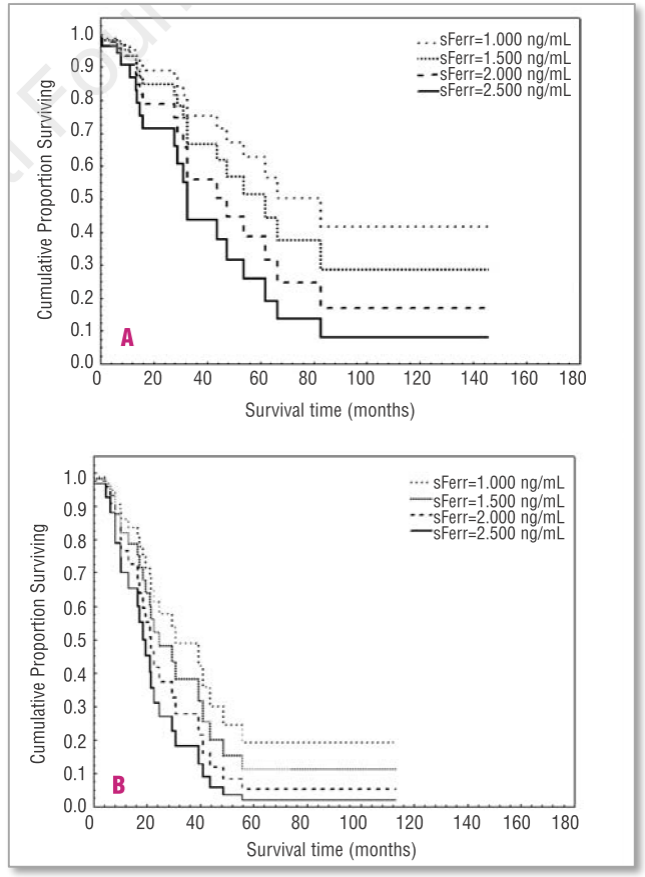
Luca Malcovati, Matteo Giovanni Della Porta, Mario Cazzola

From the Department of Hematology, University of Pavia Medical School & IRCCS Fondazione Policlinico San Matteo, Pavia, Italy. E-mail: l.malcovati@haematologica.org



RA, RS, 5q

RCMD, RCMD-RS

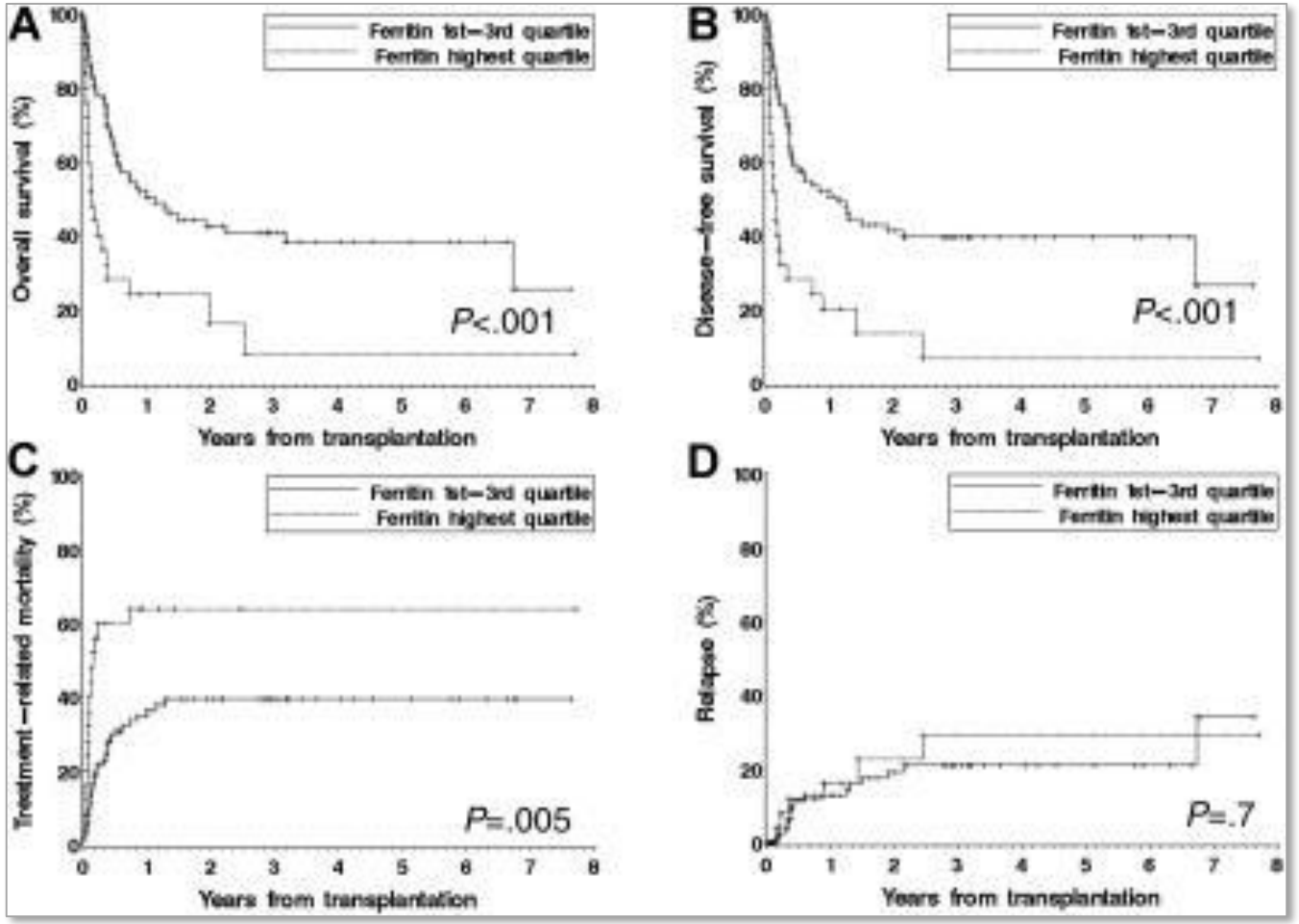


Malcovati et al., Haematologica 2006;91:1588-90.

Impact de la ferritinémie pré-transplantation

922 patients transplantés
Allo myélo-ablative

Ferritinémie élevée : + de TRM
Tendance à plus de MVO



Armand et al., Blood.2007;109:4586-4588.

Impact de la ferritinémie sur la TRM

Author	Year	Disease (patients)	Study period	Study design	Male/ Female	Median age (year)	The cut-off value of pre-transplantation SF (ng/mL)	HR (95%CI) for OS	Follow-up time (years)
Artz et al	2016	AML(626) MDS (158)	2000-2010	P	402/382	50 (18–78)	2500	1.15 (0.86–1.54)	≥4
Tachibana et al	2013	AML (118) MDS (35)	2000-2010	R	96/57	46 (18–63)	1000	1.79 (1.11–2.91)	>7
Tachibana et al	2011	AML (99) MDS (20)	2000-2008	R	64/55	41 (18–63)	1000	3.25 (1.71–6.17)	>5
Boehm et al	2014	MDS (60)	1988-2010	R	33/27	44 (18–68)	1000	1.93 (1.06–4.15)	>10
Lim et al	2009	AML (36) MDS (63)	2000-2006	R	51/48	51 (19–72)	1500	2.00 (0.97–3.57)	>10
Jang et al	2015	AML (74)	2006-2012	R	34/40	35 (15–59)	1400	1.88 (0.88–4.01)	NR
Alessandrino et al	2009	MDS (244) AML (113)	1997-2007	R	95/162	49 (18–72)	1000	1.40 (1.09–1.81)	>10
Li et al	2013	MDS (191)	2005-2010	R	119/72	50 (12–83)	500	3.53 (1.90–6.60)	>5
Komrokji et al	2012	MDS (767)	2001-2009	R	NR	69 (NR)	1000	1.40 (1.10–1.90)	>5
Kikuchi et al	2009	MDS (47)	1993-2001	R	28/19	65 (27–74)	500	1.90 (1.03–3.50)	>4

AML = acute myeloid leukemian, MDS = myelodysplastic syndromes, NR = not report, OS = overall survival, P = prospective, R = retrospective, SF = serum ferritin.

Yang et al., Medicine 2019;98:e17406

Question 4

Quelle(s) approche(s) envisager pour traiter une surcharge martiale ?

A. boire beaucoup de thé
B. déféripRone
C. déférasirox
D. déferoxamine
E. suivre un régime alimentaire pauvre en fer

Question 5

La chélation du fer :

A. peut diminuer les besoins transfusionnels
B. diminue le taux de ferritine
C. peut réduire la probabilité d'évolution d'une MDS vers la LAM
D. prolonge la survie sans événement cardiaque
E. est associée à une survie globale prolongée dans une étude prospective

Effet de la chélation sur la ferritinémie

ORIGINAL RESEARCH

Efficacy and safety of deferasirox estimated by serum ferritin and labile plasma iron levels in patients with aplastic anemia, myelodysplastic syndrome, or acute myeloid leukemia with transfusional iron overload

Il-Hwan Kim,[1] Joon-Ho Moon,[2]* Sung-Nam Lim,[1] Sang-Kyun Sohn,[2] Hoon-Gu Kim,[3] Gyeong-Won Lee,[3] Yang-Soo Kim,[4] Ho-Sup Lee,[4] Ki-Young Kwon,[5] Sung-Hyun Kim,[6] Kyung-Tae Park,[7] Joo-Seop Chung,[8] Won-Sik Lee,[9] Sang-Min Lee,[9] Myung-Soo Hyun,[10] Hawk Kim,[11] Hun-Mo Ryoo,[12] Sung-Hwa Bae,[12] and Young-Don Joo[1]*

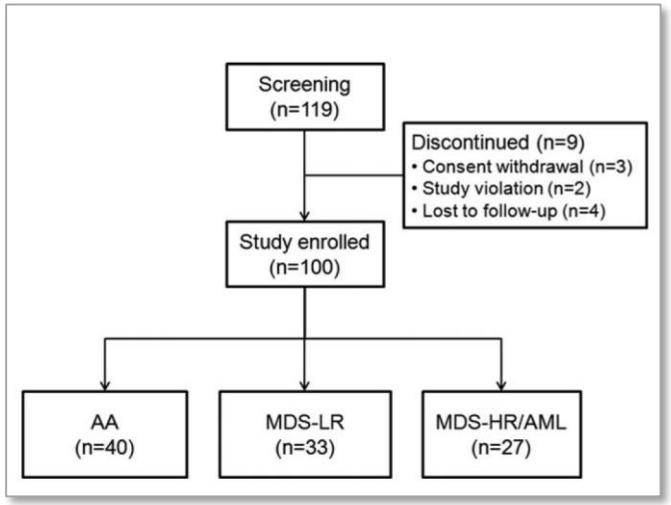


TABLE 1. Patients' characteristics and outcomes during the study

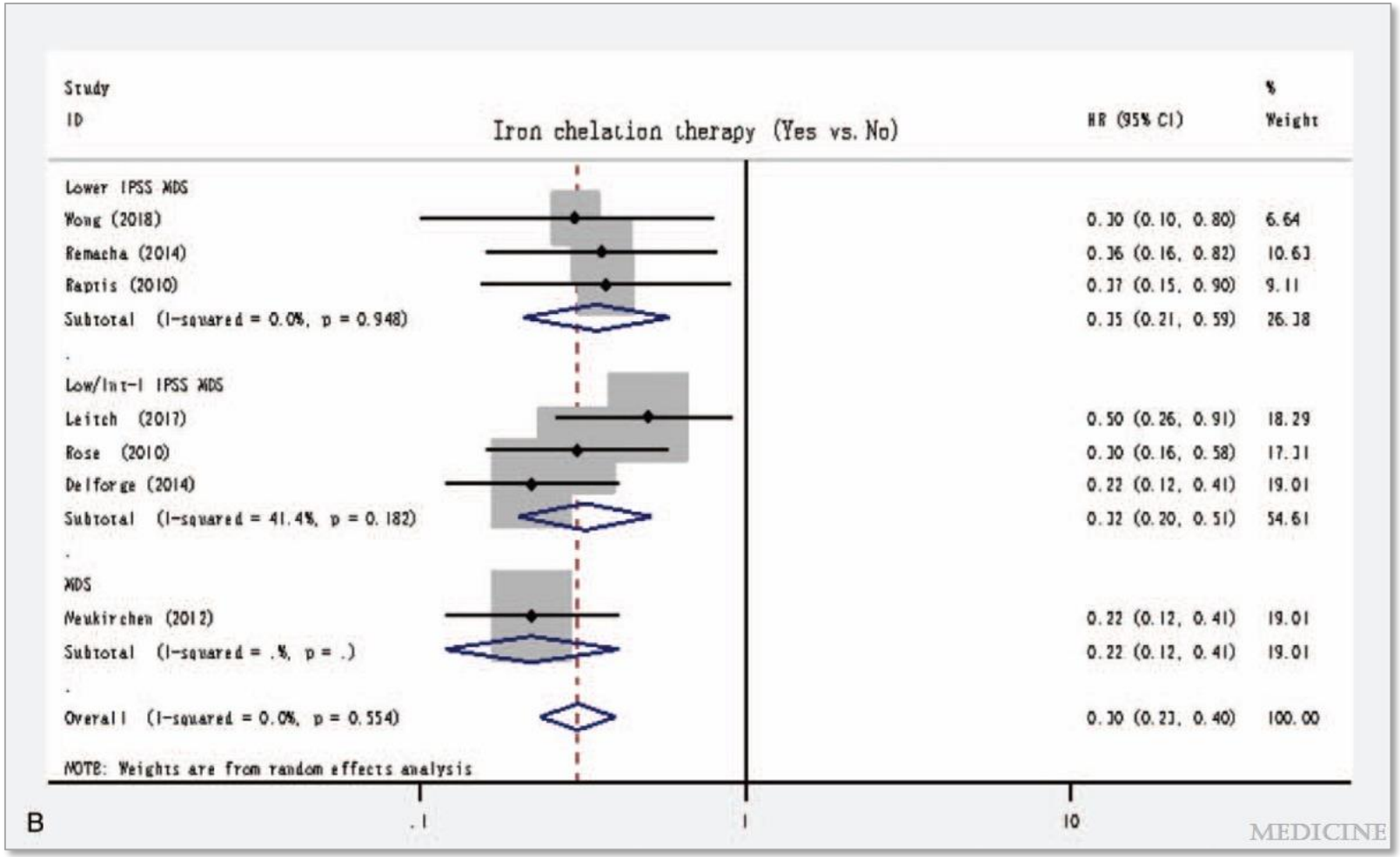
Characteristic	All patients 100 (100.0)	AA 40 (40.0)	MDS-LR 33 (33.0)	MDS-HR/AML 27 (27.0)
Age (years), median (range)	55 (17-79)	53 (17-79)	59 (20-75)	51 (18-75)
Gender, n (%)				
Male	62 (62.0)	28 (70.0)	21 (63.6)	13 (48.2)
Female	38 (38.0)	12 (30.0)	12 (36.4)	14 (51.8)
RBC transfusion before entry				
Number of times, mean ± SD	11.6 ± 7.7	11.4 ± 8.6	11.6 ± 5.6	12.0 ± 8.6
Number of units, mean ± SD	22.6 ± 16.3	22.4 ± 15.6	20.2 ± 11.7	25.8 ± 19.0
Baseline serum ferritin (ng/mL), median (range)	2000 (1073-10,446)	2000 (1073-8165)	2000 (1078-10,446)	2000 (1085-7973)
Baseline transferrin saturation (%), median (range)	88.6 (33.6-254.3)	92.2 (48.4-251.9)	95.7 (35.8-254.3)	84.8 (33.6-104.3)
Baseline LPI (μmol/L), mean (range)	0.24 (0-2.9)	0.20 (0-1)	0.16 (0-1.8)	0.32 (0-2.9)
Number of deaths, n (%)	20 (20.0)	5 (12.5)	6 (18.2)	9 (33.3)
Causes of deaths, n (%)				
Disease progression	5	1	2	2
Infection	13	4	3	6
Other	2	0	1	1

TABLE 2. Changes in serum ferritin and other iron metabolic index from baseline

Factor	All patients (n = 100)	AA (n = 40)	MDS-LR (n = 33)	MDS-HR/AML (n = 27)
DFX doses during study (mg/kg/month), mean (range)	174.0 (0.3-3451.4)	244.5 (3.9-3451.4)	124.9 (5.8-522.4)	79.6 (0.3-191.7)
RBC transfusions during study				
Number of times, mean ± SD	11.0 ± 8.8	10.7 ± 7.9	11.0 ± 10.0	11.5 ± 8.8
Number of units, mean ± SD	21.4 ± 16.8	21.6 ± 16.1	20.2 ± 17.1	23.0 ± 18.2
Serum ferritin (ng/mL), median (range)				
Baseline	2000 (1073-10,446)	2000 (1073-8165)	2000 (1079-10,446)	2000 (1086-7973)
At 1 year	1650 (97-7020)	1897 (315-5788)	1650 (97-3750)	1448 (186-7020)
Absolute change	−552 (−5428 to 5451)	−65 (−5428 to 3788)	−647 (−3040 to 1869)	−552 (−2899 to 5451)
p value	0.004	0.037	0.007	0.482
Transferrin saturation (%), median (range)				
Baseline	88.6 (33.6-254.3)	92.2 (48.4-251.9)	96.6 (35.8-254.3)	84.8 (33.6-104.3)
At 1 year	66.9 (20.2-241.0)	71.0 (33.6-241.0)	72.7 (20.9-227.9)	54.4 (20.2-112.0)
Absolute change	−10.5 (−69.4 to 71.0)	−6.9 (−58.3 to 71.0)	−10.0 (−57.4 to 52.2)	−27.6 (−69.4 to 20.8)
p value	0.013	0.531	0.374	0.002
LPI (μmol/L), mean (range)	(n = 66)	(n = 21)	(n = 19)	(n = 26)
Baseline	0.24 (0-2.9)	0.20 (0-1)	0.16 (0-1.8)	0.32 (0-2.9)
At 1 year	0.03 (0-0.3)	0.01 (0-0.1)	0.04 (0-0.2)	0.04 (0-0.3)
Absolute change	−0.23 (−2.6 to 0.2)	−0.17 (−1 to 0)	−0.21 (−1.6 to 0.2)	−0.30 (−2.6 to 0.1)
p value	0.036	0.179	0.203	0.243

Kim et al., Transfusion 2015;55:1613-20.

L'impact pronostique de la chélation *(méta-analyse d'études rétrospectives)*



Yang et al., Medicine 2019;98:e17406

Annals of Internal Medicine

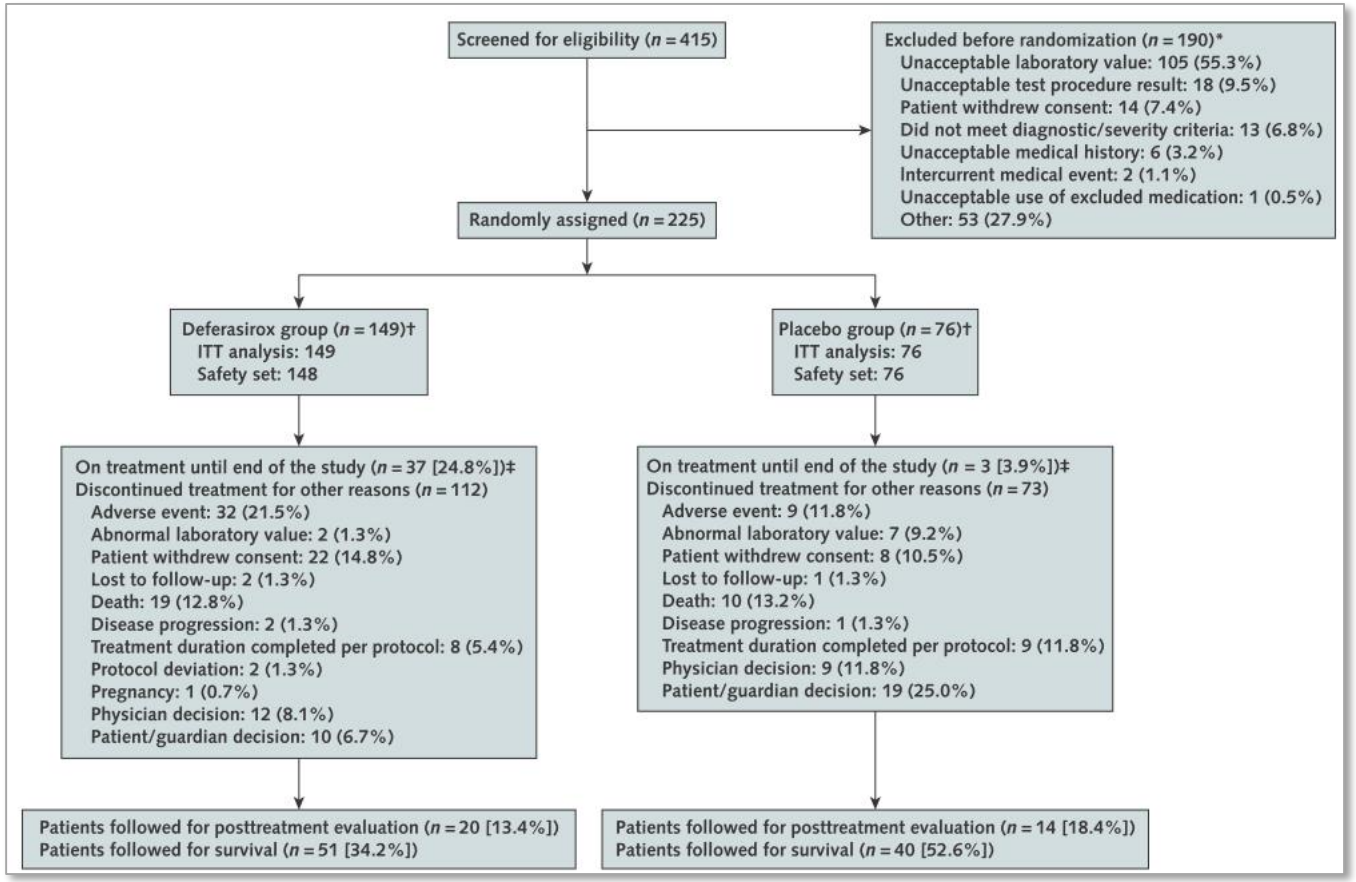
ORIGINAL RESEARCH

Iron Chelation in Transfusion-Dependent Patients With Low- to Intermediate-1–Risk Myelodysplastic Syndromes

A Randomized Trial

Emanuele Angelucci, MD; Junmin Li, MD; Peter Greenberg, MD; Depei Wu, MD; Ming Hou, MD; Efreen Horacio Montaño Figueroa, MD; Maria Guadalupe Rodriguez, MD; Xunwei Dong, MD; Jagannath Ghosh, MS; Miguel Izquierdo, MD; and Guillermo Garcia-Manero, MD; on behalf of the TELESTO Study Investigators*

Initialement 630 patients prévus
Objectif principal : EFS (dysfonction cardiaque, troubles hépatiques, cirrhose, évolution en LAM)
Recrutement lent



Angelucci et al., Ann Intern Med 2020;172:513-522.

Caractéristiques des patients

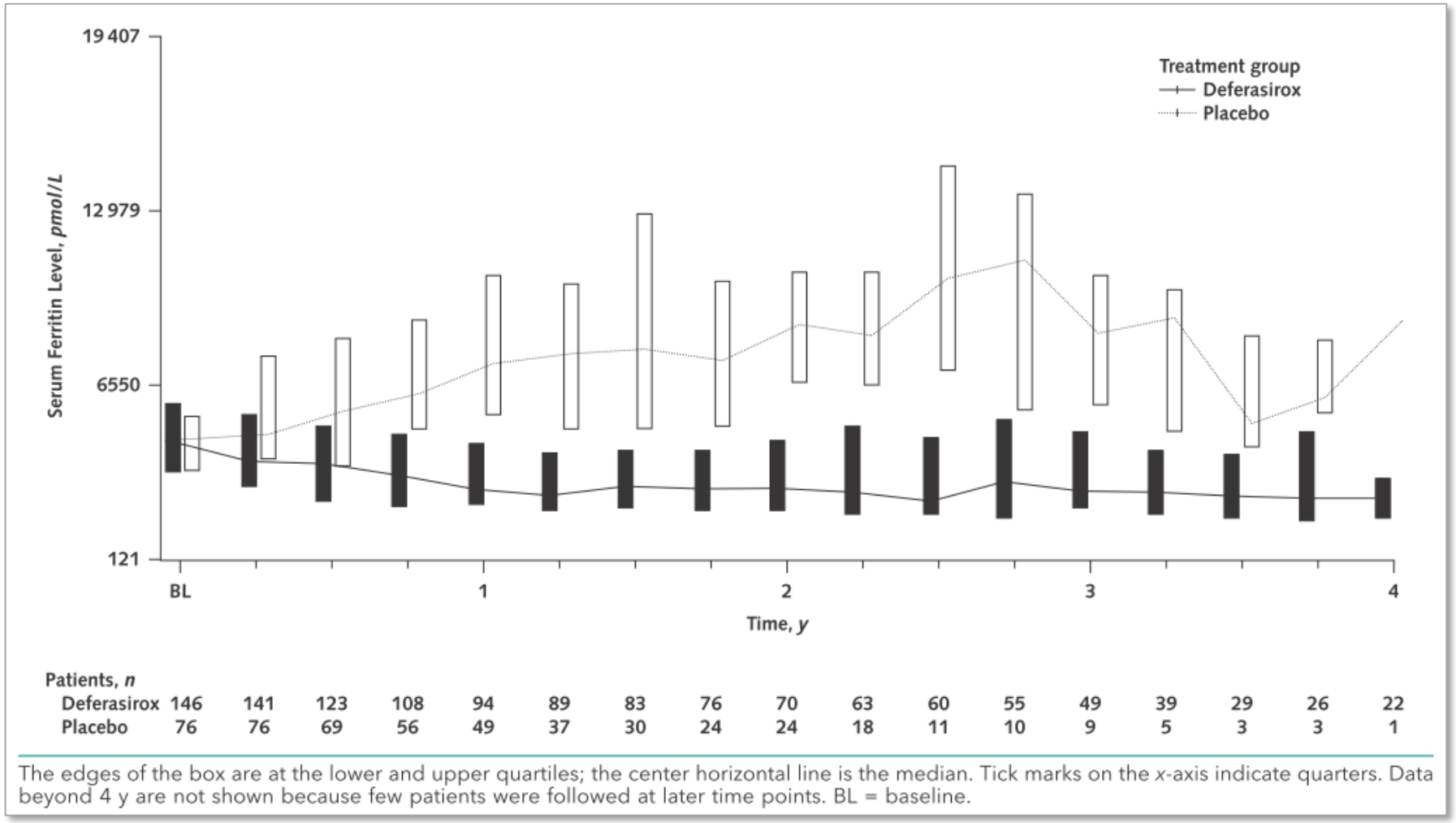
Table 1. Participant Demographic and Baseline Characteristics

Characteristic	Deferasirox Group (n = 149)	Placebo Group (n = 76)	All Patients (N = 225)
Median age (range), *y*	66 (21-88)	65 (20-80)	65 (20-80)
Age category, *n (%)*			
<65 y	71 (47.7)	37 (48.7)	108 (48.0)
≥65 y	78 (52.3)	39 (51.3)	117 (52.0)
Sex, *n (%)*			
Male	93 (62.4)	44 (57.9)	137 (60.9)
Female	56 (37.6)	32 (42.1)	88 (39.1)
Race/ethnicity, *n (%)*			
White	68 (45.6)	36 (47.4)	104 (46.2)
Asian	66 (44.3)	34 (44.7)	100 (44.4)
Other	15 (10.1)	6 (7.9)	21 (9.3)
IPSS risk score, *n (%)*			
Low	41 (27.5)	21 (27.6)	62 (27.6)
Intermediate-1	108 (72.5)	55 (72.4)	163 (72.4)
Bone marrow blasts, *n (%)*			
<5%	132 (88.6)	61 (80.3)	193 (85.8)
≥5%	9 (6.0)	10 (13.2)	19 (8.4)
Missing	8 (5.4)	5 (6.6)	13 (5.8)
Cytogenetic karyotype, *n (%)*			
Good	112 (75.2)	59 (77.6)	171 (76.0)
Intermediate	20 (13.4)	11 (14.5)	31 (13.8)
Poor	2 (1.3)	1 (1.3)	3 (1.3)
Missing	15 (10.1)	5 (6.6)	20 (8.9)
Cytopenias, *n (%)*			
0 or 1	35 (23.5)	26 (34.2)	61 (27.1)
2 or 3	83 (55.7)	35 (46.1)	118 (52.4)
Missing	31 (20.8)	15 (19.7)	46 (20.4)
Prior chelation therapy, *n (%)*	35 (23.5)	14 (18.4)	49 (21.8)
Mean (SD) transfusion units received 6 mo before randomization			
Packed RBCs	20.3 (9.8)	20.3 (13.2)	20.3 (11.0)
Platelets	52.4 (68.1)	39.0 (41.7)	48.1 (60.5)
Whole blood	4.6 (3.0)	3.1 (2.8)	3.8 (2.8)

IPSS = International Prognostic Scoring System; RBC = red blood cell.

Angelucci et al., Ann Intern Med 2020;172:513-522.

Effet sur la ferritine



The edges of the box are at the lower and upper quartiles; the center horizontal line is the median. Tick marks on the *x*-axis indicate quarters. Data beyond 4 y are not shown because few patients were followed at later time points. BL = baseline.

Angelucci et al., Ann Intern Med 2020;172:513-522.

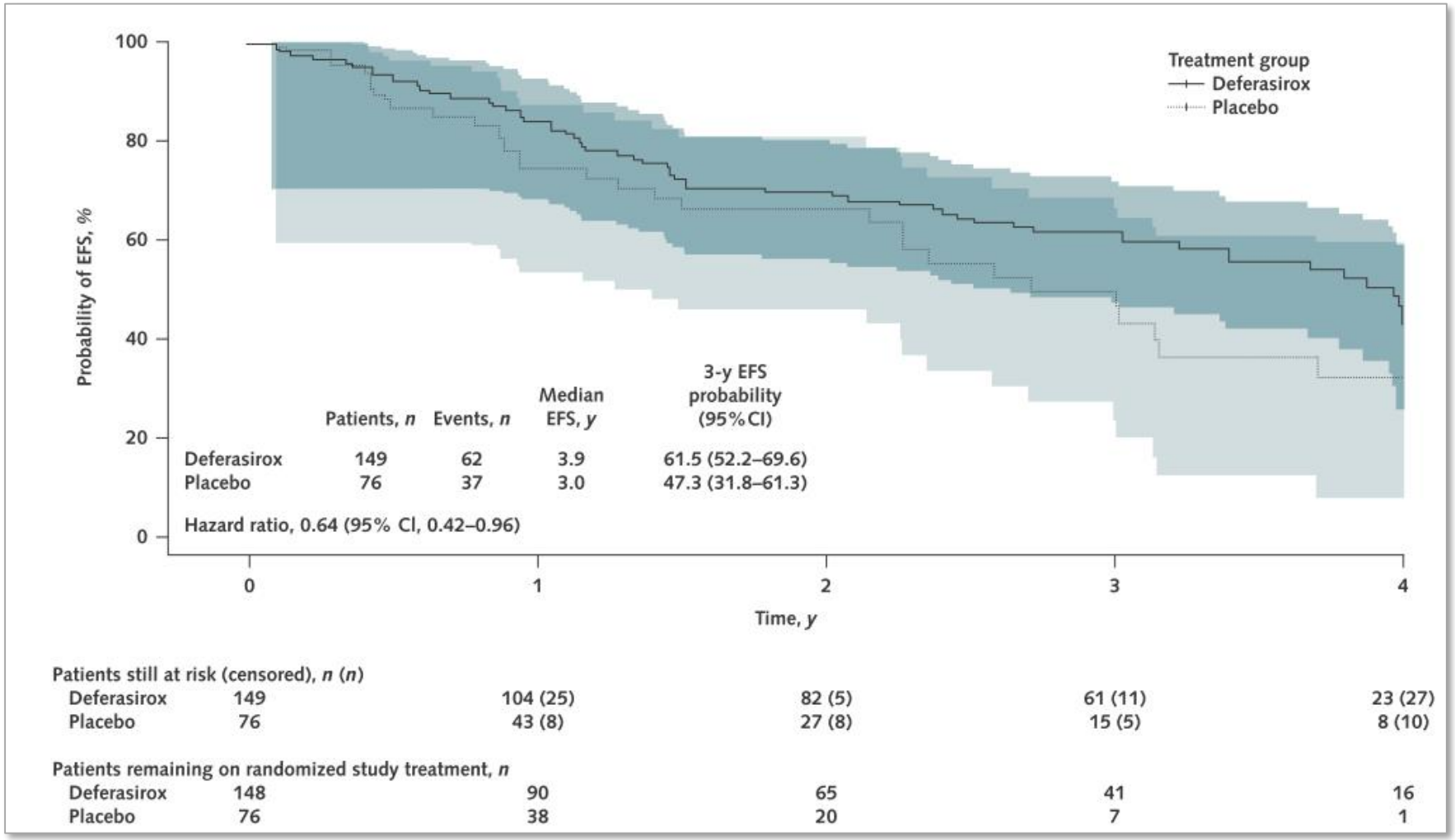
Quels sont les événements ?

Table 2. Summary of First-Occurring Nonfatal AEs or Death, and Overview of All AEs and Deaths Before Adjustment for Exposure Time

Event	Deferasirox Group, *n* (%)	Placebo Group, *n* (%)	All Patients, *n* (%)
First-occurring nonfatal AE or death*			
AE adjudicated by the EAC	27 (18.1)	17 (22.4)	44 (19.6)
AE confirmed by the EAC			
All AEs	14 (9.4)	12 (15.8)	26 (11.6)
AML	10 (6.7)	6 (7.9)	16 (7.1)
Hospitalization for CHF	1 (0.7)	3 (3.9)	4 (1.8)
Cirrhosis	0	0	0
Liver function impairment	1 (0.7)	1 (1.3)	2 (0.9)
Worsening cardiac function	2 (1.3)	2 (2.6)	4 (1.8)
Death	48 (32.2)	25 (32.9)	73 (32.4)

Angelucci et al., Ann Intern Med 2020;172:513-522.

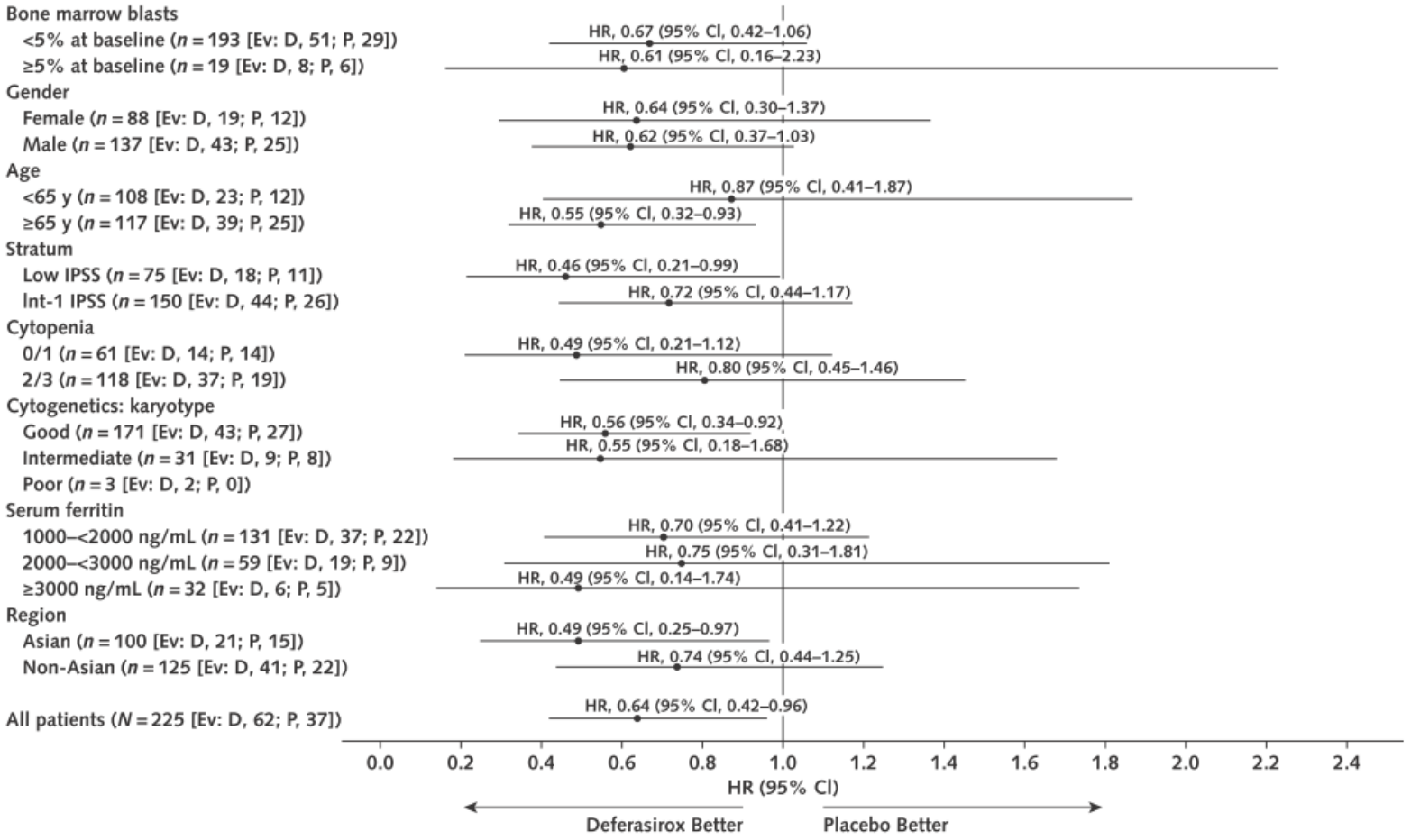
Résultats objectif principal



Angelucci et al., Ann Intern Med 2020;172:513-522.

Forest plot de l'EFS

Appendix Figure 1. Forest plot for event-free survival, by patient characteristics.

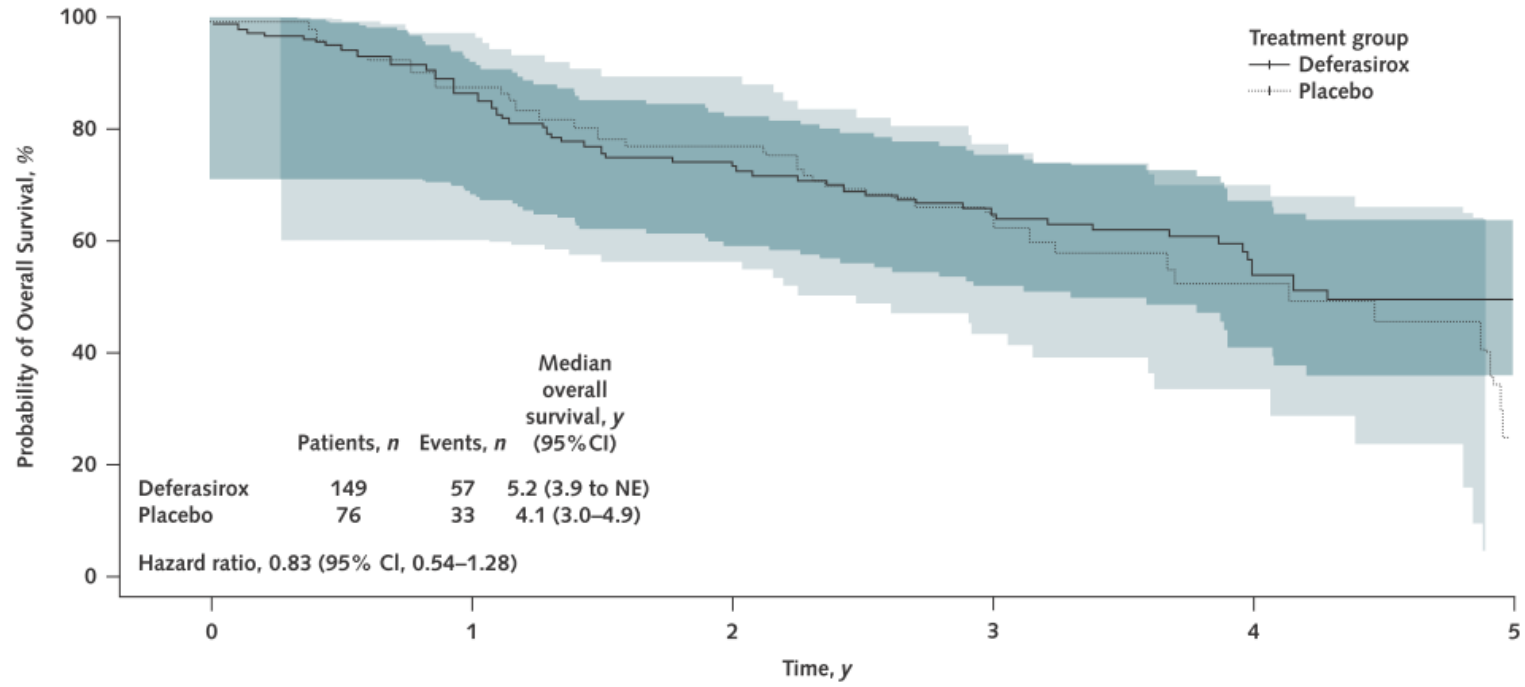


D = deferasirox group; Ev = event; HR = hazard ratio; Int-1 = intermediate-1; IPSS = International Prognostic Scoring System; P = placebo group.

Angelucci et al., Ann Intern Med 2020;172:513-522.

Survie

Appendix Figure 2. Kaplan-Meier curve of overall survival, by treatment, with 95% Hall-Wellner bands.



Patients still at risk (censored), *n* (*n*)						
Deferasirox	149	113 (19)	91 (5)	76 (5)	40 (27)	20 (17)
Placebo	76	60 (8)	45 (5)	33 (10)	18 (8)	4 (3)

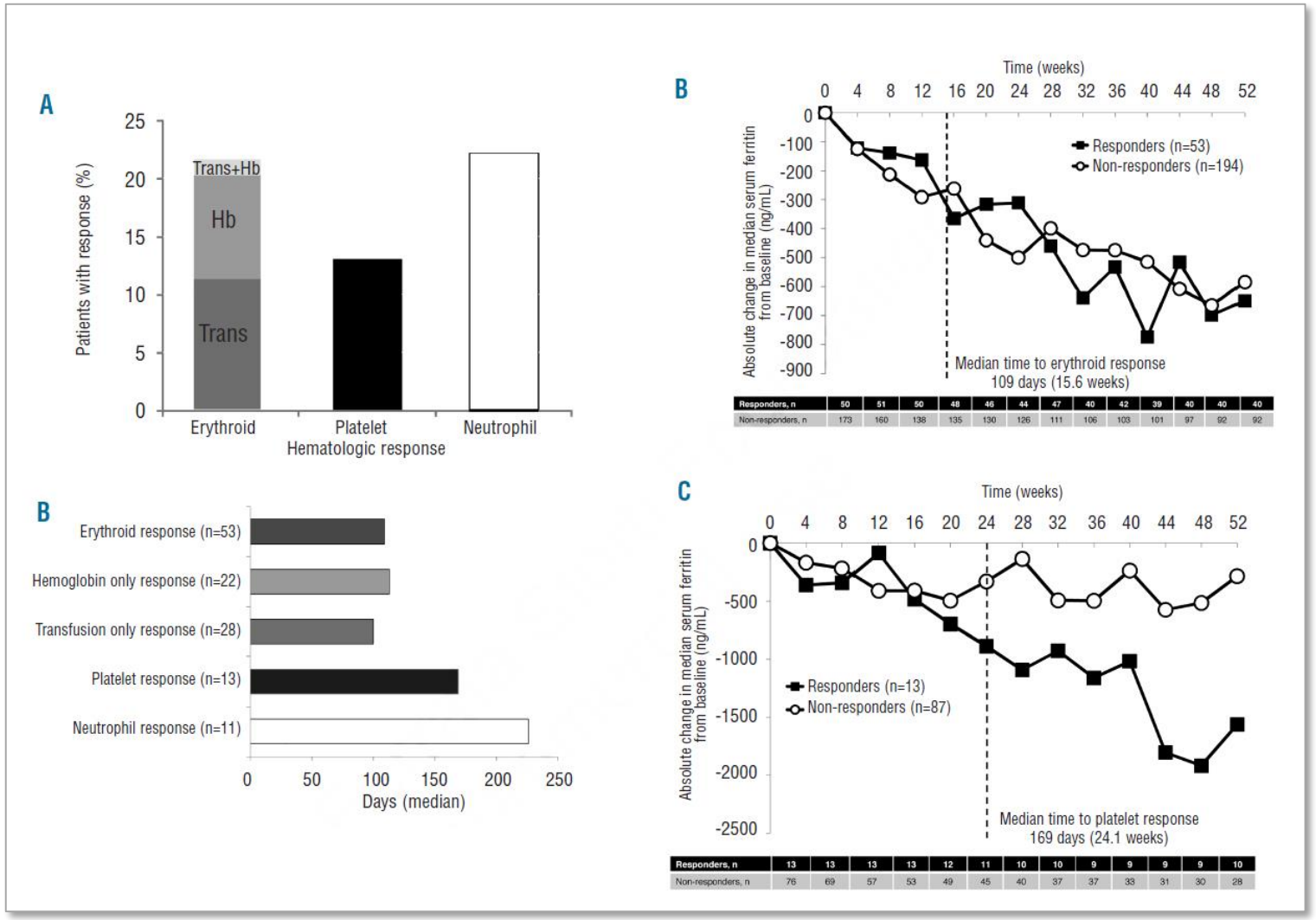
Patients remaining on randomized study treatment, *n*						
Deferasirox	148	90	65	41	16	8
Placebo	76	38	20	7	1	0

Angelucci et al., Ann Intern Med 2020;172:513-522.

Les surprises de la chélation

Etude EPIC
Patients évaluables :

- **247 E**
- **100 P**
- **50 N**



Gattermann et al., Haematologica 2012;97:1364-71.

Réponse hématologique

Appendix Table 5. Hematologic Improvement

Criterion	Analysis According to 2006 IWG Criteria			Post hoc Analysis According to More Stringent Criteria*		
	Deferasirox Group (n = 149)	Placebo Group (n = 76)	Difference	Deferasirox Group (n = 149)	Placebo Group (n = 76)	Difference
Hemoglobin increase ≥15 g/L versus pretreatment values and lasting ≥8 wk, *n (%)*	44 (29.5)	14 (18.4)	–	8 (6.6)	6 (8.8)	–
Reduction of ≥4.0 RBC transfusions over 8 wk compared with prerandomization values and lasting ≥8 wk, *n (%)*	28 (18.8)	9 (11.8)	–	21 (17.4)	11 (16.2)	–
Hematologic improvement in terms of erythroid response, *n* (% [95% CI]†)‡	59 (39.6 [31.4 to 47.8])	21 (27.6 [16.9 to 38.3])	12.0 [–1.8 to 25.7]	27 (22.3 [14.5 to 30.1])	14 (20.6 [10.2 to 30.9])	1.7 [–11.6 to 15.0]

IWG = International Working Group; RBC = red blood cell.
* Post hoc analysis that included only samples from patients who had not received transfusions within 1 mo before hemoglobin measurement for both baseline and posttreatment, or potential erythroid-modifying drugs (including erythropoiesis-stimulating agents, hypomethylating agents, or lenalidomide) during the preceding 28 d.
† 95% CIs for the frequency distribution of each variable and for the difference were computed by using the Wilson score method.
‡ Hematologic improvement in erythroid response was achieved in patients who satisfied either of the erythroid response criteria; a patient could satisfy both definitions but is only counted once in the hematologic improvement category.

Angelucci et al., Ann Intern Med 2020;172:513-522.

Impact de la chélation sur la survie

ARTICLE

Myelodysplastic Syndrome

Ferrata Storti Foundation

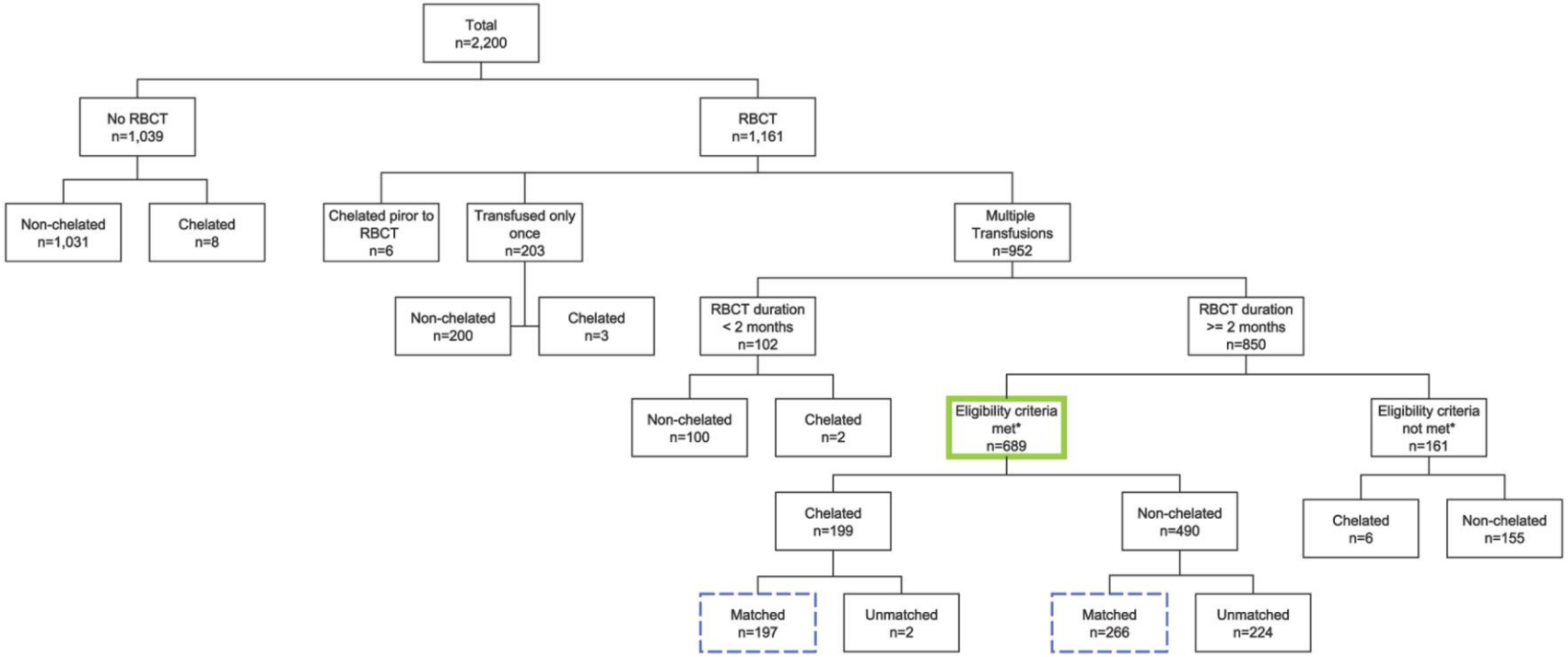
Impact of treatment with iron chelation therapy in patients with lower-risk myelodysplastic syndromes participating in the European MDS registry

Marlijn Hoeks,[1,2] Ge Yu,[3] Saskia Langemeijer,[4] Simon Crouch,[3] Louise de Swart,[4] Pierre Fenaux,[5] Argiris Symeonidis,[6] Jaroslav Čermák,[7] Eva Hellström-Lindberg,[8] Guillermo Sanz,[9] Reinhard Stauder,[10] Mette Skov Holm,[11] Moshe Mittelman,[12] Krzysztof Mądry,[13] Luca Malcovati,[14] Aurelia Tatic,[15] Antonio Medina Almeida,[16] Ulrich Germing,[17] Aleksandar Savic,[18] Njetočka Gredelj Šimec,[19] Dominic Culligan,[20] Raphael Itzykson,[5] Agnes Guerci-Bresler,[21] Borhane Slama,[22] Arjan van de Loosdrecht,[23] Corine van Marrewijk,[4] Jackie Droste,[4] Nicole Blijlevens,[4] Marian van Kraaij,[24] David Bowen,[25] Theo de Witte[26] and Alex Smith[3] on behalf of the EUMDS Registry Participants

Haematologica 2020
Volume 105(3):640-651

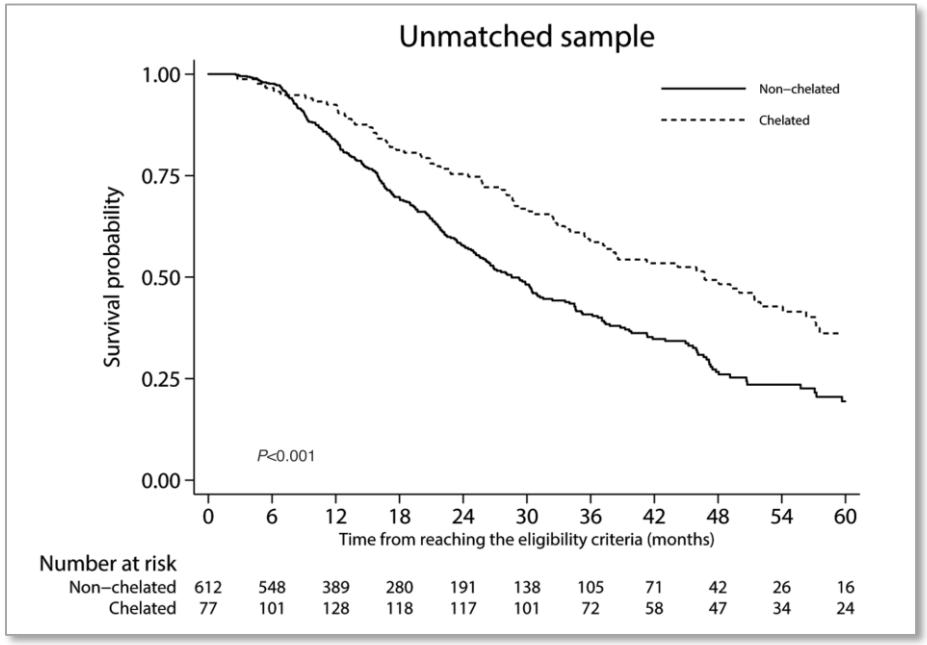
Registre européen
Patients MDS transfusés de plus de 2 mois
Score de propension pour apparier les patients chélatés vs. les non chélatés avec prise en compte :

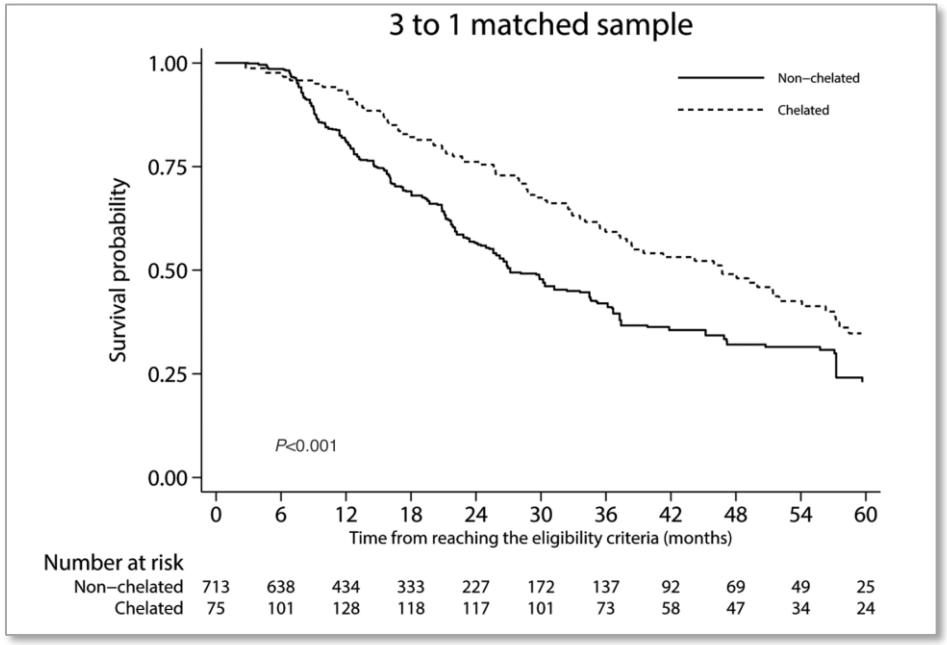
- **Age**
- **Sexe**
- **IPSS et IPSS-R**
- **Comorbidités**
- **Performance status**
- **Fardeau transfusionnel**
- **Présence de sidéroblastes en couronne**



Hoeks et al., Haematologica 2020;105:640-51.

Résultats





Hoeks et al., Haematologica 2020;105:640-51.

Recommandations thérapeutiques

Recommandations dans la littérature (1)

Guidelines	Patient selection	Treatment recommendations	Strength of evidence/ recommendation	Reference
NCCN	IPSS low/int-1 or potential HSCT candidates • > 20–30 RBC transfusions • Serum ferritin > 2500 ng/mL	• Daily ICT with SC deferoxamine or oral deferasirox • For serum ferritin > 2500 ng/mL, decrease to < 1000 ng/mL • Deferoxamine and deferasirox should not be used in patients with CrCl < 40 mL/min	Category 2A: lower-level evidence; uniform NCCN consensus	[1]
ESMO	IPSS low/int-1 or potential HSCT candidates • 20–60 RBC concentrates • Serum ferritin > 1000–2500 U/L • Cardiac T2* significantly reduced	• Deferasirox and deferoxamine are mentioned • Deferasirox should not be used in patients with renal failure • Deferiprone is not approved in most countries and can cause neutropenia	Evidence level V: expert opinion	[6]
ELN	RA, RARS, or MDS with isolated 5q deletion, or potential HSCT candidates • 25 RBC units • Serum ferritin > 1000 ng/mL	No specific ICT agents are mentioned	Recommendation level D: evidence level 3 (nonanalytic studies) or 4 (expert opinion)	[18]
British	RA, RARS, or MDS with isolated 5q deletion • 20 RBC units • Serum ferritin > 1000 ng/mL	• Deferoxamine is preferred • Deferasirox is recommended for patients who cannot tolerate deferoxamine • Deferiprone may be considered if baseline neutrophil levels are normal	Grade 2C	[19]

Zeidan & Griffiths, Blood Reviews 2018;32:368-77.

Recommandations dans la littérature (2)

Italian	IPSS low/int-1 • 20 RBC units IPSS int-2/high • Treatment response to life-expectancy-modifying therapies • HSCT candidates		Grade B Grade D	[20]
Spanish	IPSS low/int-1, WPSS very low/low/int, or IPE low risk, or HSCT candidates • Tranfusion dependent • Serum ferritin > 1000 ng/mL	Deferoxamine, deferasirox, and deferiprone are mentioned	Expert opinion	[21]
Austrian	Life expectancy > 2 years • > 2 RBC concentrates/month • Serum ferritin > 2000 ng/mL Life expectancy < 2 years • HSCT candidates • IO with organopathy or reduced QOL	• Deferoxamine should be offered first • Deferasirox is recommended for patients with an inadequate response or who cannot tolerate deferoxamine, and have no renal disease and stable creatinine clearance during the initial weeks of treatment • Drug-induced neutropenia is a consideration with deferiprone use	Expert opinion	[22]
Canadian	IPSS low/int-1, WPSS RA, RARS, or 5q-syndrome • Serum ferritin > 1000 ng/mL • HSCT candidates • Life expectancy > 1 year IPSS int-2/high • Serum ferritin > 1000 ng/mL • HSCT candidates • Life expectancy > 1 year • Evidence of iron-related organ damage • Serum ferritin > 1000 ng/mL and fasting transferrin saturation > 0.5	Either deferoxamine or deferasirox	Evidence level IV, recommendation grade C (for patient selection) Evidence level IIa, recommendation grade B (for treatment recommendations)	[23]

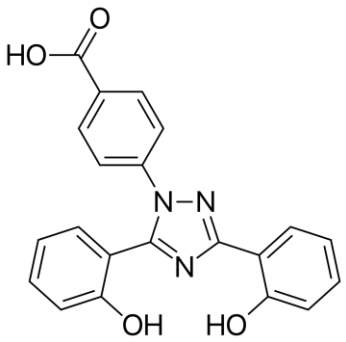
Zeidan & Griffiths, Blood Reviews 2018;32:368-77.

Question 6

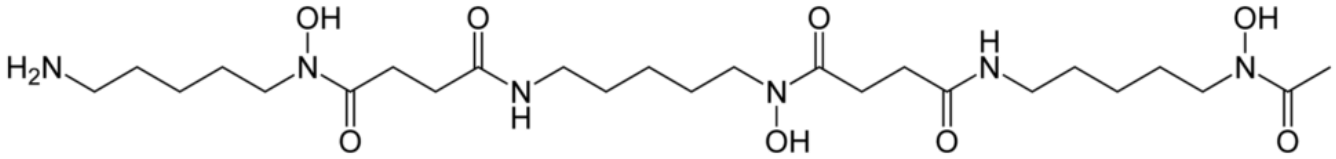
Finalement il faut chélater :

A. toute insuffisance médullaire chronique dès le début des transfusions
B. à partir de 20 concentrés érythrocytaires reçus
C. dès que la ferritine sérique atteint 2500 mg/L
D. un patient présentant une érythroblastopénie, transfusé, dont la dernière ferritinémie est à 1025 mg/L
E. tous les patients présentant la mutation SF3B1 dans la moelle

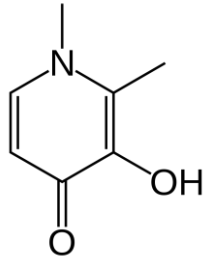
3 chélateurs du fer disponibles dans la pharmacopée



Déférasirox
EXJADE®



Déféroxamine
DESFERAL®



Défériprone
FERRIPROX®

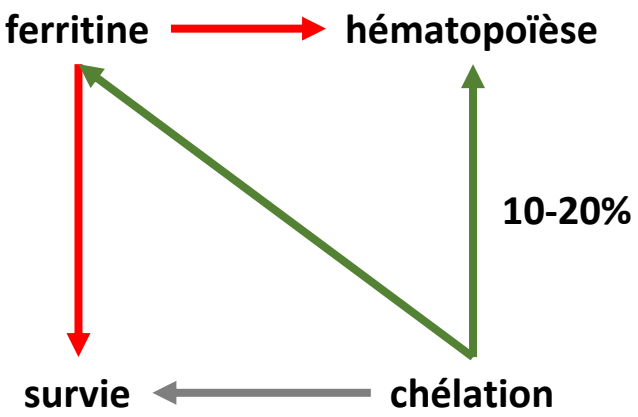
En pratique

20 CE et/ou ferritine > 1000 µg/L
Surveillance biologique et clinique
Recours éventuel à l'IRM en cas de symptômes

	Déférasirox	Déféroxamine	Déféripone
Voie d'administration	PO	SC	PO
Posologie	14 mg/kg/j	20-60 mg/kg/j	75 mg/kg/j
Toxicité principale	Rénale	Oculaire	Neutropénie
Recommandations	Surveillance mensuelle de la ferritine, paliers de modification de dose de 3 mois	Injection de préférence la nuit	Surveillance hémato+++

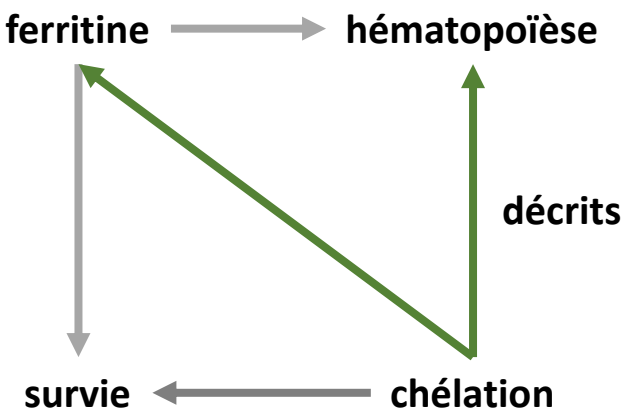
Synthèse

MDS bas risque

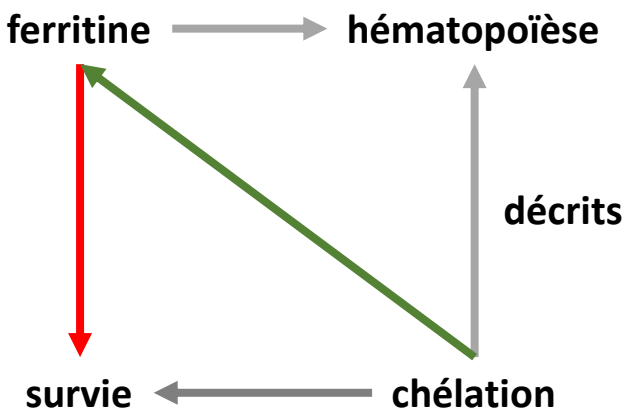


Pas démontré prospectivement
Oui rétrospectivement

Aplasie médullaire



Allogreffés



Pas en pré-greffe
Oui en post-greffe

Discussion