FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

L'attuale approccio clinico al paziente con **Sindrome Mielodisplastica**

Napoli

La terapia ferrochelante

Pellegrino Musto

Direzione Scientifica

IRCCS-CROB, Centro di Riferimento Oncologico della Basilicata

Rionero in Vulture (Pz)

My Agenda

- Iron balance and overload
- Clinical results of chelation: reduction of iron overload
- Clinical results of chelation: hematologic improvement
- Clinical results of chelation: survival
- Iron chelation in higher risk MDS
- Perspectives

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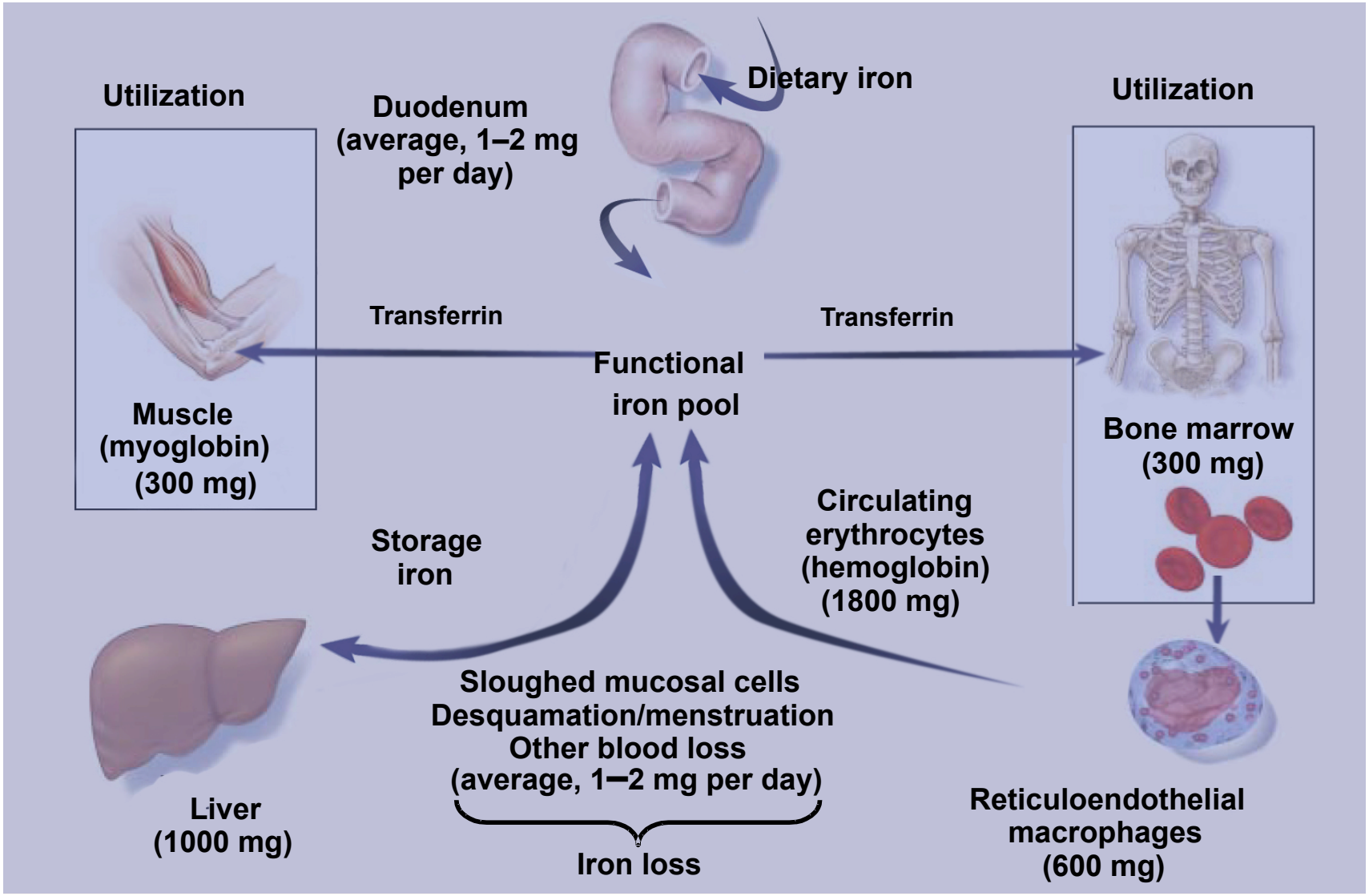
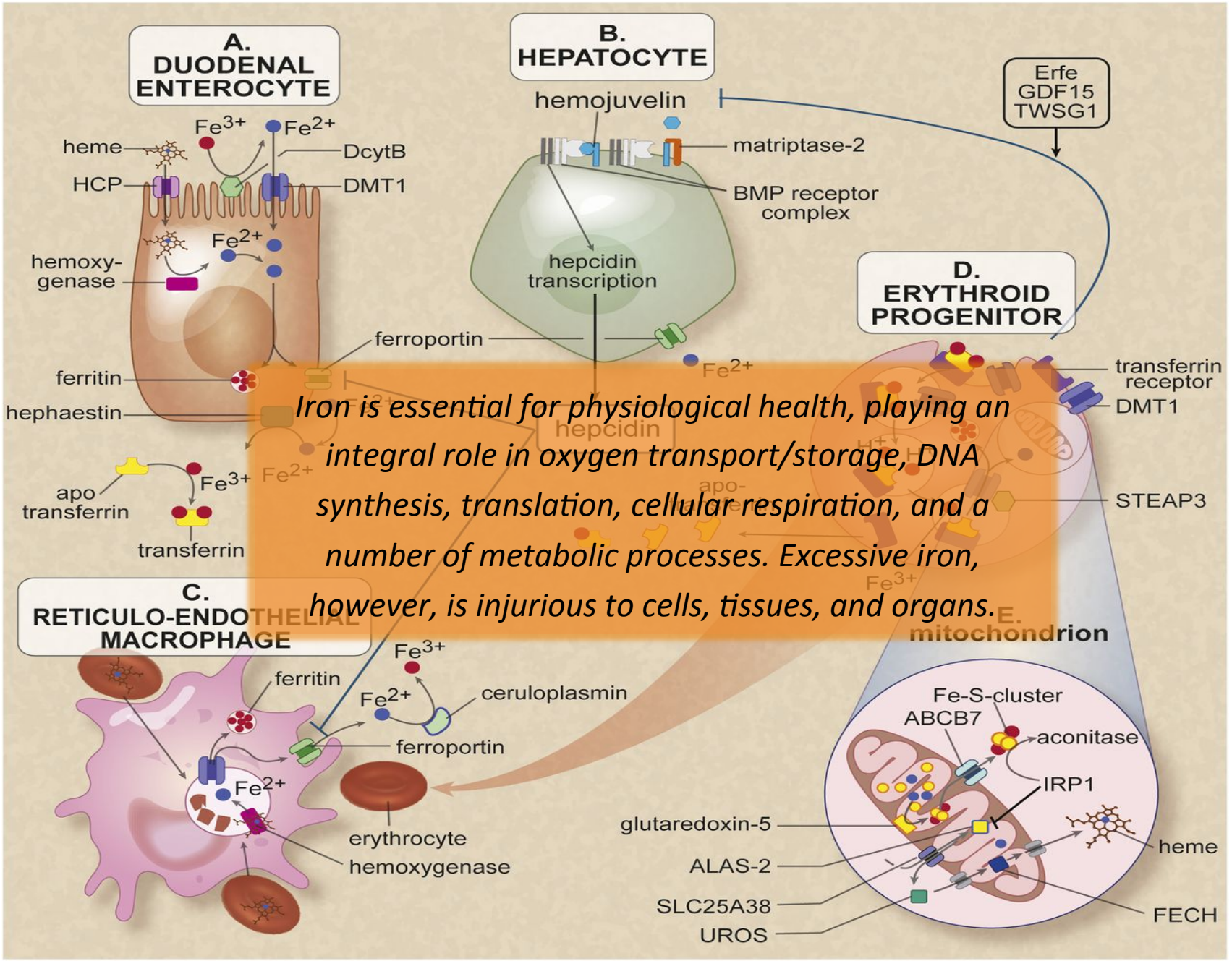
Normal body iron distribution and storage

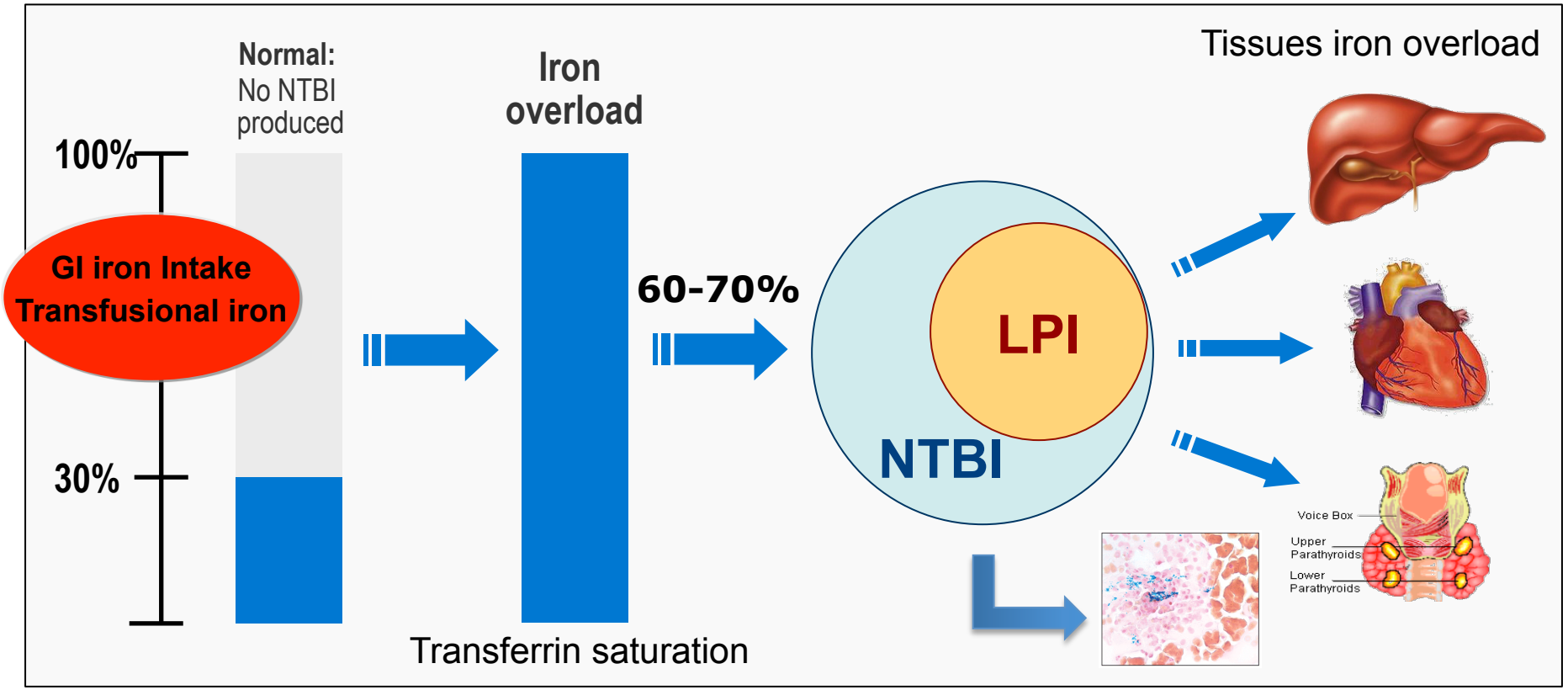


Andrews NC. *N Engl J Med* 1999;341:1986–1995, © Massachusetts Medical Society, with permission



Two to Tango: Regulation of Mammalian Iron Metabolism *Cell* Volume 142, Issue 1, Pages 24-38 (July 2010)

Non-transferrin-bound iron (NTBI) and labile plasma iron (LPI)



NTBI appears when plasma iron exceeds transferrin binding capacity (saturation > 60–70%)[1]

LPI is a **chelatable** redox-active component of NTBI[2]

1. Hershko C, Peto TE. Br J Haematol. 1987;66:149-51.
2. Cabantchik ZI, et al. Best Pract Res Clin Haematol. 2005;18:277-87
3. Ann N Y Acad Sci. 2016 Mar;1368(1):115-214

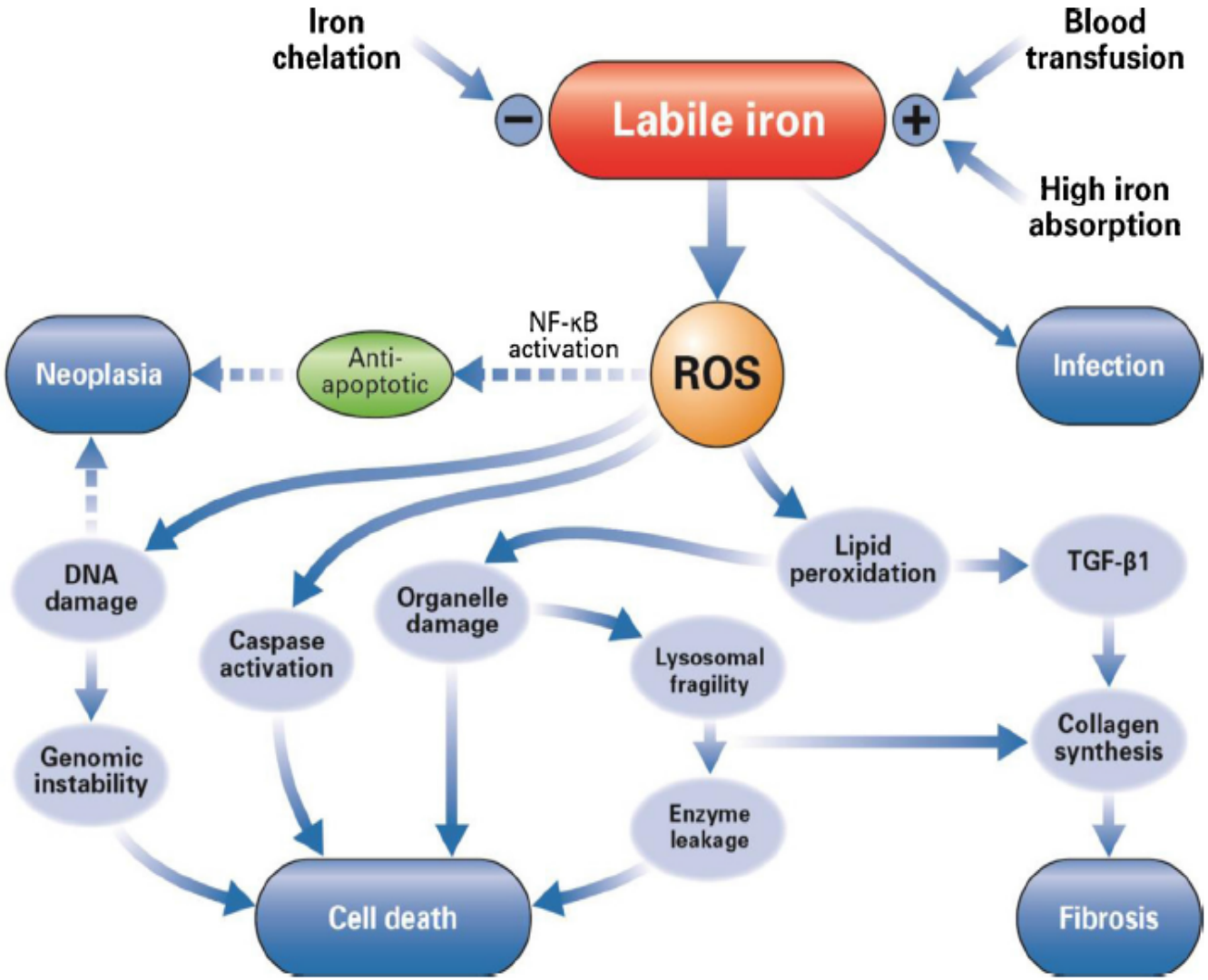
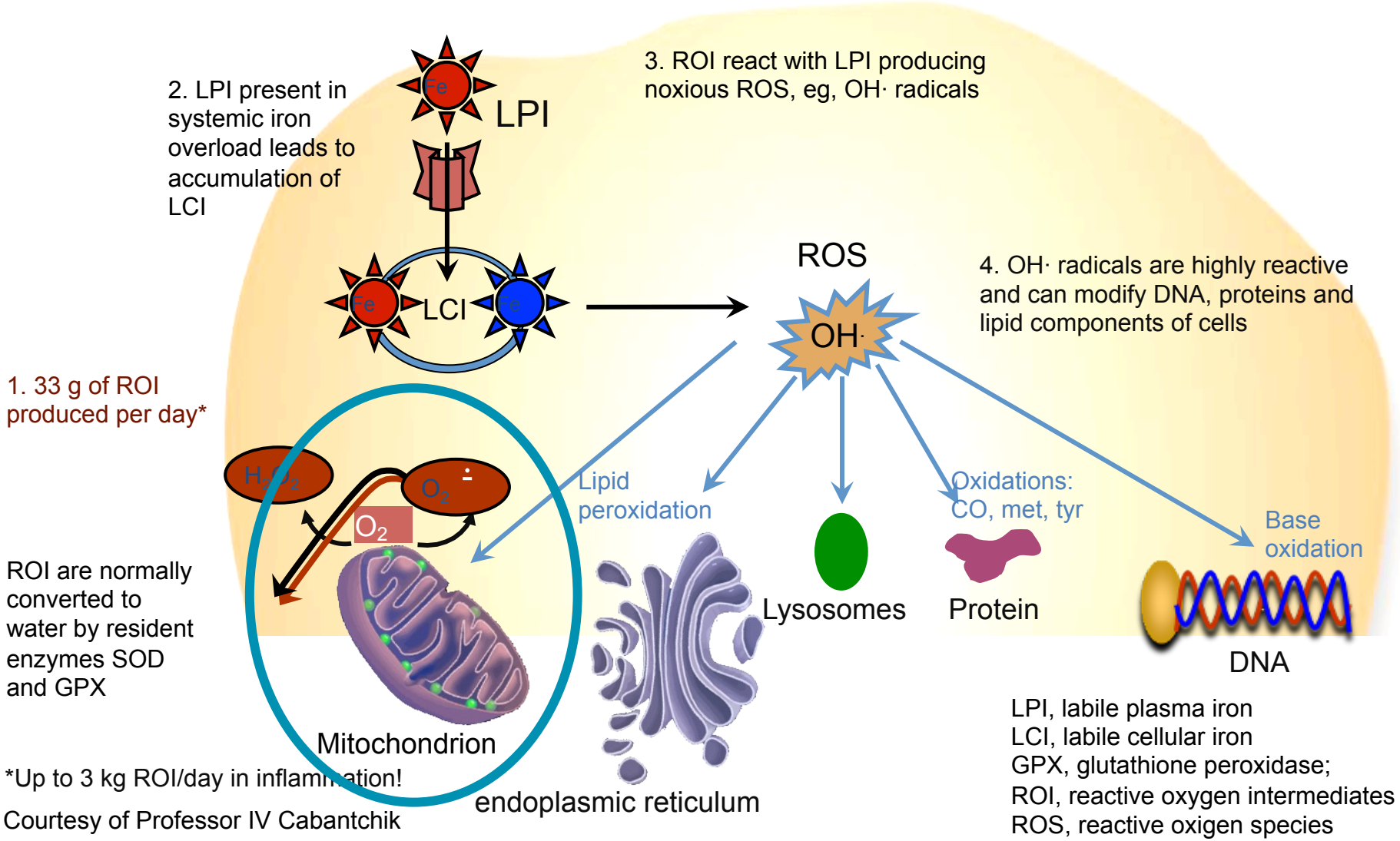
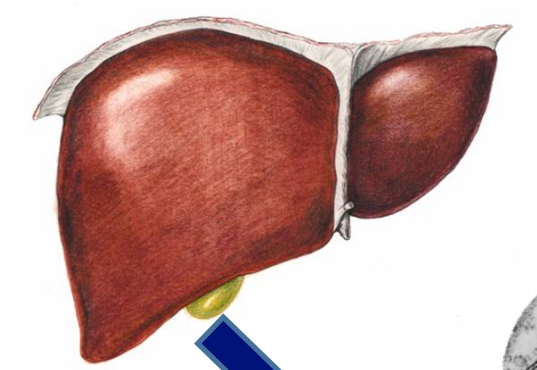


Fig. 1. Pathological mechanisms and consequences of iron overload. NF-κB, nuclear factor κB; ROS, reactive oxygen species; TGF, transforming growth factor. Adapted from Porter and Garbowski (2014) with permission from Elsevier.

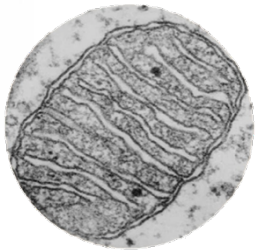
Iron toxicity on a cellular level

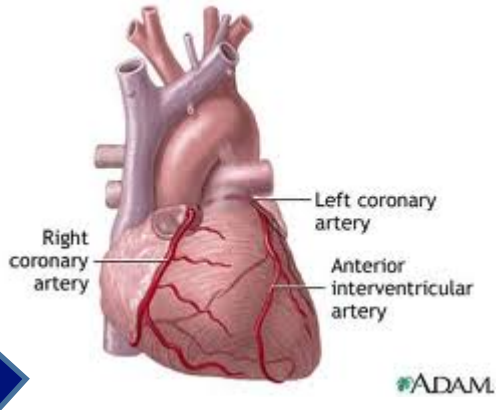


Why toxicity due to iron overload occurs mainly in liver and heart?



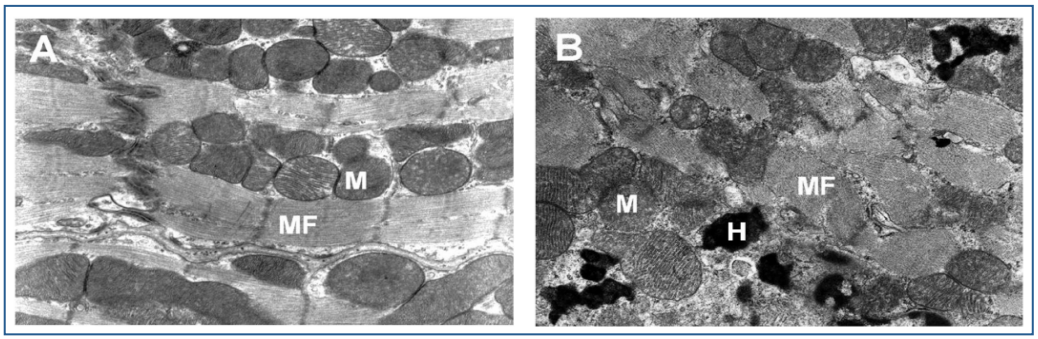
High levels of mithocondrial activity





Tissue damage

M: mitochondria
MF: myofibrils
H: electron dense iron stores



Control

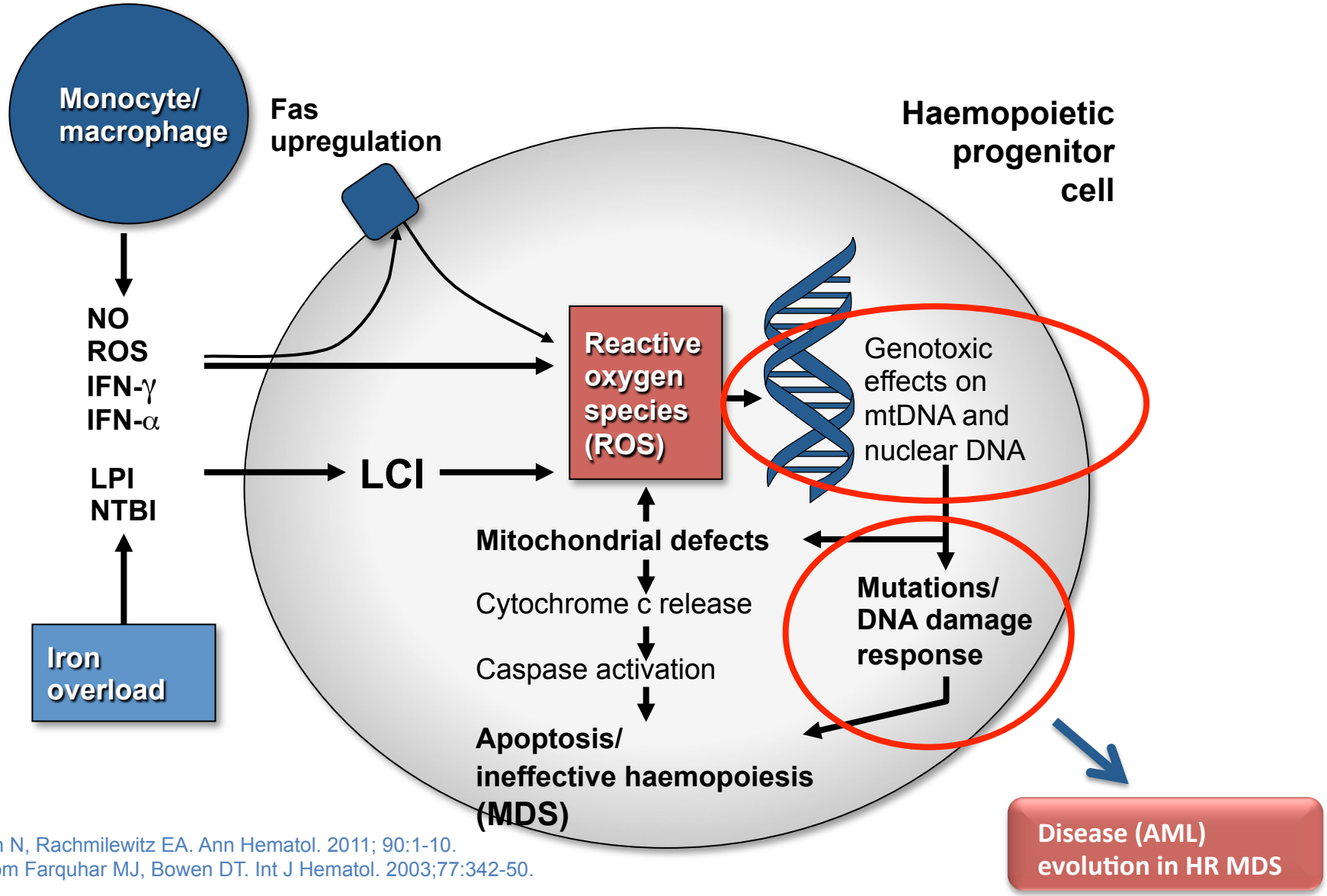
Iron loaded

ROS production

Hearts of iron-loaded mice had irregularly shaped mitochondria, electron dense material

Gao X, et al. Free Radic Biol Med. 2010 49:401–40

The role of iron overload in inducing oxidative stress in MDS



Gattermann N, Rachmilewitz EA. Ann Hematol. 2011; 90:1-10.
Adapted from Farquhar MJ, Bowen DT. Int J Hematol. 2003;77:342-50.

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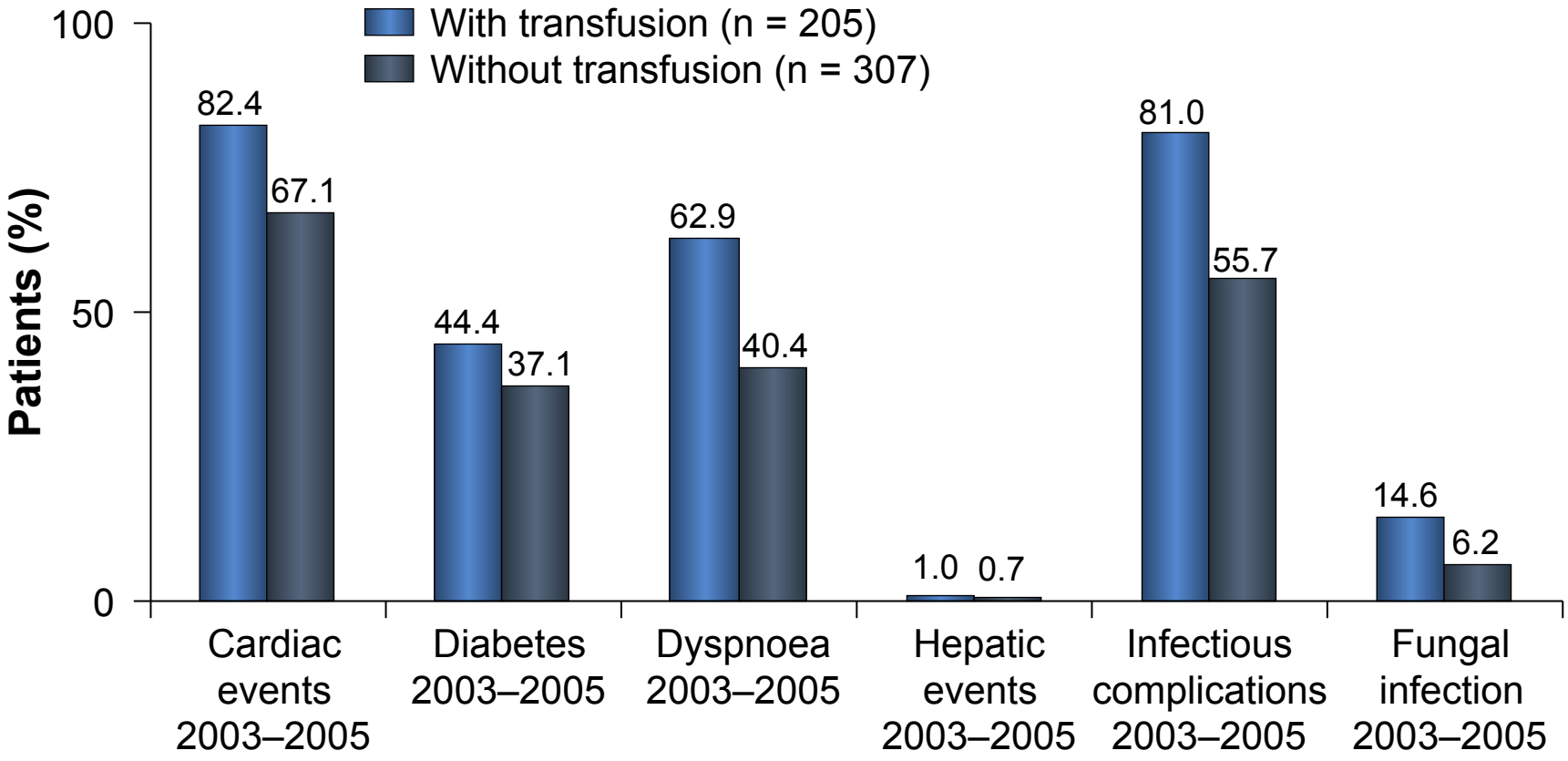
Table 2
Consequences of iron overload secondary to transfusion.

Organ	Sign/symptoms
Cardiac	Congestive heart failure, arrhythmias
GI	Cirrhosis, hepatocellular carcinoma
Endocrine	Insulin resistance, diabetes, thyroid dysfunction, sexual dysfunction
Pulmonary	Dyspnea
Immune	Increased risk of infection
Rheumatology	Arthritis
General	Fatigue

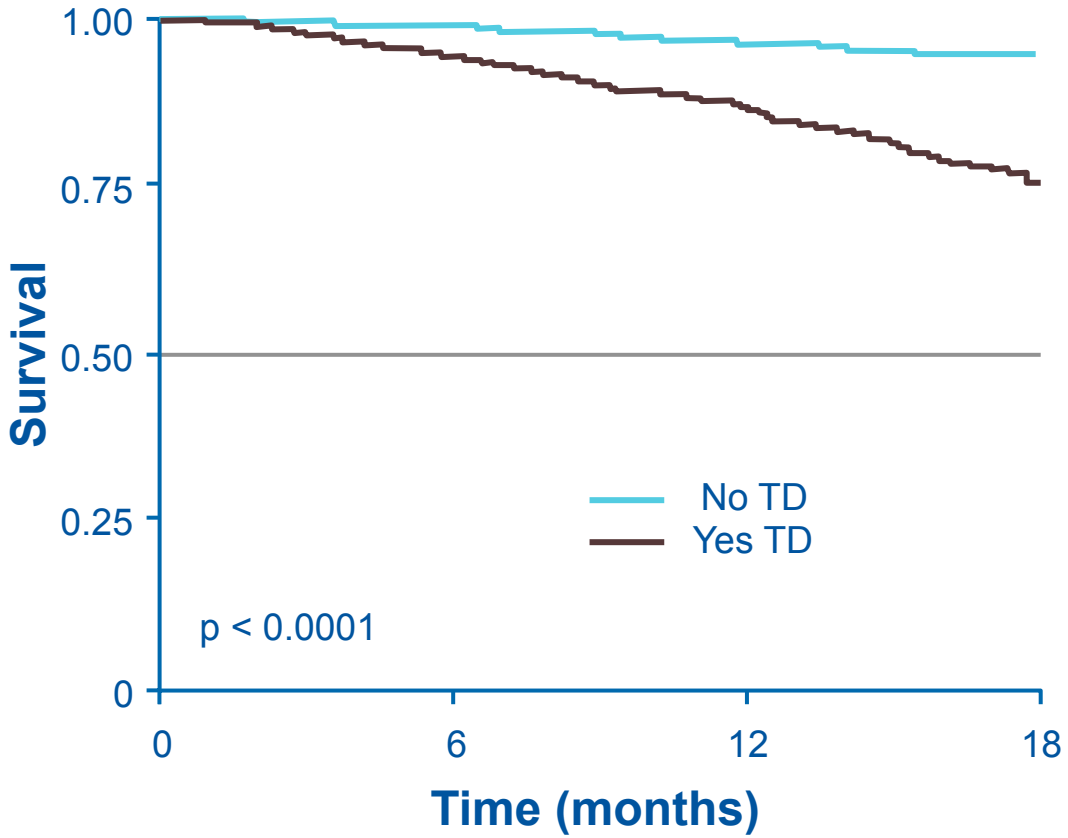
Prevalence of comorbidities in transfusion-dependent MDS



Transfused MDS patients have a higher prevalence of cardiac events, diabetes mellitus, dyspnoea, and hepatic and infectious diseases than non-transfused MDS patients

Goldberg SL, et al. J Clin Oncol. 2010;28:2847-52.

Overall survival of 1000 transfusion-dependent and non-transfusion-dependent patients with low and Int-1 IPSS risk



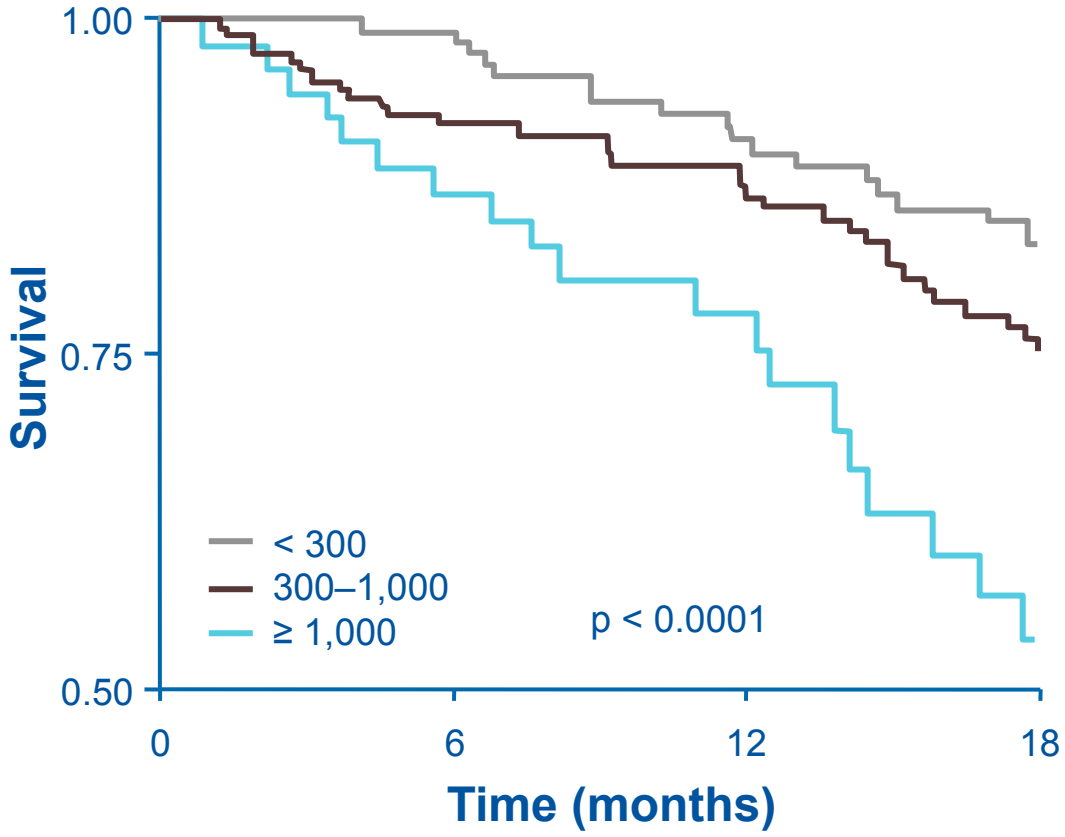
LeukemiaNet EUMDS REGISTRY

Significantly greater mortality was noted in MDS patients who were transfusion-dependent ($p < 0.0001$)

46% of patients had hypertension, 18% diabetes mellitus, 12% arrhythmia, and 12% thyroid disease.23 Survival data were further confirmed by a recent update

Adapted from de Swart L, et al. Blood. 2011;118:[abstract 2775].

Overall survival of transfusion-dependent patients by baseline serum ferritin status



LeukemiaNet EUMDS REGISTRY

Iron Health alliance

de Swart L, et al. Blood. 2011;118:[abstract 2775].

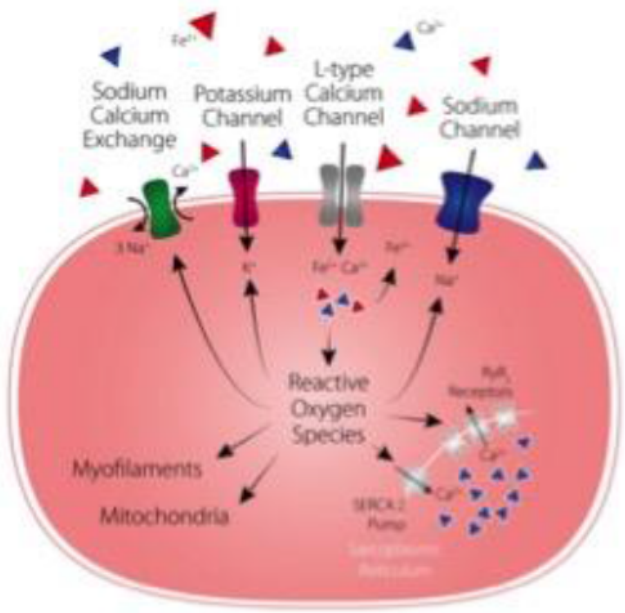
Although iron infrequently accumulates to the degree seen with iron-related target organ damage in thalassemia, its mild overload is still associated with poor prognosis in patients with MDS.

- 51% of non-leukemic causes of death were due to cardiac failure in low-risk MDS, compared with 31% due to infection and 8% due to hepatic cirrhosis. ***Malcovati et al, J Clin Oncol 2005***

- In a retrospective analysis of 840 MDS patients, 25% had cardiovascular comorbidities, and 63% of deaths were due to cardiac failure. Multivariate analyses showed that any cardiovascular comorbidity increased non-leukemic deaths significantly, with an HR of 3.7. This risk was even more pronounced in patients who are transfused. ***Della Porta et al, Haematologica 2011***

Two possible explanation of this effect:

- 1) lower, not detectable, levels of iron accumulation can have dangerous clinical negative effect
- 2) circulating "reactive iron species - free iron forms" in myocyte cells can damage without clear evidence of overload.

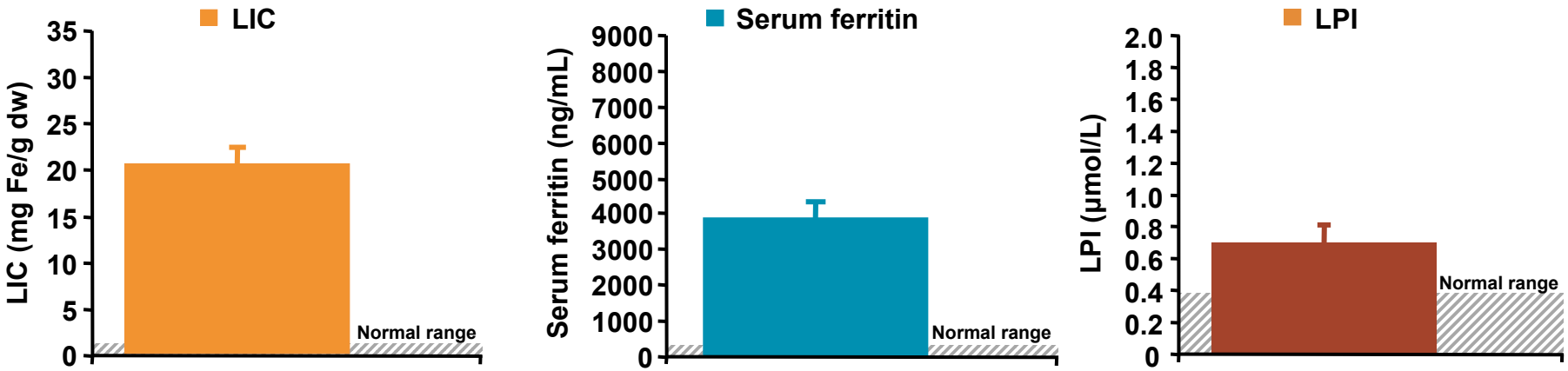


Angelucci and Pilo, 2017

Figure 2: Mechanistic illustration of disordered calcium handling (and in turn excitation-contraction coupling) and multiple ion channel disruption as a result of iron influx into the cardiac myocyte, with generation of dangerous reactive oxygen species.

US study evaluating LIC by MRI (R2) shows high baseline liver iron burdens in MDS

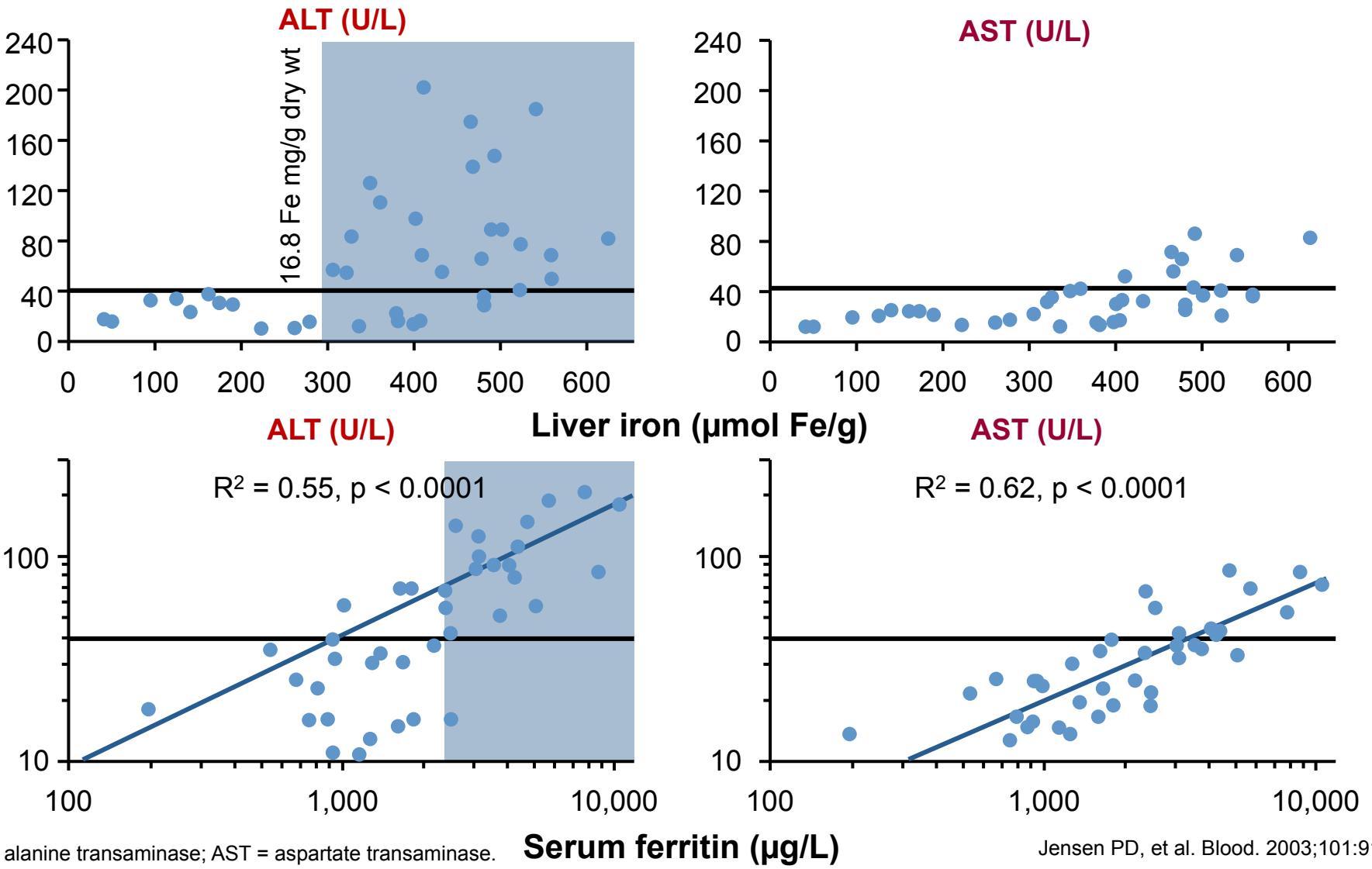
- 12-month, Phase II study to evaluate the efficacy and safety of deferasirox (20–30 mg/kg/day) in 24 patients with Low/Int-1-risk MDS
- First prospective, multicenter trial to evaluate LIC using R2 MRI technique
- Baseline iron burden patients demonstrates a high degree of iron overload (based on LIC, serum ferritin, labile plasma iron [LPI], etc)
- Iron overload meets criteria for treatment based on NCCN and Nagasaki MDS guidelines



Greenberg PL *et al*. *Leuk Res* 2010

Study US02

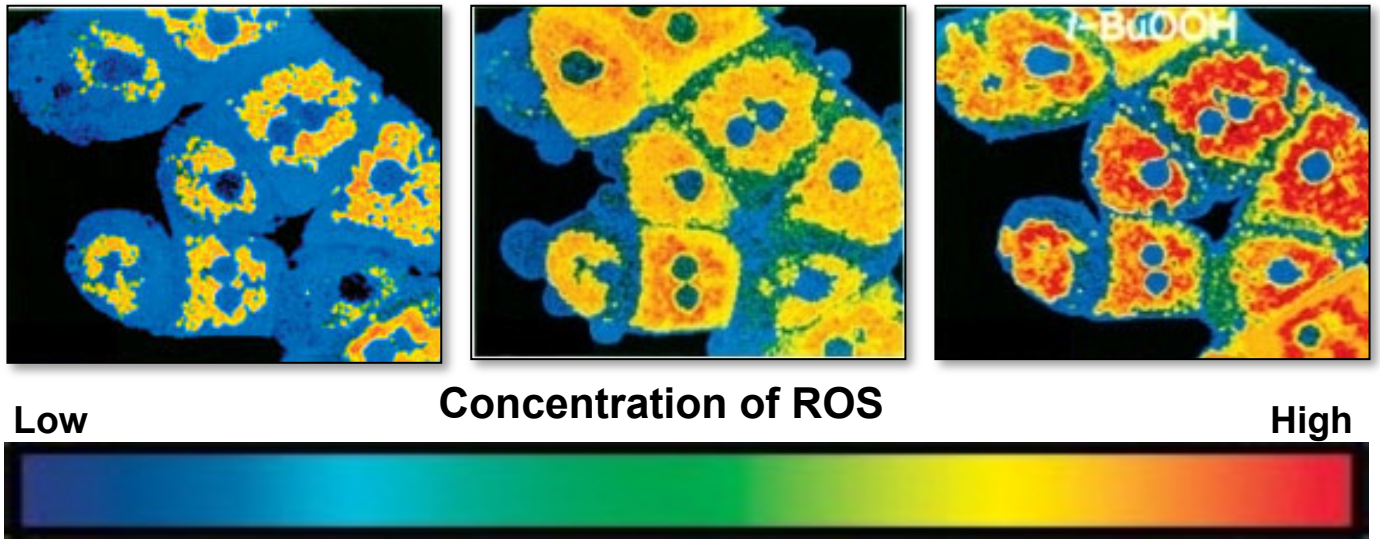
Liver enzymes increase in MDS with transfusions at LIC values > 15–20 mg Fe/g dry wt



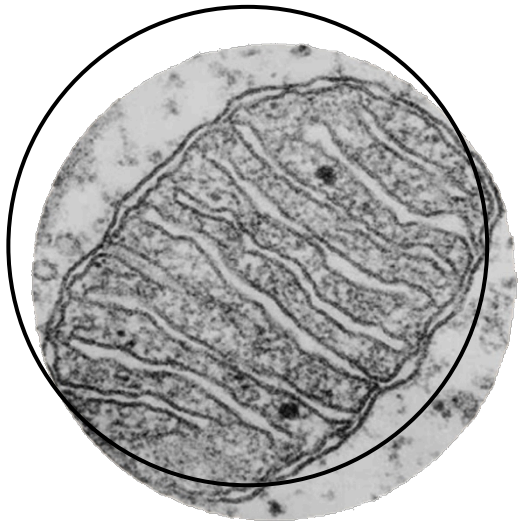
ALT = alanine transaminase; AST = aspartate transaminase.

Jensen PD, et al. Blood. 2003;101:91-6.

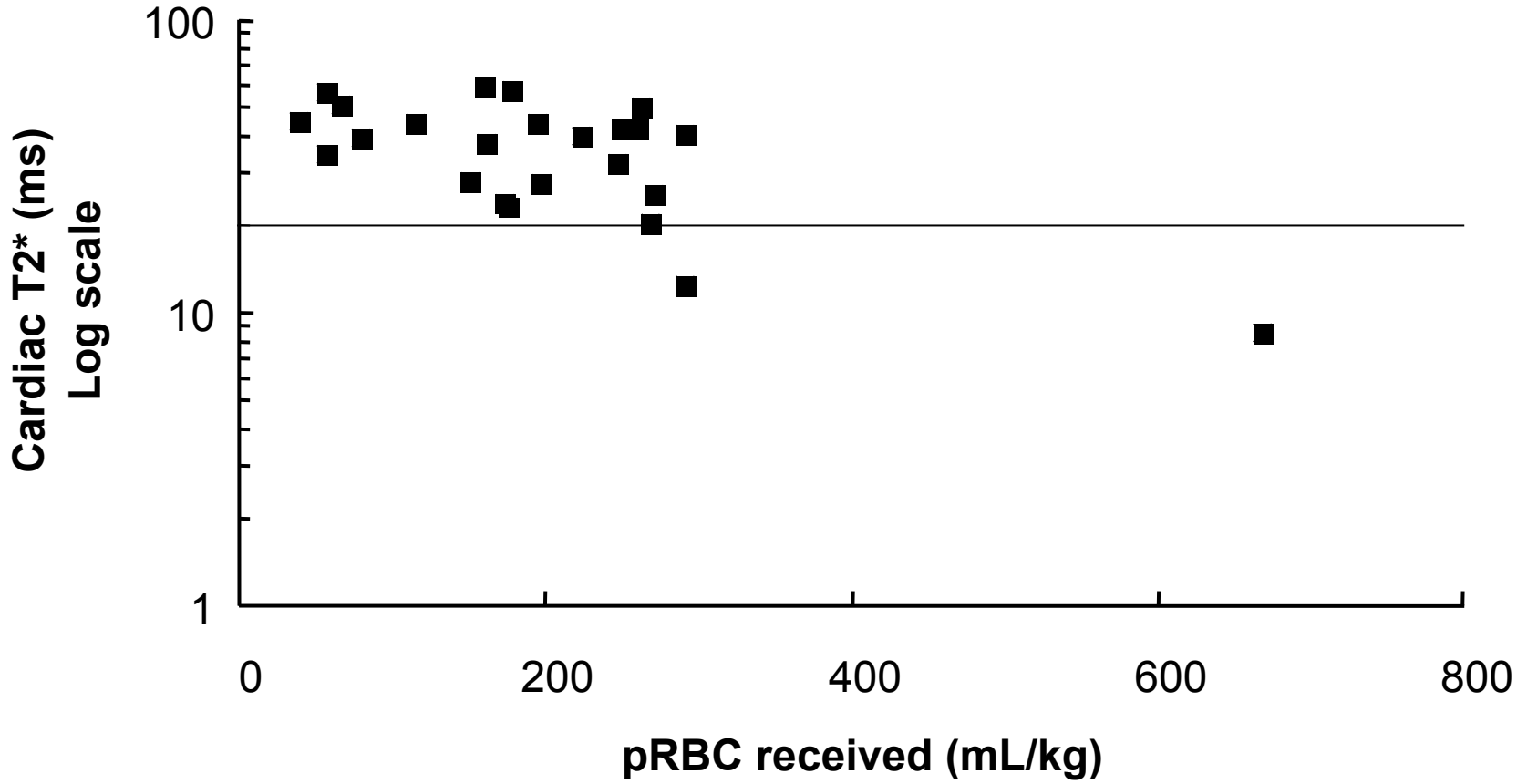
Molecular level: ROS concentration in hepatocytes increases with LIC



Iron overload and ROS stress result in mitochondrial damage



Myocardial iron in unchelated patients with MDS



Di Tucci AA. Myocardial iron overload assessment by T2* magnetic resonance imaging in adult transfusion dependent patients with acquired anemias. Haematologica Sept 2008.

Thalassemia vs hemochromatosis vs MDS: a different iron overload scenario

Table 1. Different pattern of iron overload in different diseases.

		TDT Suboptimal transfusion-chelation regimen	TDT standardized transfusion-chelation regimen (pre transfusion HB ≥ 9)	NTDT	HH	Lower risk MDS
Iron input	Transfusions	+/++	+++	-/+	-	++/+++
	GI iron adsorption	+++	+	++	++	+ (?)
Patient	Aging	-	-	-/+	++	+++
	Age related comorbidity	-	-	-/+	+/++	+++
	Anemia	+++	+	++	-	+++
Erythropoiesis	Ineffective	+++	+++	++	-	+/++
	Hyperplastic	+++	+	+++	-	+/++
		↓	↓	↓	↓	↓
Major causes of death		Anemia Cardiac disease	Cardiac disease Liver disease	Cardio-vascular disease Liver disease (?)	Liver disease	Cardiac disease infectious disease Liver disease. Acute leukemia

Legend: TDT: transfusion dependent Thalassemia, NTDT: non-transfusion dependent Thalassemia, HH: hereditary hemochromatosis.

These diseases are characterized by deep clinical differences (age, comorbidity, functionality of stem cell, anemia, non proliferative diseases, gastro intestinal iron absorption, life expectancy, etc.). Consequently MDS patient is a completely different clinical scenario whose characteristics in term of tissue and organ morbidity, quality of life, therapeutic options and finally survival is completely to be “de novo“ designed

Angelucci and Pilo, 2017

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☯]

Citation: de Montalembert M, Ribeil J-A, Brousse V, Guerci-Bresler A, Stamatoullas A, Vannier J-P, et al. (2017) Cardiac iron overload in chronically transfused patients with thalassemia, sickle cell anemia, or myelodysplastic syndrome. PLoS ONE 12(3): e0172147. doi:10.1371/journal.pone.0172147

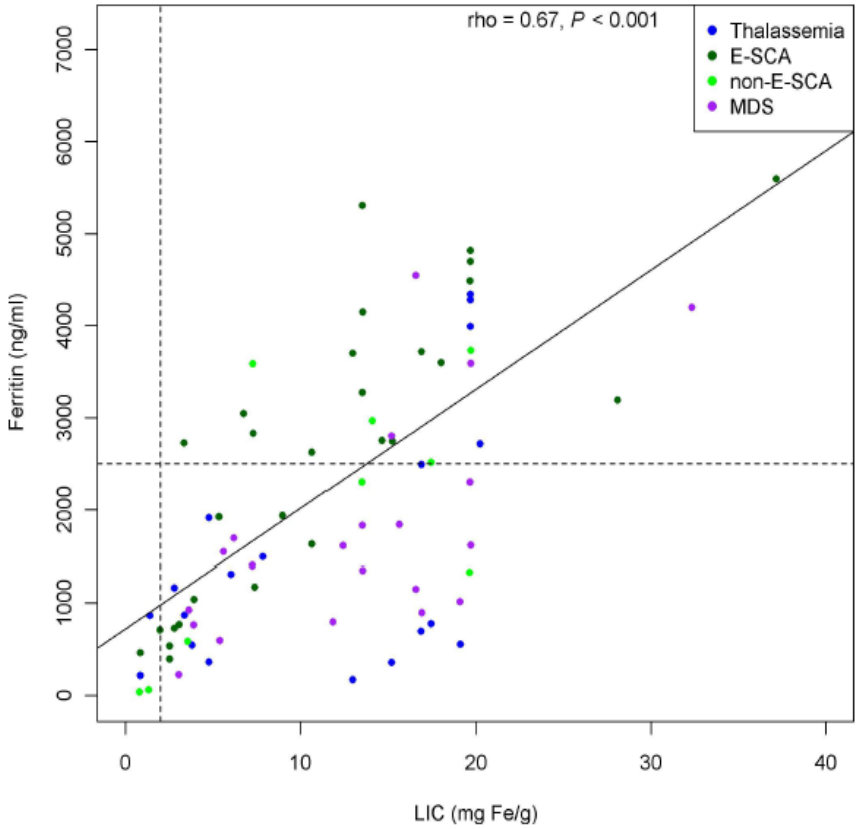


Fig 1. association between ferritin and liver iron content in the global population.

doi:10.1371/journal.pone.0172147.g001

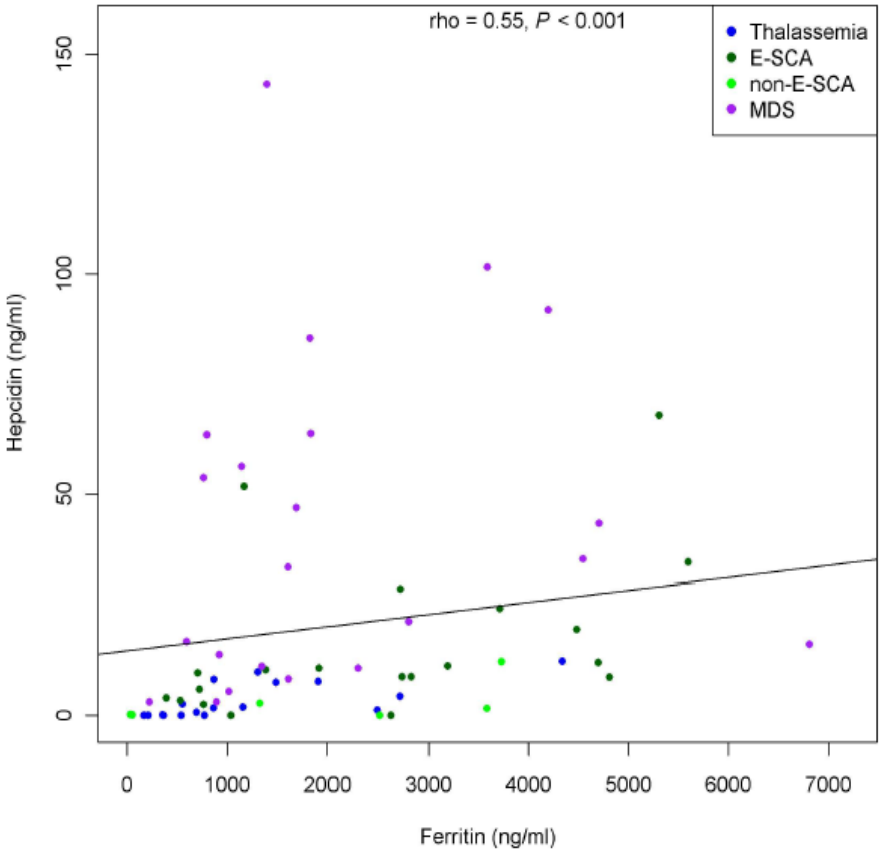


Fig 2. association between hepcidin and ferritin in the global population.

Ann Hematol (2015) 94:779–787
DOI 10.1007/s00277-014-2274-y

ORIGINAL ARTICLE

Evolution of iron overload in patients with low-risk myelodysplastic syndrome: iron chelation therapy and organ complications

Ángel F. Remacha · Beatriz Arrizabalaga · Ana Villegas · María Soledad Durán · Lourdes Hermosín · Raquel de Paz · Marta Garcia · Maria Diez Campelo · Guillermo Sanz · On behalf of the IRON-2 Study Group

Table 1 Baseline patient characteristics (N=263)

Patient characteristics	Value
Age, mean±SD, years[a]	71.9±10.5
Gender, *n* (%)[b]	
Male	150 (57.0)
Female	107 (40.7)
French–American–British classification, *n* (%):[c]	
RA	122 (46.4)
RARS	122 (46.4)
RAEB	8 (3.0)
CMML	9 (3.4)
World Health Organization classification, *n* (%):[c]	
RA	39 (14.8)
RARS	95 (36.1)
RCMD	63 (24.0)
RCMD-RS	26 (9.9)
RAEB-I	7 (2.7)
MDS-U	3 (1.1)
Myelodysplastic syndrome associated to isolated del(5q)	19 (7.2)
CMML	9 (3.4)
IPSS, *n* (%):[d]	
IPSS low risk	218 (82.9)
IPSS intermediate-1 risk	0 (0.0)
SPI, *n* (%):[e]	
SPI low risk	204 (77.6)
SPI intermediate risk	30 (11.4)
Hemoglobin level, mean±SD, g/dL[b]	9.2±1.8
Leukocyte blood count, mean±SD, × 10^9/L[f]	5.6±3.9
Monocyte blood count, mean±SD, × 10^9/L[g]	0.6±1.4
Neutrophil blood count, mean±SD, × 10^9/L[h]	3.1±2.5
Platelet count, mean±SD, × 10^9/L[i]	231.1±133.6
Transfusion frequency, mean±SD, PRBC/month:	
Overall transfusion frequency[j]	2.8±3.9
Transfusion frequency chelated patients[k]	2.5±1.6
Transfusion frequency nonchelated patients[l]	3.0±4.9
Sorror comorbidity index:[m]	
Median (interquartile range)	1.0 (0.0–2.0)
Sorror index ≥3, *n* (%)	57 (21.7)

CMML chronic myelomonocytic leukemia, *del(5q)* chromosome 5q deletion, *IPSS* International Prognostic Scoring System, *MDS-U* myelodysplastic syndrome not otherwise specified, *RA* refractory anemia, *RAEB* refractory anemia with excess blasts, *RAEB-I* refractory anemia with excess blasts type I, *RARS* refractory anemia with ringed sideroblasts, *RCMD* refractory cytopenia with multilineage dysplasia, *RCMD-RS* refractory cytopenia with dysplasia and ringed sideroblasts, *SD* standard deviation, *SPI* Spanish Prognostic Index, *PRBC* packed red blood cells

[a] Missing data, n=11
[b] Missing data, n=6
[c] Missing data, n=2
[d] Missing data, n=45
[e] Missing data, n=29
[f] Missing data, n=7
[g] Missing data, n=20
[h] Missing data, n=18
[i] Missing data, n=9
[j] Missing data, n=16
[k] Missing data, n=1
[l] Missing data, n=15
[m] Missing data, n=4

Table 2 Overall iron metabolism (N=263)

Parameter	Value
TSI at MDS diagnosis:[a]	
Mean±SD	57.4±25.0
<50 %, *n* (%)	87 (33.1)
50–75 %, *n* (%)	45 (17.1)
≥75 %, *n* (%)	55 (20.9)
SF at MDS diagnosis:[b]	
Mean±SD, µg/L	515.6±470.8
<500 µg/L, *n* (%)	144 (54.8)
500–1000 µg/L, *n* (%)	67 (25.9)
1000–2500 µg/L, *n* (%)	20 (7.6)
≥2500 µg/L, *n* (%)	3 (1.1)
SF over the course of disease:[c]	
≤1000 µg/L, *n* (%)	41 (15.6)
1000–2500 µg/L, *n* (%)	94 (35.7)
>2500 µg/L, *n* (%)	95 (36.1)

MDS myelodisplastic syndrome, *SF* serum ferritin, *TSI* transferrin saturation index

[a] Missing data, n=76
[b] Missing data, n=29
[c] Missing data, n=33

Table 3 Iron balance in patients who received deferasirox as first chelation treatment

Iron balance	Mean±SD PRBC transfusion frequency (PRBC/month)	Mean±SD deferasirox dose (mg/kg/day)	Mean±SD treatment duration (months)	Mean±SD SF before treatment (µg/L)	Mean±SD SF after treatment (µg/L)
Increased SF levels (n=27)	2.7±2.2	16.8±5.6[a]	20.8±10.7	1,634.9±673.1 p<0.001	3,094.0±1,855.2
Decreased SF levels (n=40)	2.2±1.0	18.3±3.6	24.6±11.3	2,032.3±1,143.1 p<0.001	1,056.2±634.1

PRBC packed red blood cells, *SF* serum ferritin

[a] Missing data, n=5

Table 5 Baseline and evolution of organ complications (N=263)

Complication	Total, n (%)	Mean±SD number of PRBC transfusions at start of complication	Mean±SD SF levels at start of complication, µg/L	Median (95 % CI) event-free survival, months	
				Chelated patients	Non-chelated patients
Cardiac	53 (20.2 %)[a]	53.6±61.2[b]	1945.4±1527.6[c]	137.0 (108.5–165.5)	96.0 (84.1–107.9)*
Hepatic	30 (11.4 %)[d]	58.7±73.7[e]	2387.2±1722.2[f]	–**	208.0 (– – –)
Endocrine	26 (9.9 %)[g]	60.7±59.2[f]	1839.2±1593.7[e]	–**	–**
Arthropathies	10 (3.8 %)[f]	48.1±42.4[h]	4718.2±6094.7[i]	–**	–**

CI confidence interval, *PRBC* packed red blood cells, *SD* standard deviation, *SF* serum ferritin

* p=0.017 versus chelated patients

** Median was not reached

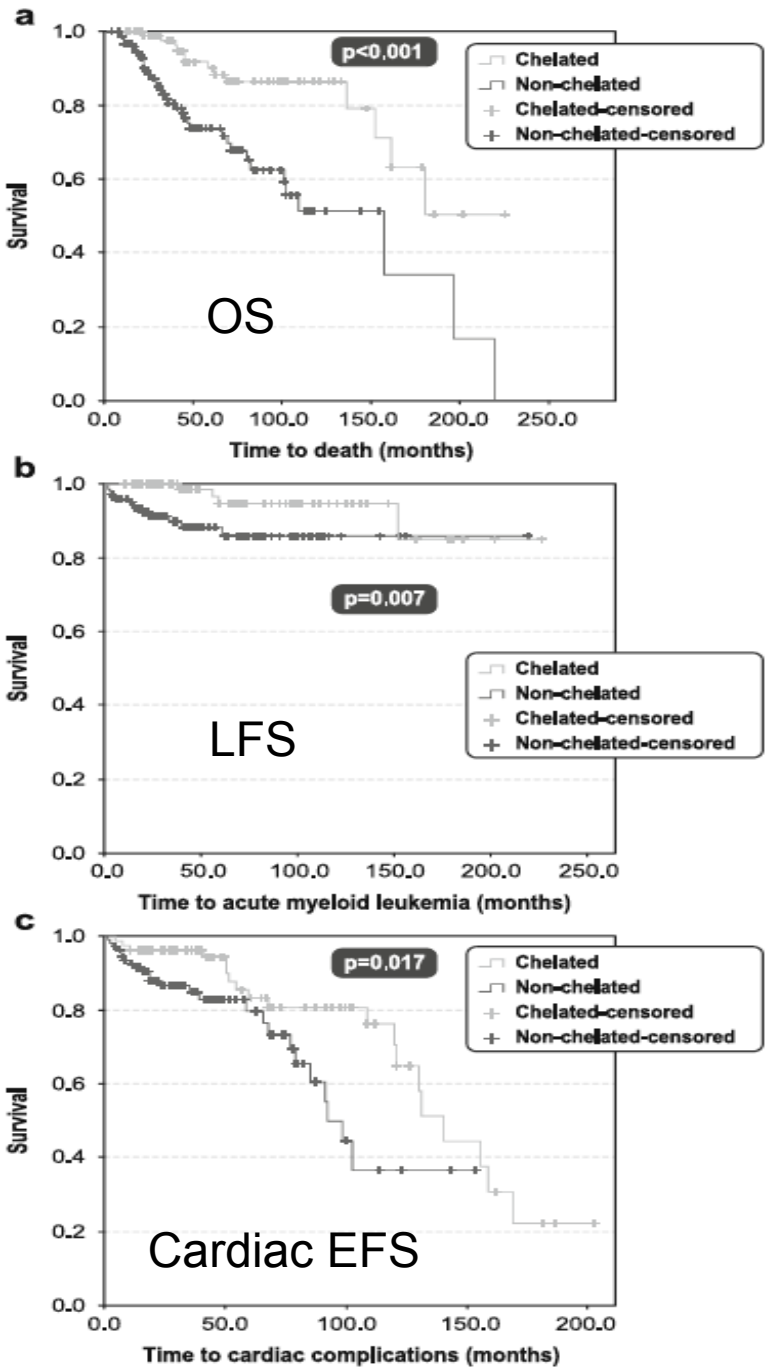


Fig. 1 Overall survival (a), leukemia-free survival (b), cardiac event-free survival (c)

Table 4 Multivariable proportional hazard regression models for overall survival, leukemia-free survival, and cardiac event-free survival

Parameter	Hazard ratio	95 % CI	*p*-value
Overall survival:			
Age	1.073	1.016–1.133	0.011
IPSS	6.859	2.498–18.833	<0.001
Chelation treatment	0.361	0.159–0.822	0.015
Leukemia-free survival:			
IPSS	9.415	1.582–56.050	0.014
Transfusion frequency	1.095	1.038–1.154	0.001
Cardiac event-free survival:			
Chelation treatment	0.405	0.170–0.961	0.040
Sorror comorbidity index	1.240	1.011–1.521	0.039

CI confidence interval

Leukemia Research 34 (2010) 1143–1150

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

Deferasirox in iron-overloaded patients with transfusion-dependent myelodysplastic syndromes: Results from the large 1-year EPIC study

Norbert Gattermann[a,*], Carlo Finelli[b], Matteo Della Porta[c], Pierre Fenaux[d], Arnold Ganser[e], Agnes Guerci-Bresler[f], Mathias Schmid[g], Kerry Taylor[h], Dominique Vassilieff[i], Dany Habr[j], Gabor Domokos[k], Bernard Roubert[k], Christian Rose[l], on behalf of the EPIC study investigators[1]

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[d] Hôpital Avicenne, Assistance Publique-Hôpitaux de Paris, Paris 13 University, Bobigny, France
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[g] University Hospital, Ulm, Germany
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[j] Novartis Pharmaceuticals, East Hanover, NJ, USA
[k] Novartis Pharma AG, Basel, Switzerland
[l] Hôpital Saint-Vincent de Paul, Lille, France

European Journal of Haematology

ORIGINAL ARTICLE

Deferasirox treatment of iron-overloaded chelation-naïve and prechelated patients with myelodysplastic syndromes in medical practice: results from the observational studies eXtend and eXjange

Norbert Gattermann[1], Andrea Jarisch[2], Rudolf Schlag[3], Klaus Blumenstengel[4], Mariele Goebeler[5], Matthias Groschek[6], Christoph Losem[7], Maria Procaccianti[8], Alexia Junkes[9], Oliver Leismann[9], Ulrich Germing[1]

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ORIGINAL REPORT

Deferasirox Reduces Serum Ferritin and Labile Plasma Iron in RBC Transfusion–Dependent Patients With Myelodysplastic Syndrome

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Presented in part at the 50th Annual Meeting of the American Society of Hematology, December 6-9, 2008, San Francisco, CA.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical Trials repository link available on JCO.org.

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A B S T R A C T

Purpose
This 3-year, prospective, multicenter trial assessed the safety and efficacy of deferasirox in low- or intermediate-1–risk myelodysplastic syndrome (MDS).

Patients and Methods
Eligible patients had serum ferritin ≥ 1,000 μg/L and had received ≥ 20 units of RBCs with ongoing transfusion requirements. The starting dose of deferasirox was 20 mg/kg/d, with dose escalation up to 40 mg/kg/d permitted.

Results
A total of 176 patients were enrolled, and 173 patients received therapy. Median serum ferritin decreased 23% in the 53% of patients who completed 12 months of treatment (n = 91), 36.7% in patients who completed 2 years (n = 49), and 36.5% in patients who completed 3 years (n = 33) despite continued transfusion requirement. Reduction in serum ferritin significantly correlated with ALT improvement ($P < .001$). Labile plasma iron (LPI) was measured quarterly during the first year of the study. Sixty-eight patients (39.3%) had elevated LPI at baseline. By week 13, LPI levels normalized in all patients with abnormal baseline level. Fifty-one (28%) of 173 patients experienced hematologic improvement by International Working Group 2006 criteria; of these, only seven patients received growth factors or MDS therapy. Over the 3-year study, 138 (79.8%) of 173 patients discontinued therapy, 43 patients (24.8%) because of adverse events or disease progression and 23 patients (13.2%) because of abnormal laboratory values. The most common drug-related adverse events were gastrointestinal disturbances and increased serum creatinine. There were 28 deaths, none of which were considered related to deferasirox.

Conclusion
Deferasirox reduces serum ferritin and LPI in transfusion-dependent patients with MDS. A subset of patients had an improvement in hematologic and hepatic parameters.

J Clin Oncol 30:2134-2139. © 2012 by American Society of Clinical Oncology

Ann Hematol
DOI 10.1007/s00277-012-1481-7

ORIGINAL ARTICLE

Deferasirox treatment for myelodysplastic syndromes: "real-life" efficacy and safety in a single-institution patient population

Massimo Breccia · Paola Finsinger · Giuseppina Loglisci · Vincenzo Federico · Michelina Santopietro · Gioia Colafigli · Luigi Petrucci · Adriano Salaroli · Alessandra Serrao · Roberto Latagliata · Giuliana Alimena

Received: 1 November 2011 / Accepted: 25 April 2012

EPIC study, MDS cohort

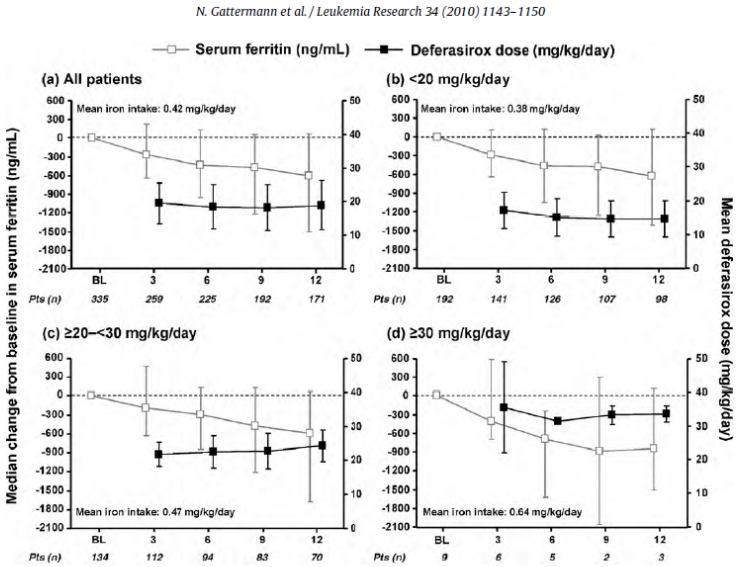


Fig. 2. Mean deferasirox dose (±SD) and median change in serum ferritin (±25th/75th percentiles), by mean actual dose categories (full analysis set).

FERRITIN

US03 study

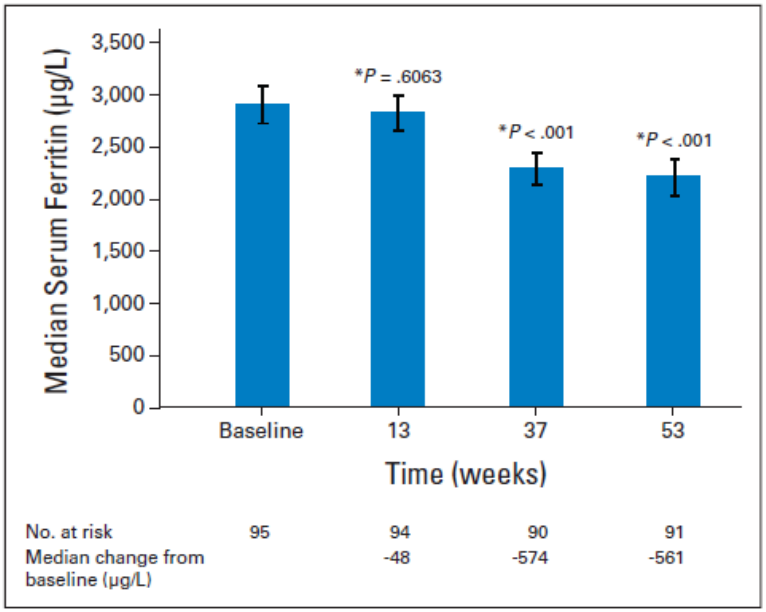


Fig 1. Median serum ferritin (± SEM) in patients who completed 12 months of deferasirox. (*) Versus baseline.

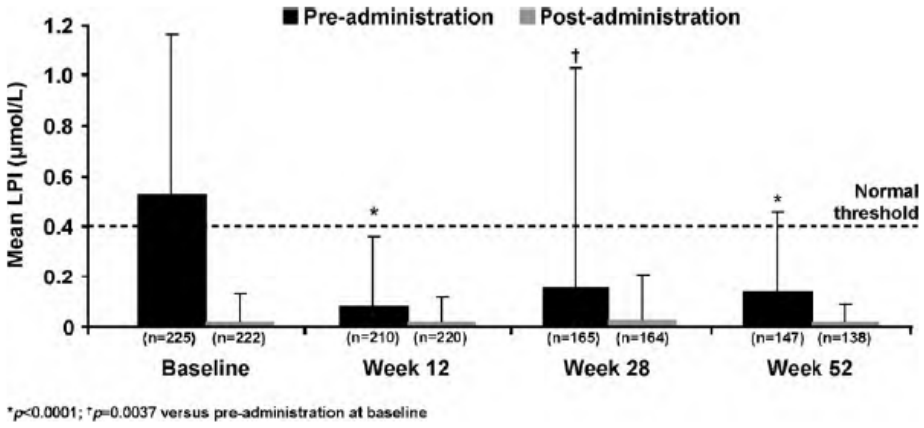


Fig. 3. Mean LPI (+SD), pre- and post-deferasirox administration at baseline and after repeat doses.

LPI

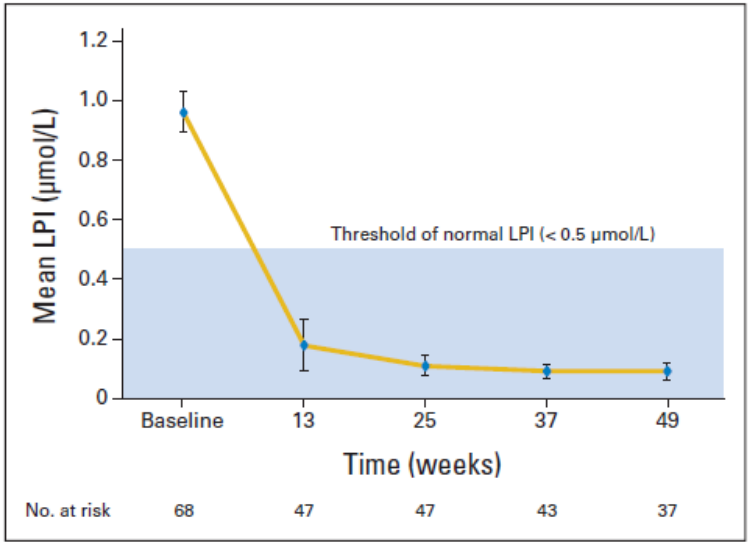
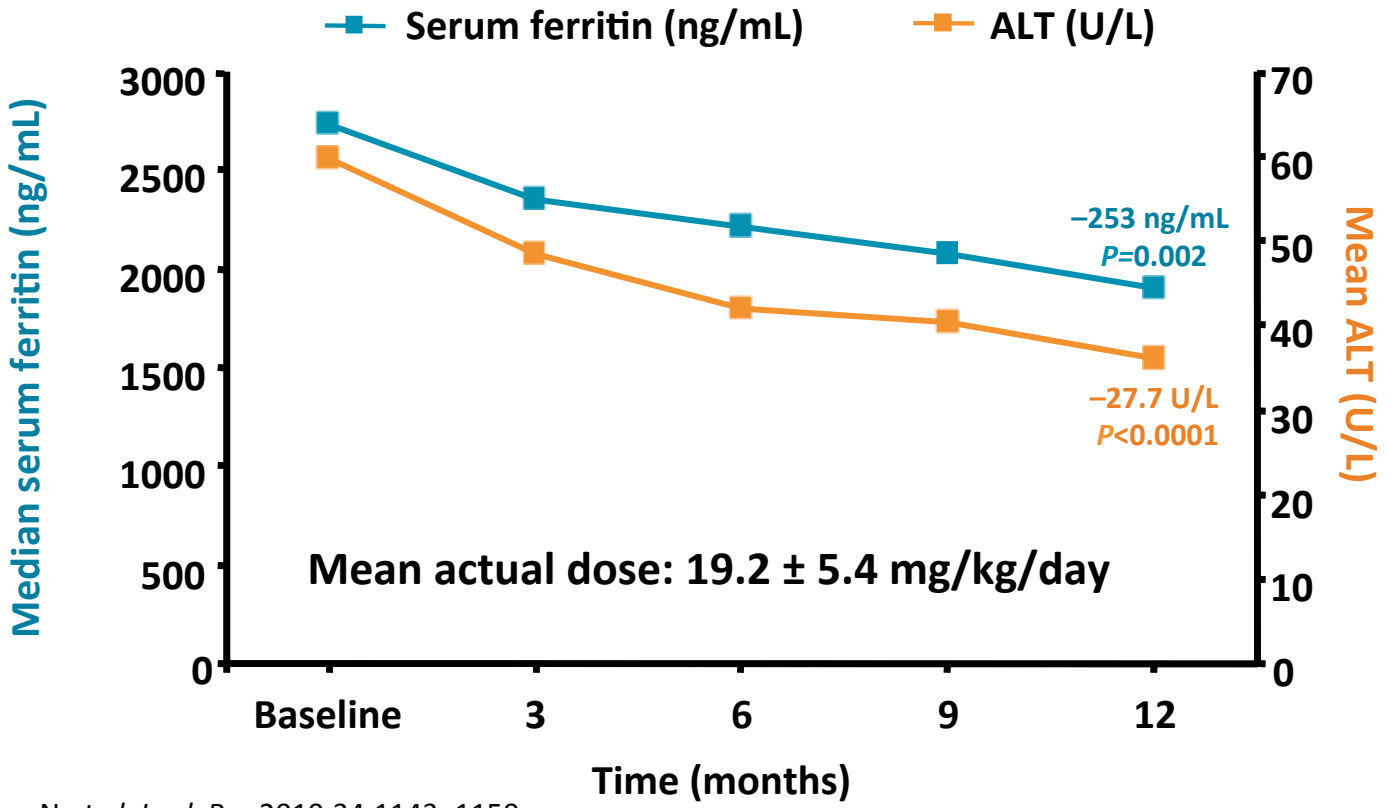


Fig 2. Mean labile plasma iron (LPI; ± SEM) over 12 months in patients with abnormal LPI (> 0.5 µmol/L) at baseline.

1. Data from List AF, et al. J Clin Oncol. [Epub ahead of print 2012 Apr 30]
2. Data from Gattermann N, et al. Leuk Res 2010;34:1143-50.

EPIC study: Correlation between decreased serum ferritin and improved ALT during deferasirox treatment

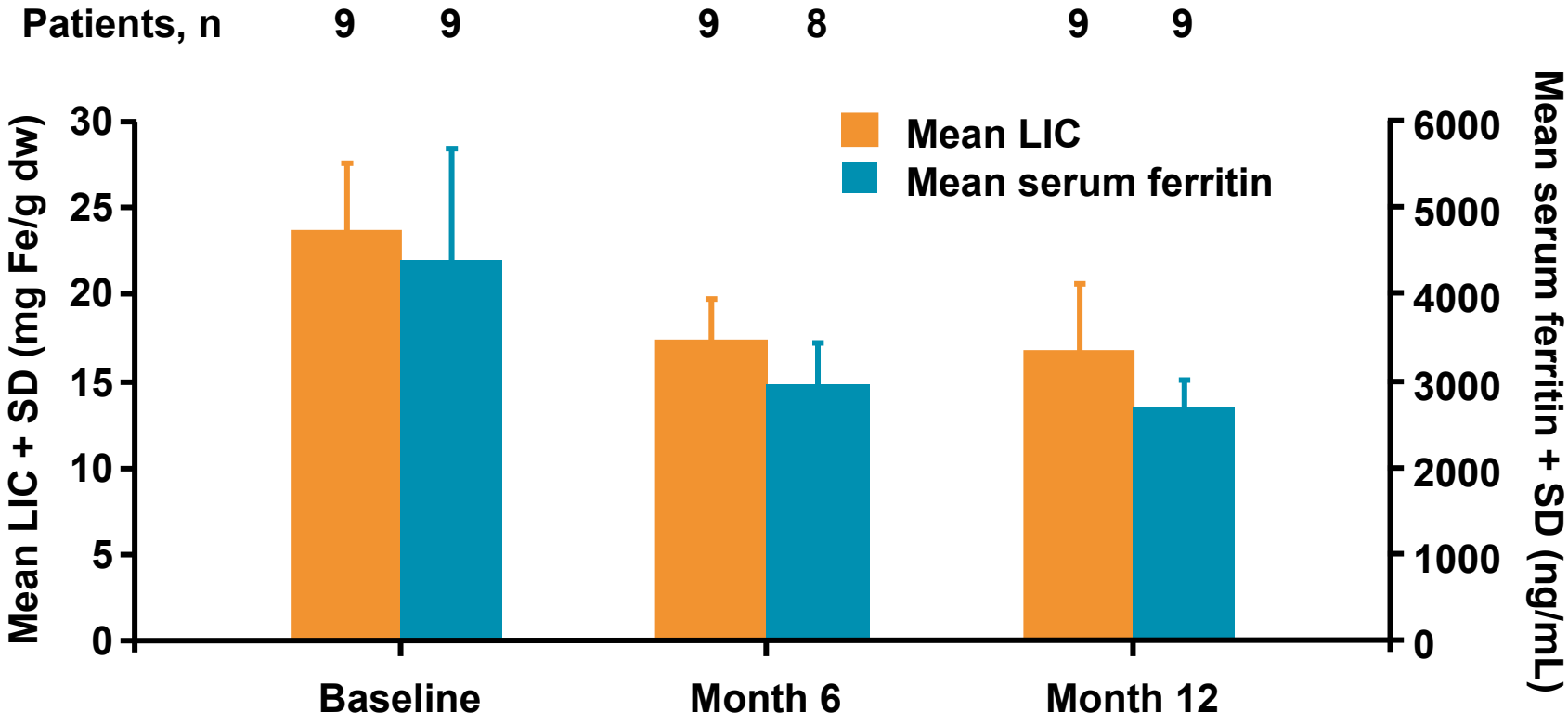
- **At 12 months, there were significant reductions in**
  - **Median serum ferritin (−253 ng/mL; *P*=0.002)**
  - **Mean ALT (−27.7 ± 37.4 U/L; *P*<0.0001)**



Gattermann N *et al*. *Leuk Res* 2010;34:1143–1150

Reductions in LIC (MRI R2) and serum ferritin with deferasirox in patients with MDS

Mean LIC (Liver Iron Concentration) and serum ferritin (±SEM) for completed patients



- **LPI normalised in 80% of patients**

Greenberg PL *et al*. *Leuk Res* 2010

Study US02

European Journal of Haematology

European Journal of Haematology 98 (97–105)

ORIGINAL ARTICLE

Cardiac iron load and function in transfused patients treated with deferasirox (the MILE study)

P. Joy Ho[1], Lay Tay[2], Juliana Teo[3], Paula Marlton[4], Andrew Grigg[5], Tim St Pierre[6], Greg Brown[7], Caro-Anne Badcock[8], Robert Traficante[8], Othon L. Gervasio[9], Donald K. Bowden[10]

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Abstract

Objectives: To assess the effect of iron chelation therapy with deferasirox on cardiac iron and function in patients with transfusion-dependent thalassemia major, sickle cell disease (SCD), and myelodysplastic syndromes (MDS). *Methods:* This phase IV, single-arm, open-label study over 53 wk evaluated the change in cardiac and liver iron load with deferasirox (up to 40 mg/kg/d), measured by magnetic resonance imaging (MRI). *Results:* Cardiac iron load (myocardial T2*) significantly improved ($P = 0.002$) overall ($n = 46$; $n = 36$ thalassemia major, $n = 4$ SCD, $n = 6$ MDS). Results were significant for patients with normal and moderate baseline cardiac iron ($P = 0.017$ and $P = 0.015$, respectively), but not in the five patients with severe cardiac iron load. Liver iron concentration (LIC) significantly decreased overall [mean LIC 10.4 to 8.2 mg Fe/g dry tissue (dw); $P = 0.024$], particularly in those with baseline LIC >7 mg Fe/g dw (19.9 to 15.6 mg Fe/g dw; $P = 0.002$). Furthermore, myocardial T2* significantly increased in patients with LIC <7 mg Fe/g dw, but not in those with a higher LIC. Safety was consistent with previous reports. *Conclusions:* Once-daily deferasirox over 1 yr significantly increased myocardial T2* and reduced LIC. This confirms that single-agent deferasirox is effective in the management of cardiac iron, especially for patients with myocardial T2* >10 ms (Clinicaltrials.gov identifier: NCT00673608).

Key words cardiac iron; hepatic iron; deferasirox; magnetic resonance imaging iron assessment; transfusional siderosis

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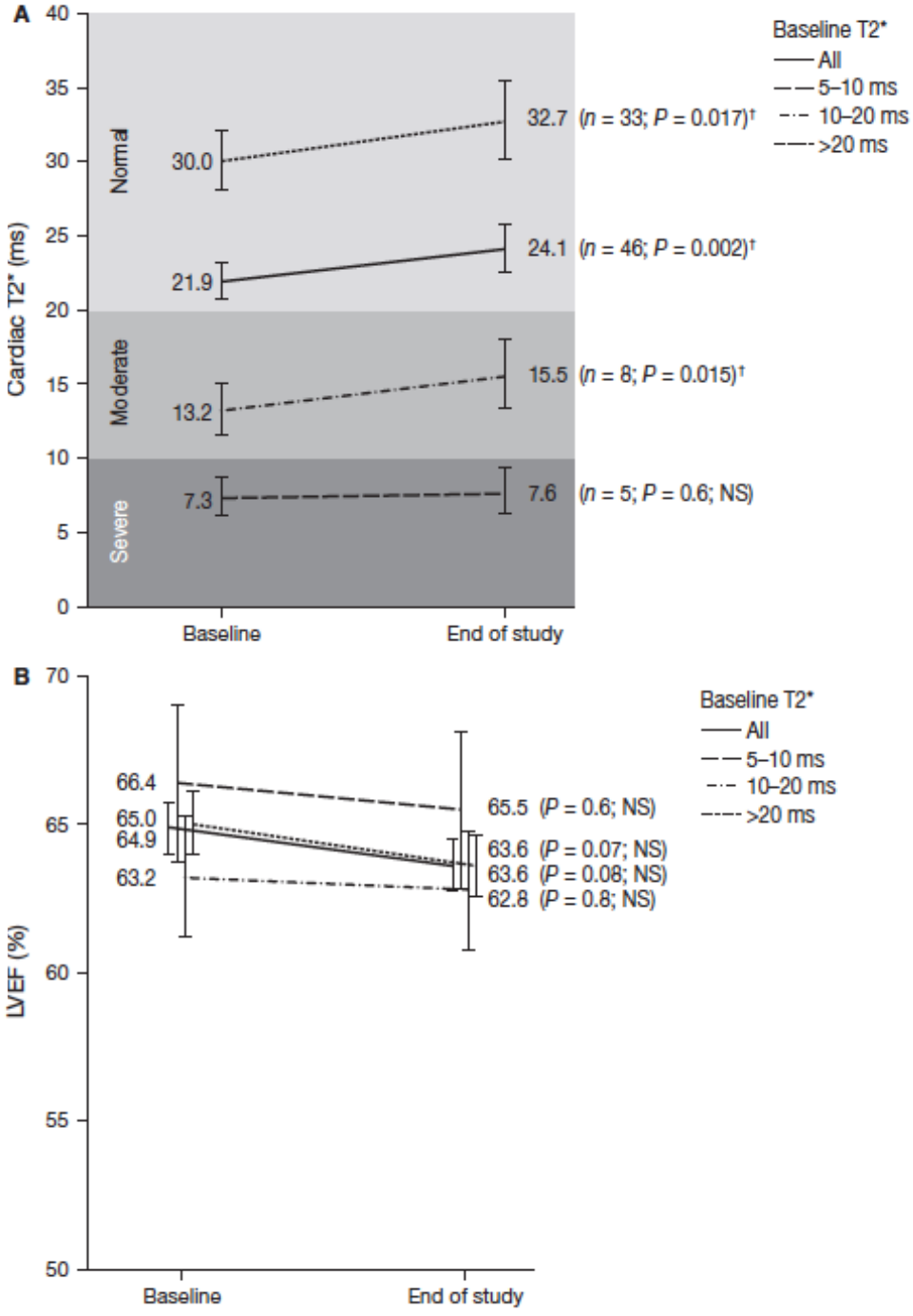

Figure 1 Change in (A) myocardial T2* and (B) LVEF after 12 months. (A) Results are presented as the adjusted means on back-transformed T2* values ± 95% confidence intervals after the analysis model. †Statistically significant. (B) Results are presented as the adjusted means ± standard error of the mean after the analysis model. LVEF, left ventricular ejection fraction; NS, nonsignificant.

European Journal of Haematology

European Journal of Haematology

ORIGINAL ARTICLE

Deferasirox chelation therapy in patients with transfusion-dependent MDS: a 'real-world' report from two regional Italian registries: Gruppo Romano Mielodisplasie and Registro Basilicata

Luca Maurillo[1], Massimo Breccia[2], Francesco Buccisano[1,3], Maria Teresa Voso[1,3], Pasquale Niscola[4], Giulio Trapè[5], Caterina Tatarelli[6], Ada D'Addosio[7], Roberto Latagliata[2], Susanna Fenu[8], Anna Lina Piccioni[9], Alberto Fragasso[10], Maria A. Aloe Spiriti[6], Marco Refrigeri[1], Marianna Criscuolo[11], Pellegrino Musto[11,12], Adriano Venditti[1,3]

Table 2 Biochemical characteristics of patients at baseline

Characteristic	Median (range)
Hb (g/dL)	8.2 (5.9–11.5)
WBC (cells/mm^3)	3650 (740–17060)
PMN (absolute)	1780 (130–12500)
Platelets (cells/mm^3)	193 000 (7000–849 000)
Serum iron (μg/dL)	178 (12–730)
Ferritin (ng/mL)	1782 (691–7339)
Transferrin (mg/dL)	152 (1–308)
Bone marrow blasts (%)	2 (0–17)
GOT (IU/L)	30 (5–160)
GPT (IU/L)	42 (6–245)
Creatinine (mg/dL)	0.8 (0–94)
Urea (mg/dL)	31.4 (1–98)

Hb, haemoglobin; GOT, glutamic oxaloacetic transaminase; GPT, glutamate pyruvate transaminase; PMN, polymorphonuclear neutrophils; WBC, white blood cell count.

Table 1 Demographic and clinical characteristics of patients at baseline

Characteristics	Patients
Male, *n* (%)	66 (55.9)
Female, *n* (%)	52 (44.1)
Median age, years (range)	70.5 (34–90)
Diagnosis, *n* (%)	
RA	60 (50.8)
RARS	15 (12.7)
RAEB-1	12 (10.2)
RAEB-2	12 (10.2)
RCMD	8 (6.8)
5q-	5 (4.2)
Transfusion requirement, units/month; mean (range)	2.0 (1.0–6.0)
Prognosis (IPSS), *n* (%)	
Low	55 (46.6)
Intermediate-1	34 (28.8)
Intermediate-2	14 (11.9)
High	2 (1.7)
Abnormal cytogenetics, *n* (%)	35 (29.7)
Concomitant treatment (at any point in the study)	
Azacitidine or lenalidomide	31 (26.3)
Erythropoietin	18 (15.3)
Prednisone	12 (10.2)

IPSS, International Prognostic Scoring System; RA, refractory anaemia; RARS, refractory anaemia with ringed sideroblasts; RAEB, refractory anaemia with excess blasts; RCMD, refractory cytopenia with multilineage dysplasia.

Table 3 Adverse events

Adverse event	Overall frequency (Grade 1–4)	Grade 3 or 4 frequency
Gastrointestinal	33.0%	7.4%
Renal toxicity	16.0%	9.6%
Cutaneous	10.6%	5.3%
Joint pain	4.3%	3.2%
Liver toxicity	3.2%	3.2%

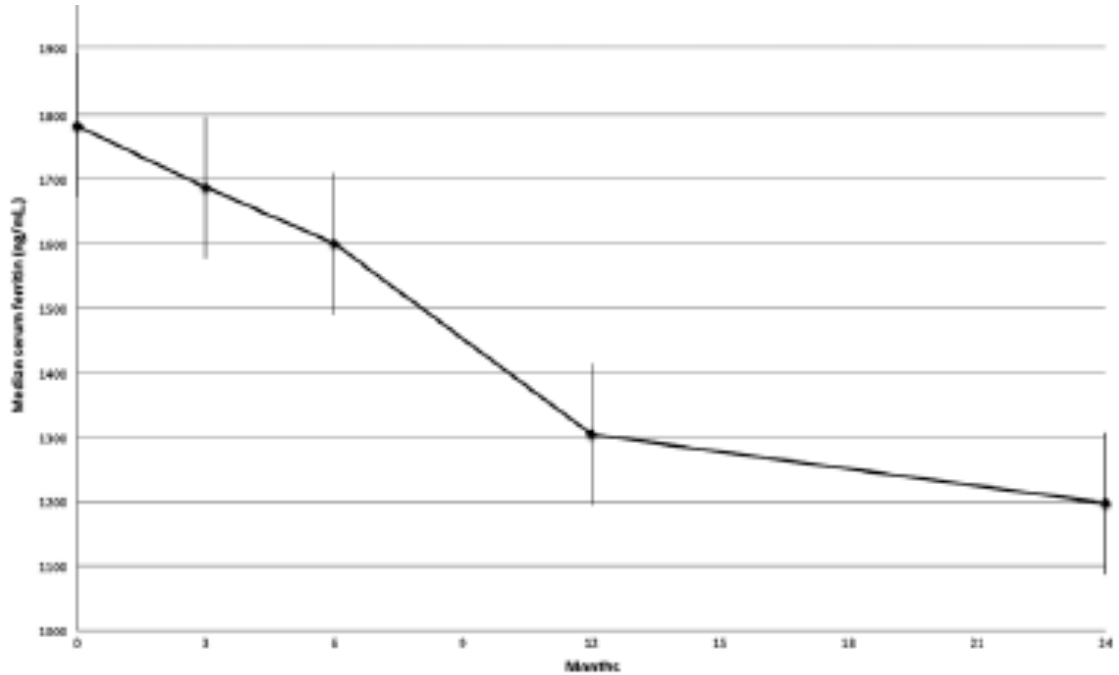

Figure 1 Reduction in median serum ferritin levels over time.

EUROPEAN JOURNAL OF Haematology

European Journal of Haematology 92 (527–536)

ORIGINAL ARTICLE

Deferasirox for transfusion-dependent patients with myelodysplastic syndromes: safety, efficacy, and beyond (GIMEMA MDS0306 Trial)

Emanuele Angelucci[1], Valeria Santini[2], Anna Angela Di Tucci[1], Giulia Quaresmini[3], Carlo Finelli[4], Antonio Volpe[5], Giovanni Quarta[6], Flavia Rivellini[7], Grazia Sanpaolo[8], Daniela Cilloni[9], Flavia Salvi[10], Giovanni Caocci[11], Alfredo Molteni[12], Daniele Vallisa[13], Maria Teresa Voso[14], Susanna Fenu[15], Lorenza Borin[16], Giancarlo Latte[17], Giuliana Alimena[18], Sergio Storti[19], Alfonso Piciocchi[20], Paola Fazi[20], Marco Vignetti[20], Sante Tura[21]

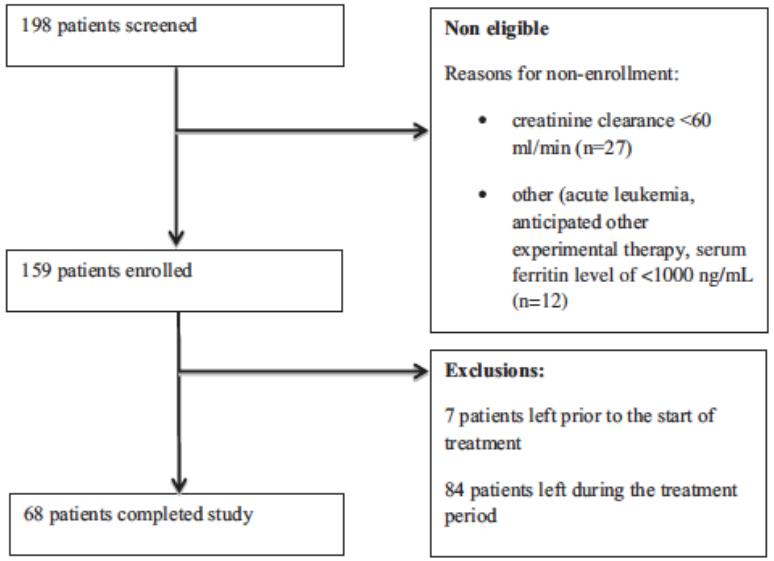

Figure 1 Consolidated Standards on Reporting Trials (CONSORT) diagram of the study population.

Table 1 Baseline characteristics at enrollment for patients that proceeded to treatment

Characteristic	*n* = 152
Age (yr)	72 (IQR 66–77, range 24–87)
Sex, *n* (%)	
Male	96 (63.2)
Female	56 (36.8)
IPSS score, *n* (%)	
Low	61 (40.7)
Intermediate	89 (59.3)
CIRS comorbidity index	0 (IQR 0–1, range 0–2)
CIRS severity index	0.2 (IQR 0.1–0.5, range 0–5)
MDS-Specific Comorbidity Index, *n* (%)	
Low	111 (74.0)
Intermediate	33 (22.0)
High	6 (4.0)
Time since initial MDS diagnosis (months)	32 (IQR 17–54, range 3–204)
Time since starting transfusion (months)	21 (IQR 10–36, range 2–120)
Units of packed red cells transfused	37 (IQR 22–63, range 20–420)
Pretransfusion hemoglobin (g/dL) (mean ± SD)	8.3 ± 0.9
Serum ferritin (ng/mL)	1966 (IQR 1416–2998, range 709–13395)

Values are median (IQR) unless otherwise indicated. IPSS indicates International Prognostic Scoring System; CIRS, cumulative illness rating scale; and MDS, myelodysplastic syndrome. Numbers may not equal sum of study population (*n* = 152) due to missing data. Data were missing with respect to IPSS group (*n* = 2), CIRS comorbidity index (*n* = 3), CIRS severity index (*n* = 2), and MDS-Specific Comorbidity Index (*n* = 2).

- **Of 159 participants enrolled from 37 Italian centers, 152 received ≥1 dose of deferasirox (initiated at 10–20 mg/kg/day and titrated as appropriate), and 68 completed the study.**
- **Median serum ferritin level fell from 1966 ng/mL to 1475 ng/mL ($P < 0.0001$).**

Table 2 Reasons for discontinuation of deferasirox therapy

Cause	*n* (%)
Adverse event	28 (33.3)
Death	22 (26.2)
Disease progression	8 (9.5)
Withdrawal of consent	9 (10.7)
Lost at follow-up	8 (9.5)
No response	2 (2.4)
Serum ferritin <500 ng/mL	2 (2.4)
Medical decision	5 (6.0)
Total	84 (100)

Table 3 Univariate and multivariate analysis of risk factors for study dropout using the Fine -Gray model

	Univariate analysis			Multivariate analysis		
Variable	HR	(95% CI)	*P*	HR	(95% CI)	*P*
Duration of disease (months)	0.99	(0.98–1.00)	0.007	0.98	(0.97–0.99)	0.004
Serum ferritin (ng/mL)	1.02	(1.01–1.04)	0.004	1.02	(1.01–1.04)	0.002
CIRS	1.74	(0.96–3.17)	0.07	–	–	–
MDS-CI	1.45	(1.14–1.84)	0.003	1.42	(1.13–1.78)	0.003
Deferasirox dose (mg/kg/d)	0.95	(0.90–0.99)	0.02	–	–	–

CIRS, Cumulative Illness Rating Scale; MDS-CI, Myelodysplastic Syndrome-Specific Comorbidity Index.

Table 4 Adverse events by severity grade, causal likelihood, and organ system

Relationship	Events	Patients* *n* (%)
Treatment-related		
Grade 1	38	24 (15.8)
Grade 2	40	29 (19.1)
Grade 3	14	11 (7.2)
Non-related		
Grade 1	71	36 (23.7)
Grade 2	70	41 (27.0)
Grade 3	40	25 (16.4)
Grade 4	8	6 (3.9)
Grade 5	22	22 (13.8)
Total	303	107 (70.4)

Organ system	Treatment-related events		
Grade	1	2	3
Cardiac	–	1	–
Eye	1	–	–
Gastrointestinal	17	19	6
General disorders and administration site conditions	–	–	1
Hepato-biliary	–	3	2
Investigations	8	6	–
Metabolism and nutrition	–	1	2
Musculoskeletal and connective tissue	1	3	–
Renal and urinary	10	4	1
Skin and subcutaneous tissue	1	3	2
Total	38	40	14

*Patients may be listed multiple times in case of multiple adverse events, and therefore, total counts of adverse events do not correspond with patient numbers.

Health-related quality of life in transfusion-dependent patients with myelodysplastic syndromes: a prospective study to assess the impact of iron chelation therapy

Fabio Efficace,[1] Valeria Santini,[2] Giorgio La Nasa,[3] Francesco Cottone,[1] Carlo Finelli,[4] Lorenza Borin,[5] Giulia Quaresmini,[6] Anna Angela Di Tucci,[7] Antonio Volpe,[8] Daniela Cilloni,[9] Giovanni Quarta,[10] Grazia Sanpaolo,[11] Flavia Rivellini,[12] Flavia Salvi,[13] Alfredo Molteni,[14] Maria Teresa Voso,[15] Giuliana Alimena,[16] Susanna Fenu,[17] Franco Mandelli,[1] Emanuele Angelucci[7]

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ABSTRACT

Objective The primary objective of this study was to evaluate the health-related quality of life (HRQOL) in lower-risk, transfusion-dependent patients with myelodysplastic syndromes (MDS) treated with deferasirox. A secondary objective was to investigate the relationship between HRQOL, serum ferritin levels and transfusion dependency.

Patients and methods This was a prospective multicentre study enrolling 159 patients, of whom 152 received at least one dose of deferasirox. HRQOL was assessed with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) at baseline and then at 3, 6, 9 and 12 months. Primary analysis was performed estimating mean HRQOL scores over time by a linear mixed model on selected scales.

Results The median age of treated patients was 72 years (range 24–87 years). No statistically significant changes over time were found in mean scores for global health status/quality of life (p=0.564), physical functioning (p=0.409) and fatigue (p=0.471) scales. Also, no significant changes were found for constipation (p=0.292), diarrhoea (p=0.815) and nausea and vomiting (p=0.643). Serum ferritin levels were not associated with HRQOL outcomes. A higher patient-reported baseline pain severity was an independent predictive factor of an earlier achievement of transfusion independence with a HR of 1.032 (99% CI 1.004 to 1.060; p=0.003).

Conclusions HRQOL of transfusion-dependent patients with MDS receiving deferasirox therapy remains stable over time. HRQOL assessment might also provide important predictive information on treatment outcomes.

Trial registration number NCT00469560.

CrossMark

To cite: Efficace F, Santini V, La Nasa G, *et al*. *BMJ Supportive & Palliative Care* 2016;**6**:80–88.

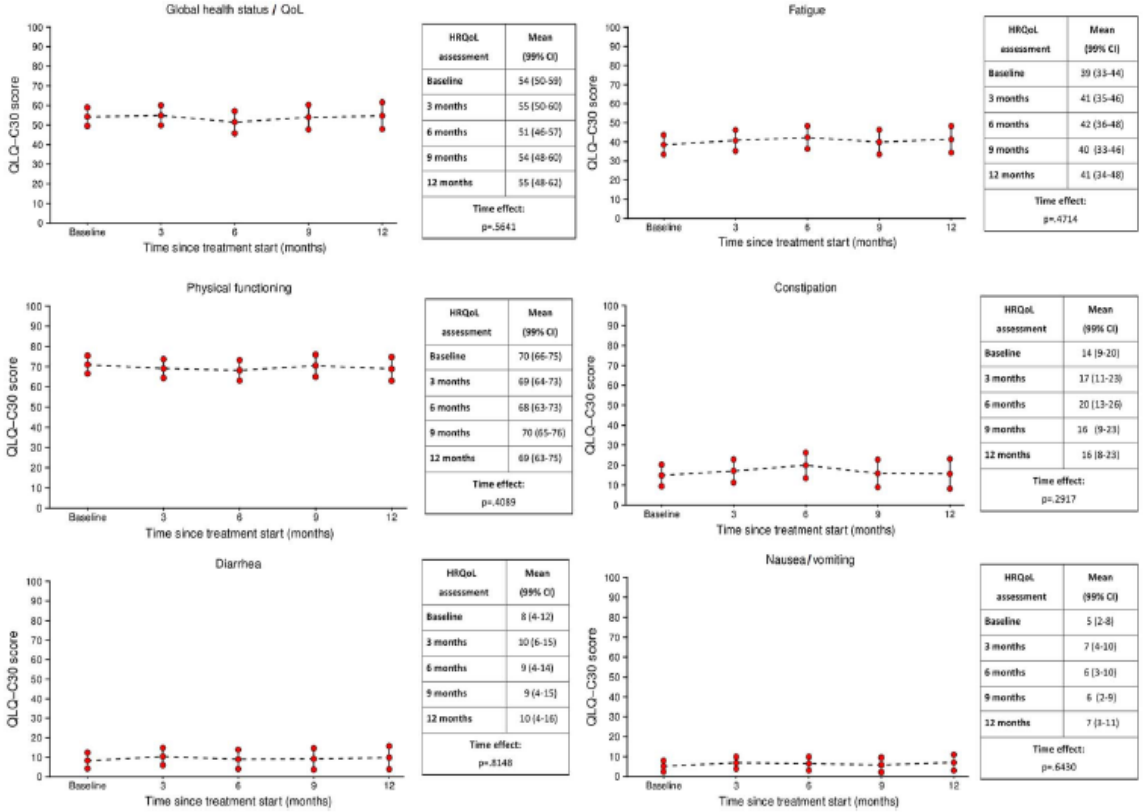

Figure 1 EORTC-QLQC30 mean scores and 99% CIs over the study period. Mean scores and the corresponding 99% CIs were estimated by a linear mixed model with a one-step autoregressive covariance structure. EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; HRQOL, health-related quality of life; QoL, quality of life.

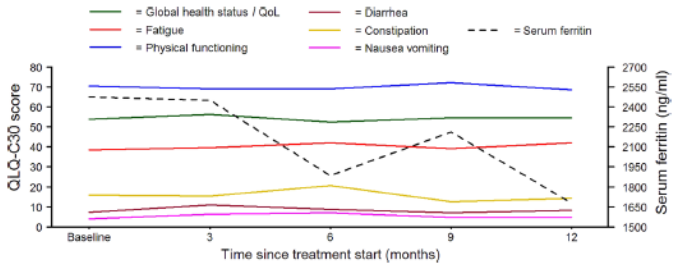

Figure 2 Selected HRQOL scales and ferritin levels over the study period. Figure shows mean observed ferritin levels and scores of HRQOL primary scales over time. For the EORTC QLQ-C30, higher scores on physical functioning and global health status/QoL indicate better outcomes. Higher scores on fatigue, constipation, diarrhoea and nausea and vomiting indicate higher severity of symptoms. EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; HRQOL, health-related quality of life; QoL, quality of life.

Frequency of adverse events (AEs) during deferasirox treatment

Leukemia Research 39 (2015) 1028–1033

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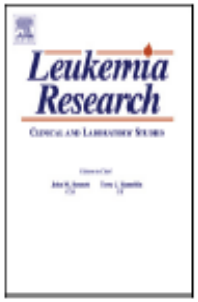


Review

Updated recommendations on the management of gastrointestinal disturbances during iron chelation therapy with Deferasirox in transfusion dependent patients with myelodysplastic syndrome – Emphasis on optimized dosing schedules and new formulations

Florian Nolte[a,*], Emanuele Angelucci[b], Massimo Breccia[c], Norbert Gattermann[d], Valeria Santini[e], Norbert Vey[f], Wolf-Karsten Hofmann[a]

EXJADE® (deferasirox) Core Data Sheet 2011. Novartis Pharma AG. National Prescribing Information should be followed

SUPPORTIVE CARE[kk]

- Clinical monitoring
- Psychosocial support (See NCCN Guidelines for Survivorship)
- Quality-of-life assessment
- Transfusions[ll]:
  - RBC transfusions (leuko-reduced) are recommended for symptomatic anemia, and platelet transfusions are recommended for thrombocytopenic bleeding. However, they should not be used routinely in patients with thrombocytopenia in the absence of bleeding unless platelet count <10,000/mcL.[mm] Irradiated products are suggested for transplant candidates.
  - Cytomegalovirus (CMV)-negative or leuko-reduced blood products are recommended whenever possible for CMV-negative transplant candidates.
- Antibiotics are recommended for bacterial infections, but no routine prophylaxis is recommended except in patients with recurrent infections.
- Aminocaproic acid or other antifibrinolytic agents may be considered for bleeding refractory to platelet transfusions or profound thrombocytopenia.
- Iron chelation:
  - If >20 to 30 RBC transfusions have been received, consider daily chelation with deferoxamine subcutaneously or deferasirox orally to decrease iron overload, particularly for patients that have lower-risk MDS or who are potential transplant candidates LOW/INT-1. For patients with serum ferritin levels >2500 ng/mL, aim to decrease ferritin levels to <1000 ng/mL.[mm] (See Discussion).
  - Patients with low creatinine clearance (<40 mL/min) should not be treated with deferasirox or deferoxamine.
- Cytokines:
  - EPO: See Anemia Pathway (MDS-6)
  - G-CSF or GM-CSF:
    - Not recommended for routine infection prophylaxis.
    - Consider use in neutropenic patients with recurrent or resistant infections.
    - Combine with EPO for anemia when indicated. See Anemia Pathway (MDS-6).
    - Platelet count should be monitored.
- Clinically significant thrombocytopenia
  - In patients with lower-risk MDS who have severe or life-threatening thrombocytopenia, consider treatment with a thrombopoietin-receptor agonist.[nn]

[kk] See NCCN Guidelines for Supportive Care.

[ll] Avoid transfusions for arbitrary hemoglobin thresholds in the absence of symptoms of active coronary disease, heart failure, or stroke. In situations where transfusions are necessary, transfuse the minimum units necessary to relieve symptoms of anemia or to return the patient to a safe hemoglobin level. Hicks L, Bering H, Carson K, et al. The ASH Choosing Wisely campaign: five hematologic tests and treatments to question. Blood. 2013;122:3879-3883.

[mm] Clinical trials in MDS are currently ongoing with oral chelating agents.

[nn] Giagounidis A, Mufti GJ, Fenaux P, et al. Results of a randomized, double-blind study of romiplostim versus placebo in patients with low/intermediate-1-risk myelodysplastic syndrome and thrombocytopenia. Cancer 2014;120:1838-1846. Platzbecker U, Wong RS, Verma A, et al. Safety and tolerability of eltrombopag versus placebo for treatment of thrombocytopenia in patients with advanced myelodysplastic syndromes or acute myeloid leukaemia: a multicentre, randomised, placebo-controlled, double-blind, phase 1/2 trial. Lancet Haematology 2015;2: E417-E426.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Table 1
Guidelines on iron chelation therapy in patients with MDS [22–32].

Countries	Transfusion status	Serum ferritin (ng/Ml)	Patient profile	Target serum ferritin level
Italian (Ref. [22])	≥50 RBC units	NR	• Life expectancy > 6 months	NR
UK (Ref. [23])	~25 RBC units (5 g iron)	NR	• Pure sideroblastic anaemia • del 5q	<1000
US (Ref. [24])	20–30 RBC units (≥5–10 g iron)	>2500	• IPSS low or Int-1 • Potential transplant patients	For pts with SF > 2500, aim to decrease to<1000
International (Ref. [25])	Transfusion-dependent	>1000–2000	• RA, RARS, del 5q • IPSS low or Int-1	NR
Japanese (Ref. [26])	>40 Japanese units	>1000	• Life expectancy > 1 year	500–1000
Canadian (Ref. [27])	Transfusion-dependent	>1000	• RA, RARS, del 5q • IPSS low or Int-1 • IPSS Int-2 or high (if SF > 1000 and • SCT candidates/life expectancy > 1 year)	NR; reduce dose when < 2000; discontinue chelator when <1000
Spanish (Ref. [28])	Transfusion-dependent	>1000	• IPSS low or Int-1 • WPSS very low, Low, or Int • Spanish prognostic index low risk	NR
Austrian (Ref. [29])	Transfusion-dependent	>2000	• Life expectancy > 2 years	NR
Israeli (Ref. [30])	20–25 RBC units	>1000	• Low or Int-1 (IPSS) • Candidates for SCT	<500 – <1000
MDS Foundation (Ref. [31])	2 RBC units/month for ≥1 year	>1000	• Life expectancy > 1 year	NR
Italian update (Ref. [32])	≥20 RBC units (4 g iron)	NR	• Low or Int-1 (IPSS) • Int-2, high when responding to disease-modifying agent or candidates for SCT	NR

My Agenda

- Iron balance and overload
- Clinical results of chelation: reduction of iron overload
- **Clinical results of chelation: hematologic improvement**
- Clinical results of chelation: survival
- Iron chelation in higher risk MDS
- Perspectives

Ann Hematol (2015) 94:771–777
DOI 10.1007/s00277-015-2341-z

REVIEW ARTICLE

An increase in hemoglobin, platelets and white blood cells levels by iron chelation as single treatment in multitransfused patients with myelodysplastic syndromes: clinical evidences and possible biological mechanisms

Massimo Breccia · Maria Teresa Voso · Maria Antonietta Aloe Spiriti · Susanna Fenu · Luca Maurillo · Francesco Buccisano · Agostino Tafuri · Giuliana Alimena

DFX can improve haemopoiesis in MDS: first reports

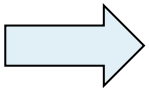
Study	n	IPSS risk	RBC response	Neutrophil response	Platelet response
Breccia M, et al. 2010[1]	1	Low	Major	NR	NA
Capalbo S, et al. 2009[2]	1	Low	Major	NA	NA
Messa E, et al. 2008[3]	4	Int-1 Int-1 High	Minor Major Major	NA NA Major	NA NA NR
Okabe H, et al. 2009[4]	1	NR	Major	Major	NR
Oliva EN, et al. 2010[5]	1	Low	Major	NA	NA
Guariglia R, et al. 2011[6]	1	Int-1	Major	Major	NA
List AF, et al. 2009[7]	6	Low/Int-1	2 Major 1 Minor[a]	1 Major 1 Major[b]	1 Major 1 Major[b]
Badawi MA, et al. 2010[8]	1	Int-1	Major[c]	NA	NA
Nishiuchi T, et al. 2010[9]	1	Int-1	Major[d]	Major[d]	NA
Molteni A, et al. 2010[10]	6	NR	5 Minor	1 Major	NA

RBC, platelet, and neutrophil responses were assessed according to IWG 2000 criteria.
[a] The patient also received darbopoietin treatment. [b] The patient also received G-CSF and decitabine treatment.
[c] Response duration was 38 months; cutaneous leukaemic infiltration was observed. [d] Response duration was more than 12 months.

1. Breccia M, et al. Acta Haematol. 2010;124:46-8. 2. Capalbo S, et al. Acta Haematol. 2009;121:19-20. 3. Messa E, et al. Acta Haematol. 2008;120:70-4. 4. Okabe H, et al. Rinsho Ketsueki. 2009;50:1626-9. 5. Oliva EN, et al. Transfusion. 2010;50:1568-70. 6. Guariglia R, et al. Leuk Res. 2011;35:566-70. 7. List AF, et al. Blood. 2009;114:abstract 3829. 8. Badawi MA, et al. Adv Hematol. 2010;2010:164045. 9. Nishiuchi T, et al. Int J Hematol. 2010;91:333-5. 10. Molteni A, et al. Haematologica. 2010;95 Suppl 2:abstract 1410.

Hematological response to ICT: Retrospective Italian study

105 patients with hematologic malignancies who received ICT (92 for ≥3 months)



Deferasirox (N=68)
(9 PMF, 5 AA, 3 CMML, 51 MDS)

Deferasirox after deferoxamine (N=7)
(1 PMF, 6 MDS)

Deferoxamine (N=30)
(6 PMF, 3 AA, 1 CMML, 2 AML, 18 MDS)

- IWG 2006 criteria used
- 25 pts were receiving EPO, started ≥6 mos before ICT, without significant clinical improvement
- 3 patients were receiving a JAK2 inhibitor started ≥1 year before ICT
- Patients receiving any kind of therapy able to modify the erythroid response were excluded

Cilloni D *et al. Blood* 2011;118;abst 611

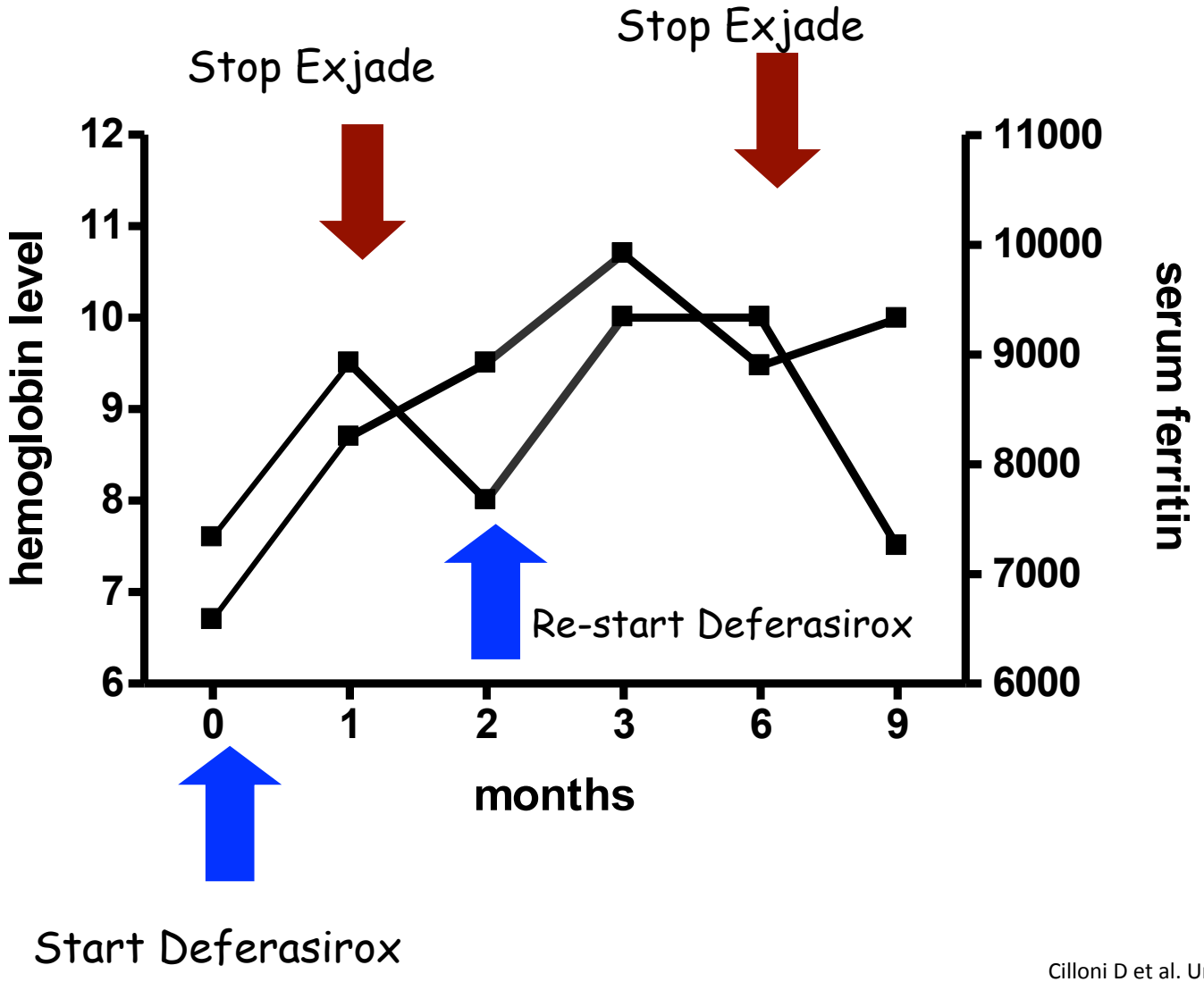
Hematological Response (RBC)

	DFO	DFX	DFO---DFX	TOT
Patients	**29**	**57**	**6**	**92**
RBC transfusion independency	**5** (17,2%)	**12** (21%)	**1** (16%)	18 (19,5%)
HI-e (reduction of 4 U /8 weeks)	**4** (13,7%)	**9** (15,7%)	**3** (50%)	16 (17,3%)
HI-e (increase of 1,5 gr/dL)	**2** (6,8%)	**5** (8,7%)	**0**	7 (7,6%)
TOTAL	11 (**37%**)	26 (**45,6%**)	4 (**66%**)	**41 (44,5%)**

➢3 patients achieving complete erythroid response (2 with DFO and 1 with DFX) were receiving concomitant Epo from 15, 17 and 53 months with stable transfusion requirement at the time of ICT

IWG response criteria: Cheson et al. Blood 2006

Cilloni D, et al. Blood. 2011;118;[abstract 611].



Cilloni D et al. Unpublished data

DFX can improve haemopoiesis in MDS: recent data

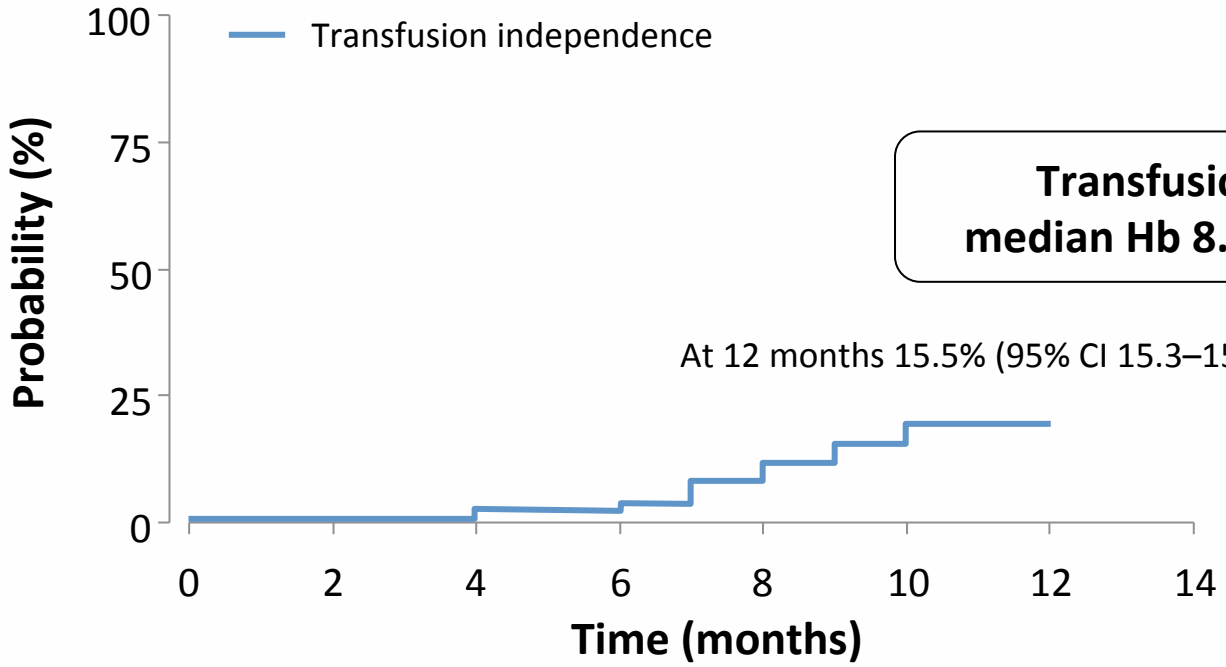
Study	n	IPSS risk	RBC response	Neutrophil response	Platelet response
Cilloni D, et al. 2011[1]	57	Low/Int-1	45.6%	NR	NR
Molteni A, et al. 2013[2]	53	Low/Int-1	35.1%	76.4%	61%
Cheong JW, et al. 2014[3]	96 (43 MDS)	Low/Int-1	Hb level increased by 1.36 g/dL	NS	PLTs increased by 10.7 x 10^9
List A, et al. 2012[4]	173 52 77	Low/Int-1	15%	15%	22%
Gattermann N, et al. 2012[5]	247 50 100	Low/Int-1	21.5%	22%	13%
Nolte F, et al. 2013[6]	50	Low/Int-1	11%	NR	NR
Angelucci E, et al. 2014[7]	152	Low/Int-1	11%	3%	15%

RBC, platelet, and neutrophil responses are assessed according to IWG 2006 criteria (1–3).

1. Cilloni D, et al. Blood. 2011;118:abstract 611. 2. Molteni A. Leuk Res 2013;37:1233-40. 3. Cheong JW, et al, Transfusion. 2014;54:1542-51. 4. List A, et al. J Clin Oncol. 2012;30:2134-9. 5. Gattermann N, et al. Haematologica. 2012;97:1364-71. 6. Nolte F, et al. Ann Hematol. 2013;92:191-8. 7. Angelucci E, et al. Eur J Haematol. 2014;92:527-36.

GIMEMA prospective trial: probability of acquiring transfusion independence

All responses to last ≥ 12 weeks



Transfusion-free patients: median Hb 8.1 g/dL (IQR 7.6–8.6)

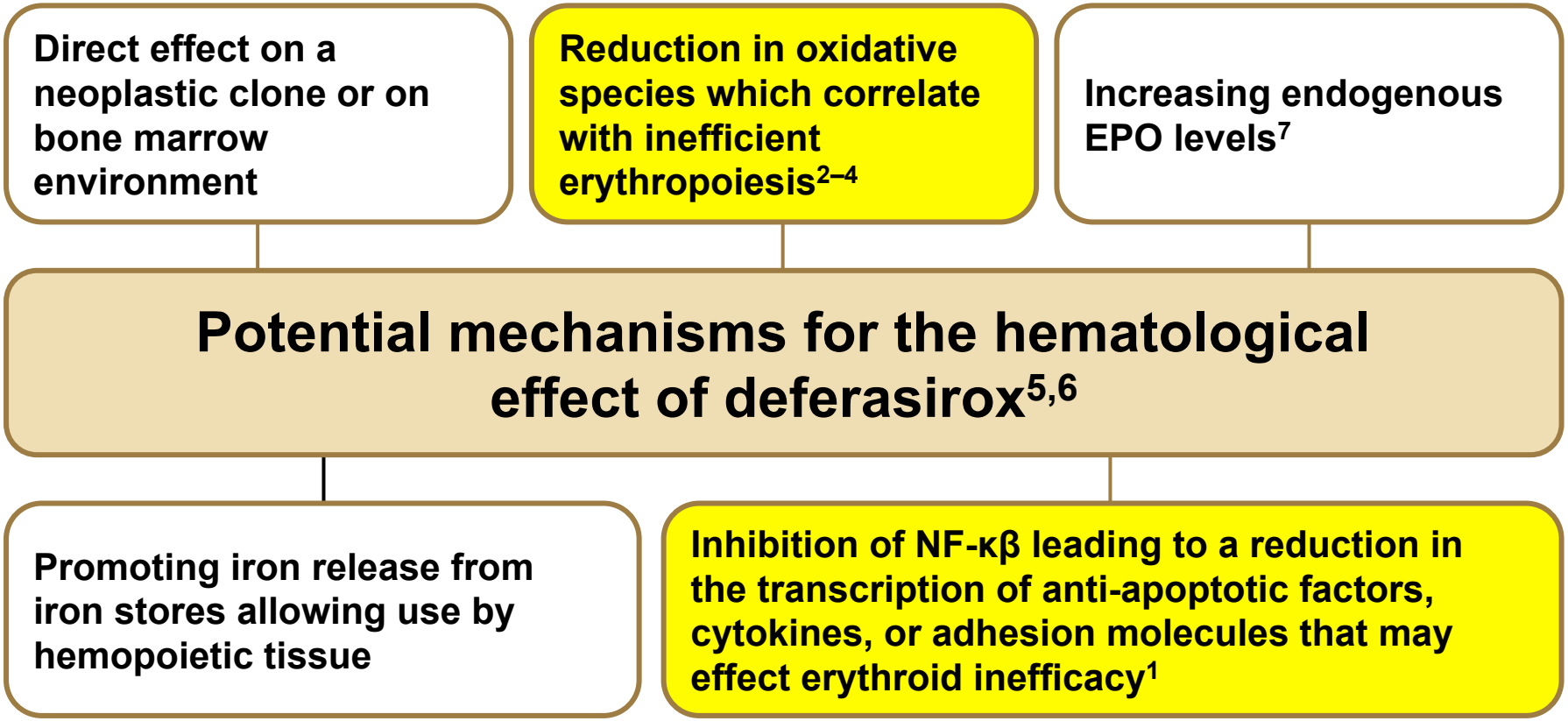
Patients at risk	138	107	86	68

Non-parametric cumulative incidence estimator
Drop-out, progression, and death were considered competitive risks

The cumulative incidence of transfusion independence, adjusted for death and disease progression, was 2.6%, 12.3%, and 15.5% after 6, 9, and 12 months, respectively.

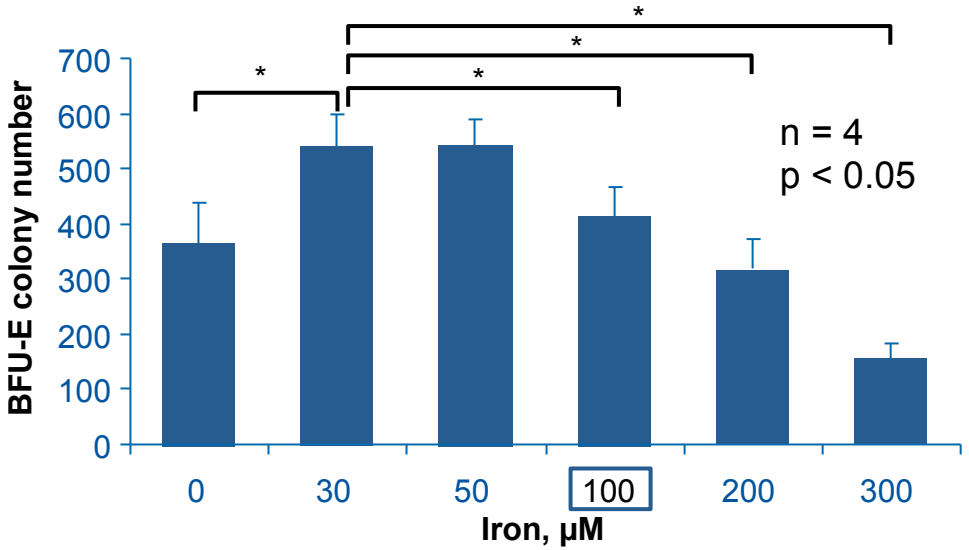
Updated data from Angelucci E, et al. Eur J Haematol. 2014;92:527-36.

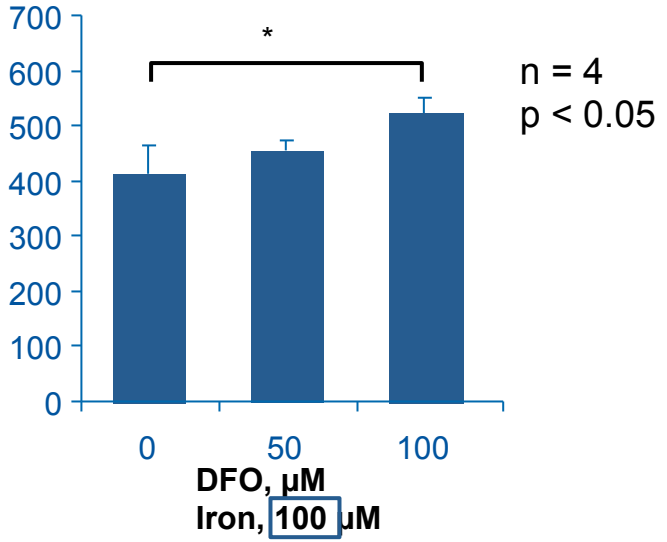
Potential Mechanisms for the Hematologic Effect of Deferasirox

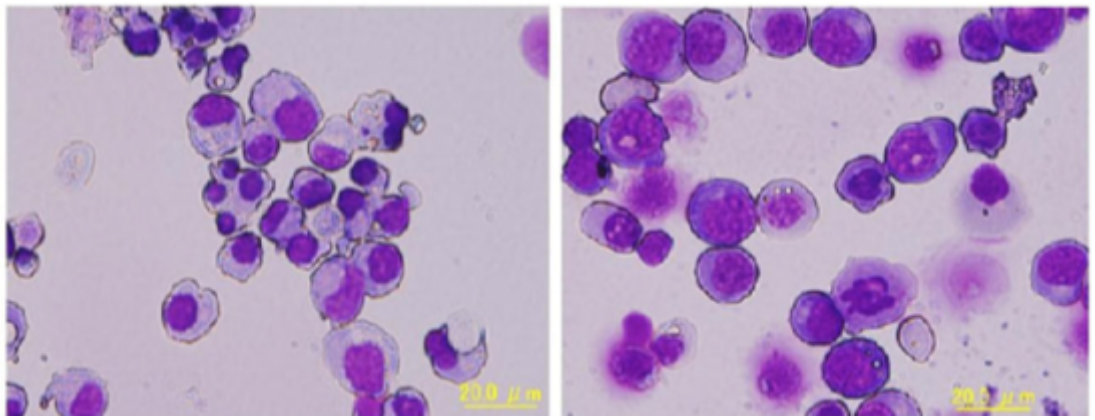


1. Messa E, et al. *Haematologica*. 2010;95:1308-16. 2. Ghoti H, et al. *Eur J Haematol*. 2007;79:463-7.
3. Hartmann J, et al. *Blood*. 2008;112:[abstract 2694]. 4. Chan LSA, et al. *Blood*. 2008;112:[abstract 2685].
5. Breccia M, et al. *Acta Haematol*. 2010;124:46-8. 6. Guariglia R, et al. *Leuk Res*. 2011;35:566-70.
7. Ren X, et al. *J Appl Physiol*. 2000;89(2):680-6.

The effect of iron overload and chelation on erythroid differentiation

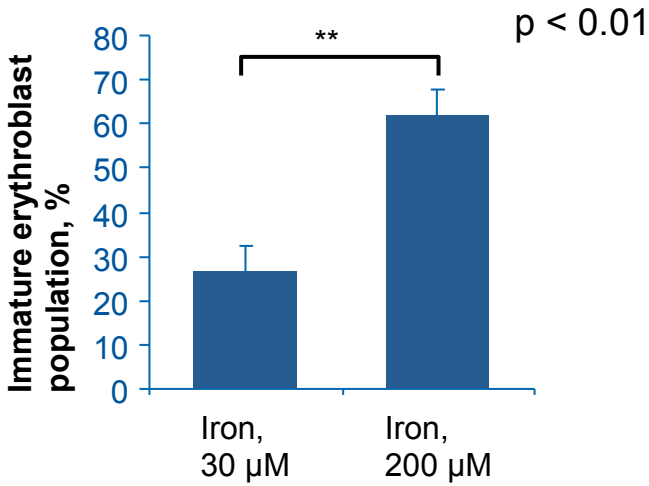






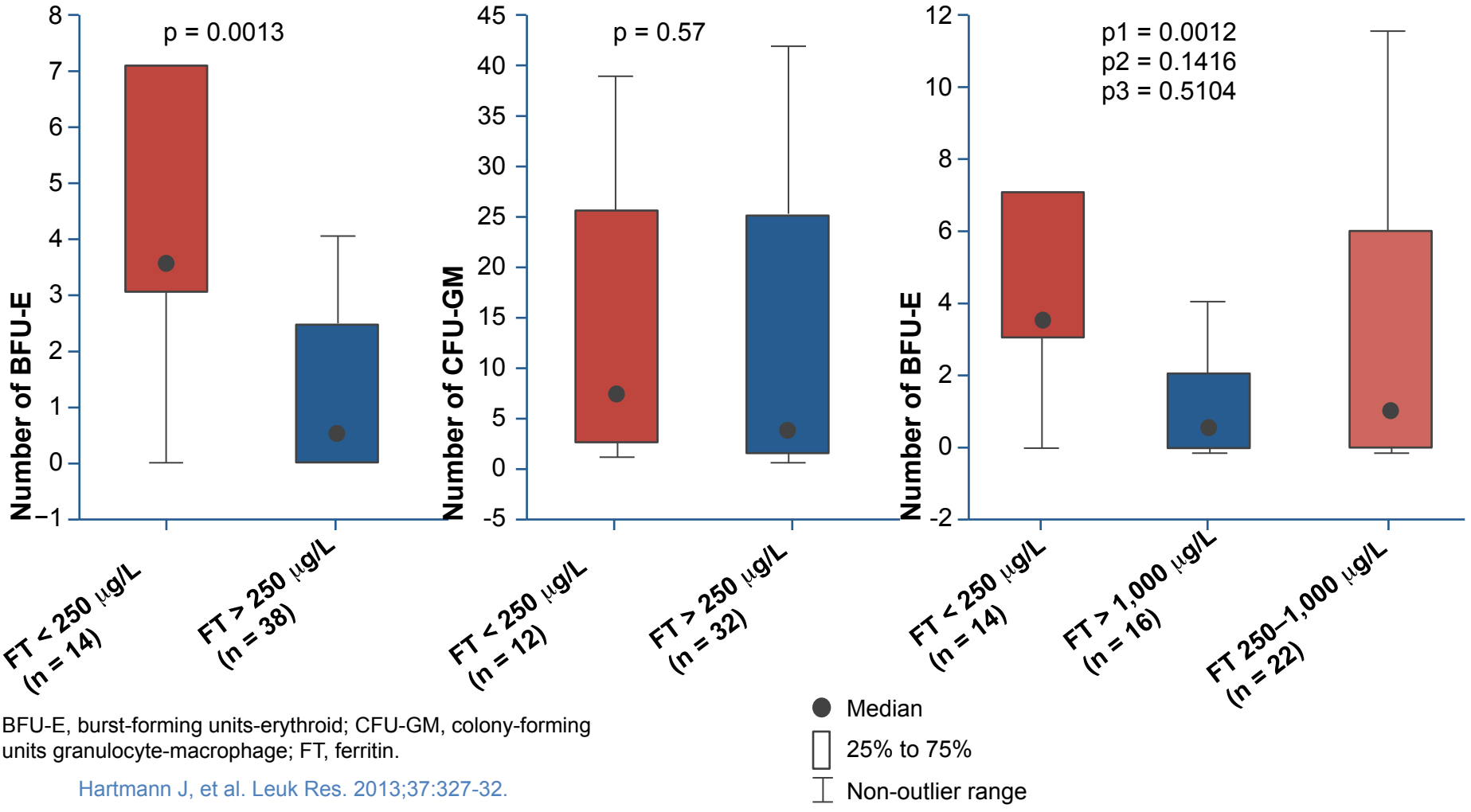
Iron, 30 μM

Iron, 200 μM



Taoka K, et al. Int J Hematol. 2012;95:149-59.

Proliferation of BFU-E in patients with normal and elevated serum ferritin



BFU-E, burst-forming units-erythroid; CFU-GM, colony-forming units granulocyte-macrophage; FT, ferritin.

Hartmann J, et al. Leuk Res. 2013;37:327-32.

SCIENTIFIC REPORTS

OPEN

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ROS-mediated iron overload injures the hematopoiesis of bone marrow by damaging hematopoietic stem/progenitor cells in mice

Xiao Chai[1,3], Deguan Li[2], Xiaoli Cao[1], Yuchen Zhang[1], Juan Mu[1], Wenyi Lu[1], Xia Xiao[1], Chengcheng Li[2], Juanxia Meng[1], Jie Chen[1], Qing Li[1], Jishi Wang[3], Aimin Meng[2] & Mingfeng Zhao[1]

Iron overload, caused by hereditary hemochromatosis or repeated blood transfusions in some diseases, such as beta thalassemia, bone marrow failure and myelodysplastic syndrome, can significantly induce injured bone marrow (BM) function as well as parenchyma organ dysfunctions. However, the effect of iron overload and its mechanism remain elusive. In this study, we investigated the effects of iron overload on the hematopoietic stem and progenitor cells (HSPCs) from a mouse model. Our results showed that iron overload markedly decreased the ratio and clonogenic function of murine HSPCs by the elevation of reactive oxygen species (ROS). This finding is supported by the results of NAC or DFX treatment, which reduced ROS level by inhibiting NOX4 and p38MAPK and improved the long-term and multi-lineage engrafment of iron overload HSCs after transplantation. Therefore, all of these data demonstrate that iron overload injures the hematopoiesis of BM by enhancing ROS through NOX4 and p38MAPK. This will be helpful for the treatment of iron overload in patients with hematopoietic dysfunction.

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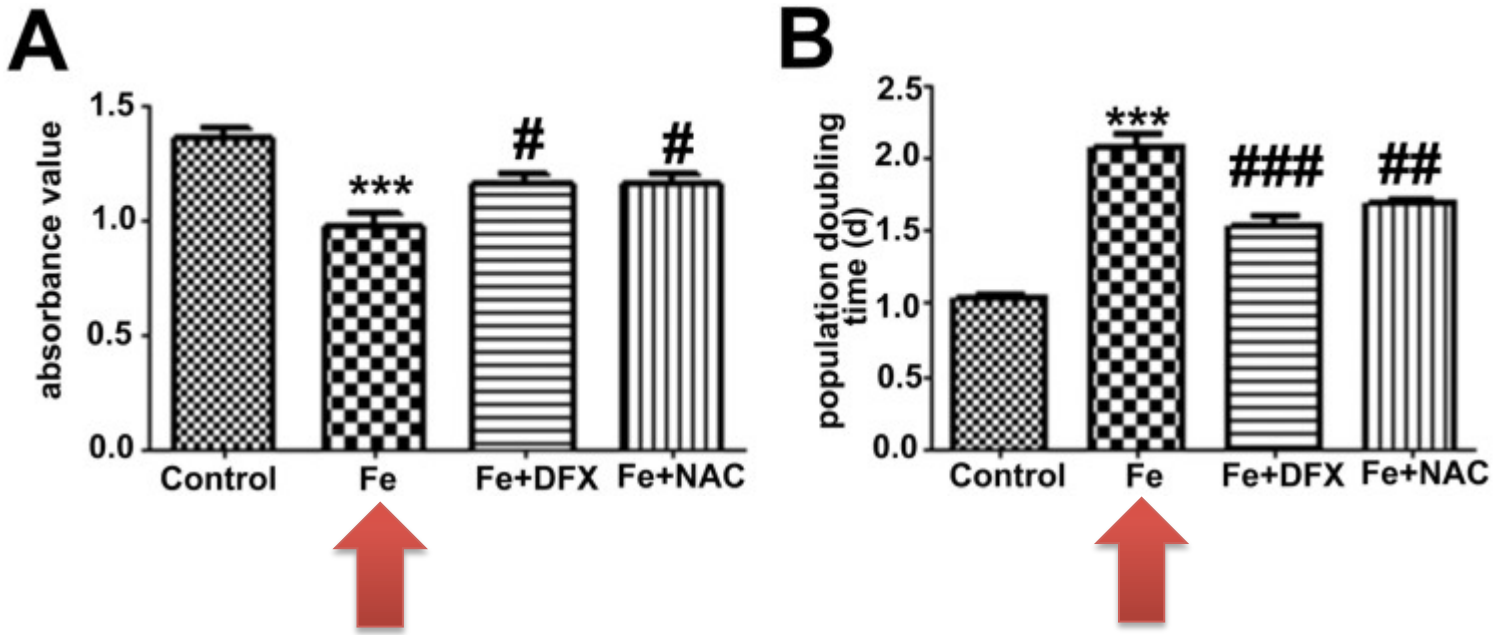
Yuchen Zhang et al.PLoS One. 2015; 10(3): e0120219
Effects of Iron Overload on the **Bone Marrow Microenvironment** in Mice

Iron overload inhibited BM-MSCs proliferation ability.



(B) The IO BM-MSCs showed a longer double time (2.07 ± 0,14 days) than control .The effect was reversed by DFX or NAC.

Free Radical Biology and Medicine 53 (2012) 643–648

Contents lists available at SciVerse ScienceDirect

Free Radical Biology and Medicine

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

Original Contribution

Improvement of iron-mediated oxidative DNA damage in patients with transfusion-dependent myelodysplastic syndrome by treatment with deferasirox

Shohei Kikuchi, Masayoshi Kobune, Satoshi Iyama, Tsutomu Sato, Kazuyuki Murase, Yutaka Kawano, Kohichi Takada, Kaoru Ono, Yumiko Kaneko, Koji Miyanishi, Yasushi Sato, Tsuyoshi Hayashi, Rishu Takimoto, Junji Kato*

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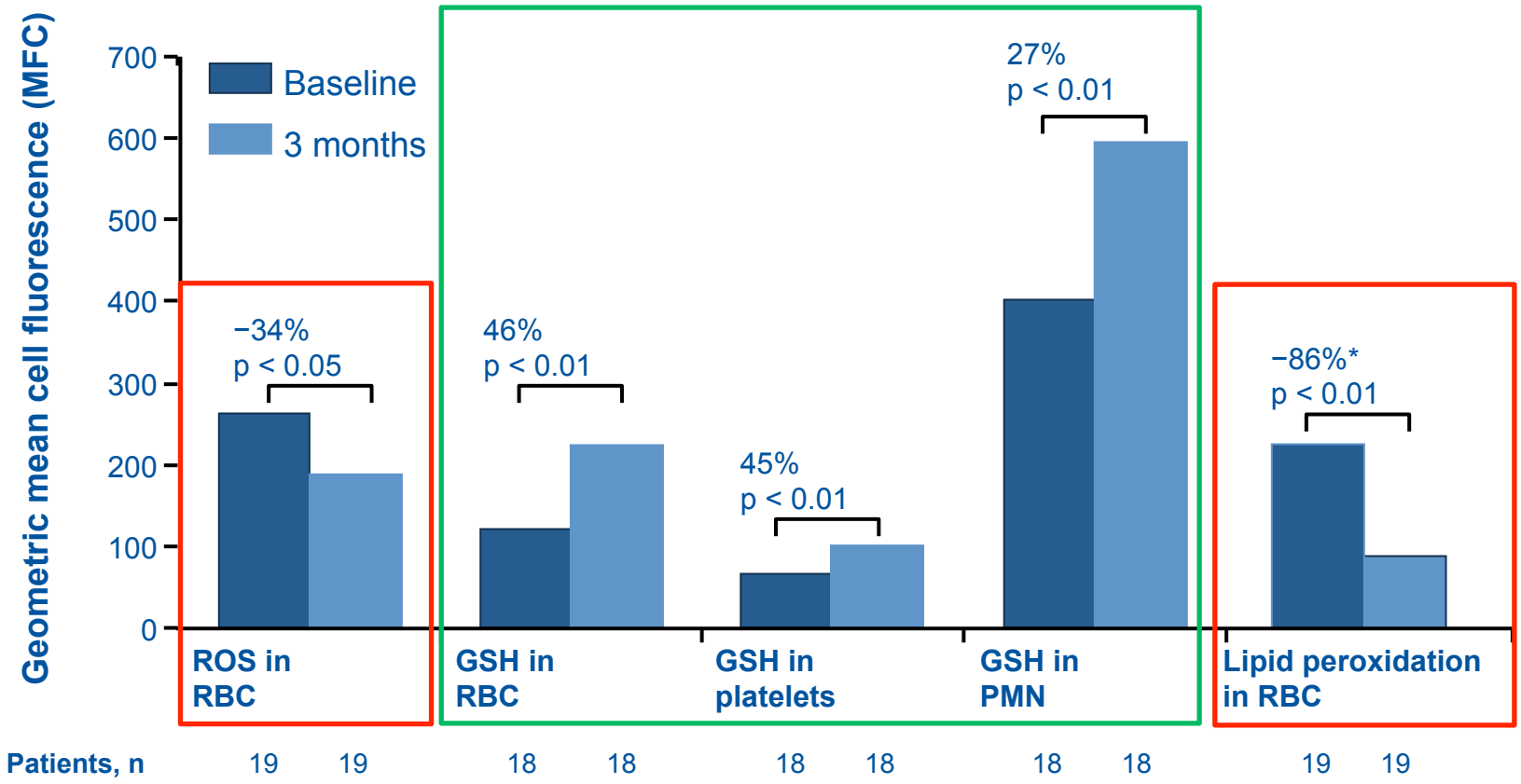
Iron chelation

ABSTRACT

Myelodysplastic syndrome (MDS) is characterized by dysplastic and ineffective hematopoiesis, peripheral blood cytopenias, and a risk of leukemic transformation. Most MDS patients eventually require red blood cell (RBC) transfusions for anemia and consequently develop iron overload. Excess free iron in cells catalyzes generation of reactive oxygen species that cause oxidative stress, including oxidative DNA damage. However, it is uncertain how iron-mediated oxidative stress affects the pathophysiology of MDS. This study included MDS patients who visited our university hospital and affiliated hospitals ($n=43$). Among them, 13 patients received iron chelation therapy when their serum ferritin (SF) level was greater than 1000 ng/mL or they required more than 20 RBC transfusions (or 100 mL/kg of RBC). We prospectively analyzed 8-hydroxy-2′-deoxyguanosine (8-OHdG) levels in peripheral blood mononuclear cells (PBMC) obtained from MDS patients before and after iron chelator, deferasirox, administration. We showed that the 8-OHdG levels in MDS patients were significantly higher than those in healthy volunteers and were positively correlated with SF and chromosomal abnormalities. Importantly, the 8-OHdG levels in PBMC of MDS patients significantly decreased after deferasirox administration, suggesting that iron chelation reduced oxidative DNA damage. Thus, excess iron could contribute to the pathophysiology of MDS and iron chelation therapy could improve the oxidative DNA damage in MDS patients.

Changes in oxidative stress parameters in RBC, platelets, and PMN, at baseline and after a mean of 3 months of deferasirox treatment



*Cell fluorescence is proportional to ROS and GSH, but inversely proportional to lipid peroxidation.

GSH = glutathione; PMN = polymorphonuclear neutrophils; ROS = reactive oxygen species.

Ghoti H, et al. Haematologica. 2010;95:1433-4.

Leukemia Research 36 (2012) 966–973

Contents lists available at SciVerse ScienceDirect

Leukemia Research

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

Deferasirox exposure induces reactive oxygen species and reduces growth and viability of myelodysplastic hematopoietic progenitors

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Progenitors
Iron chelators
Deferasirox

ABSTRACT

We examined the effect of deferasirox (DFX) on CD34+ hematopoietic progenitors from MDS patients. Progressive, dose-dependent suppression of MDS progenitor proliferation in culture was observed with DFX concentrations ranging from 5 μM to 20 μM. This effect was more pronounced in MDS compared to CD34+ progenitors isolated from umbilical cord blood or normal peripheral blood. There was reduced viability of MDS progenitors but not normal progenitors at 20 μM DFX which increased with duration of exposure. Exposure to 20 μM DFX for 14 days markedly suppressed colony growth of MDS progenitors. Reactive oxygen species levels were elevated above control at concentrations of DFX above 5 μM. We conclude that exposure to DFX results in dose-dependent inhibition of proliferation, and survival in MDS progenitors.

bjh research paper

The iron chelator deferasirox affects redox signalling in haematopoietic stem/progenitor cells

Tiziana Tataranni,[1] Francesca Agriesti,[1] Carmela Mazzoccoli,[1] Vitalba Ruggieri,[1] Rosella Scrima,[2] Ilaria Laurenzana,[1] Fiorella D'Auria,[3] Franca Falzetti,[4] Mauro Di Ianni,[5] Pellegrino Musto,[6] Nazzareno Capitanio[2] and Claudia Piccoli[1,2]

[1]Laboratory of Pre-Clinical and Translational Research, IRCCS-CROB, Referral Cancer Centre of Basilicata, Rionero in Vulture (Pz), [2]Department of Clinical and Experimental Medicine, University of Foggia, Foggia, [3]Laboratory of Clinical Research and Advanced Diagnostics, IRCCS-CROB, Referral Cancer Centre of Basilicata, Rionero in Vulture (PZ), [4]Haematology and Clinical Immunology Section, University of Perugia, Perugia, [5]Department of Internal Medicine and Public Health, University of L'Aquila, L'Aquila, and [6]Scientific Direction, IRCCS-CROB, Referral Cancer Centre of Basilicata, Rionero in Vulture (PZ), Italy

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Summary

The iron chelator deferasirox (DFX) prevents complications related to transfusional iron overload in several haematological disorders characterized by marrow failure. It is also able to induce haematological responses in a percentage of treated patients, particularly in those affected by myelodysplastic syndromes. The underlying mechanisms responsible for this feature, however, are still poorly understood. In this study, we investigated the effect of DFX-treatment in human haematopoietic/progenitor stem cells, focussing on its impact on the redox balance, which proved to control the interplay between stemness maintenance, self-renewal and differentiation priming. Here we show, for the first time, that DFX treatment induces a significant diphenyleneiodonium-sensitive reactive oxygen species (ROS) production that leads to the activation of POU5F1 (*OCT4*), *SOX2* and *SOX17* gene expression, relevant in reprogramming processes, and the reduction of the haematopoietic regulatory proteins CTNNB1 (β-Catenin) and BMI1. These DFX-mediated events were accompanied by decreased CD34 expression, increased mitochondrial mass and up-regulation of the erythropoietic marker CD71 (TFRC) and were compound-specific, dissimilar to deferoxamine. Our findings would suggest a novel mechanism by which DFX, probably independently on its iron-chelating property but through ROS signalling activation, may influence key factors involved in self-renewal/differentiation of haematopoietic stem cells.

Keywords: deferasirox, reactive oxygen species, haematopoietic stem cell, differentiation, myelodysplastic syndromes.

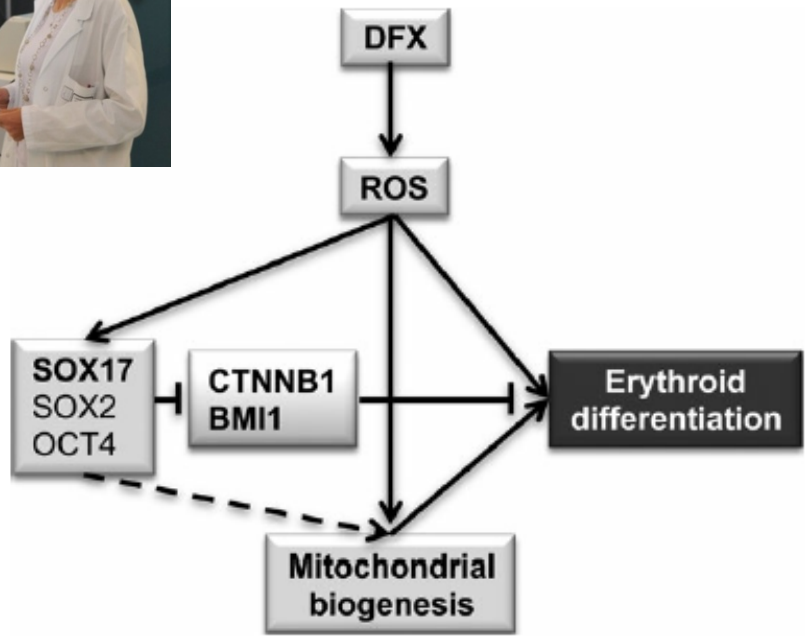
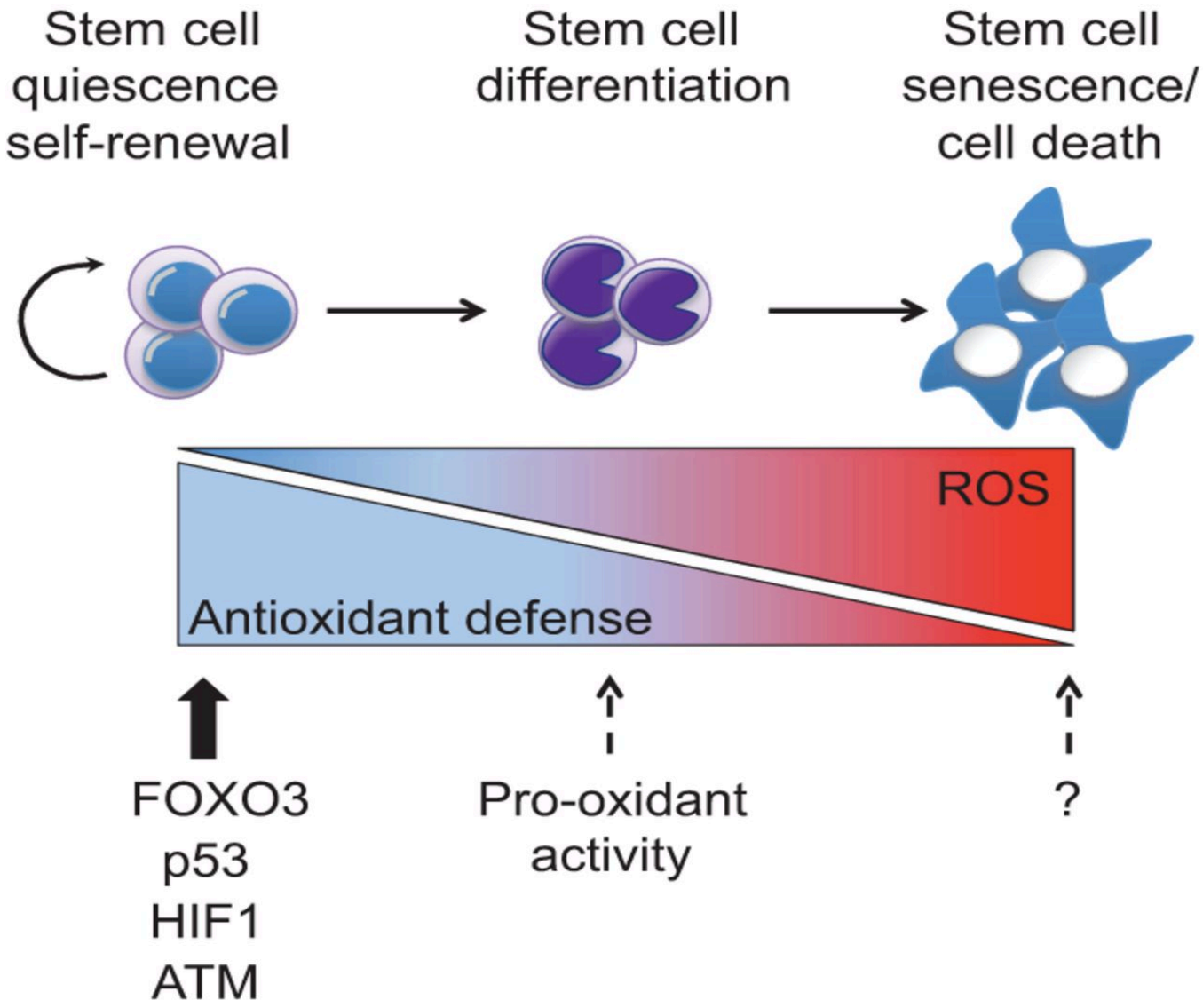


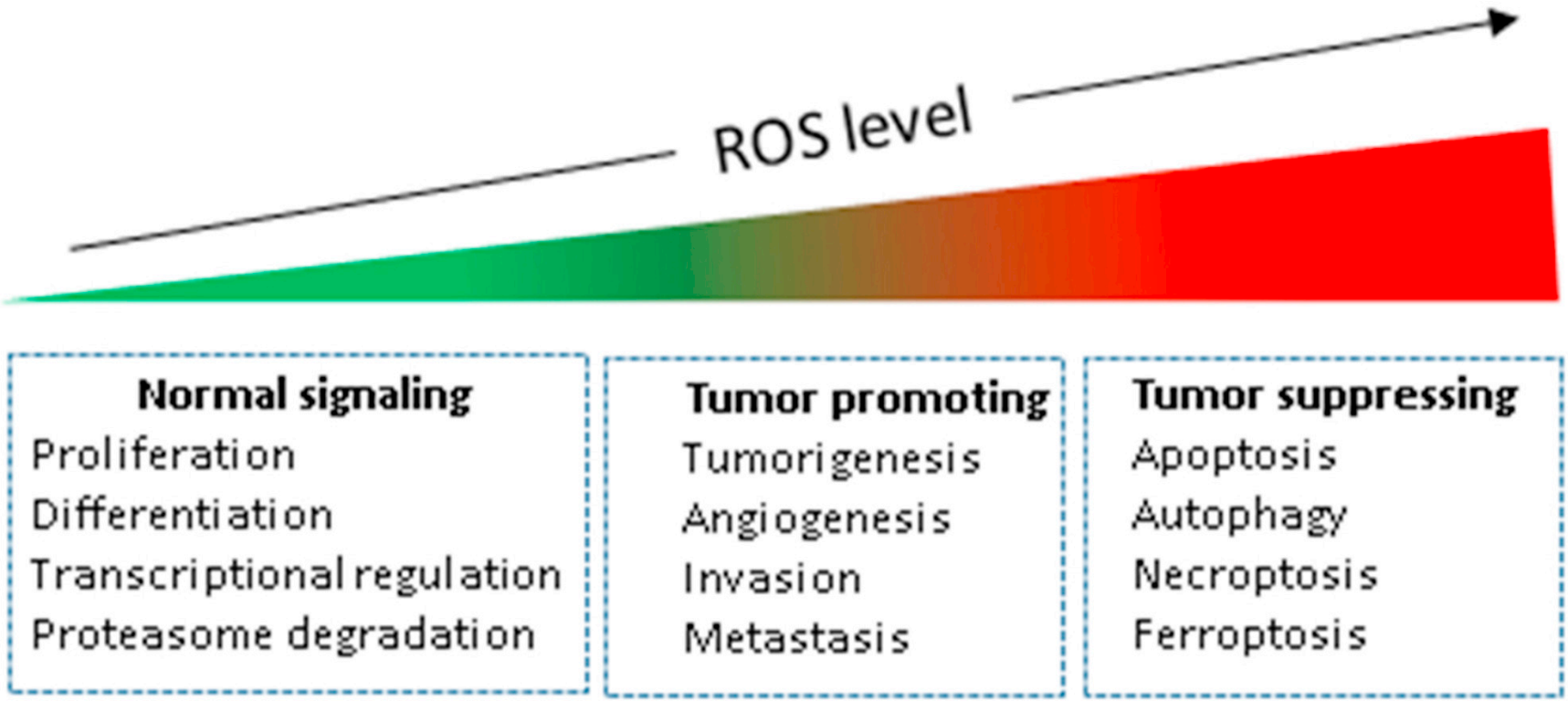
Fig 5. Suggested mechanism of action of DFX in HSPCs. The scheme shows the possible interplay between DFX-mediated ROS production, activation of transcription/regulatory factors, mitochondrial biogenesis and erythroid commitment in HSPCs as suggested by the present study; see *Discussion* for details. DFO, deferoxamine; DFX, deferasirox; ROS, reactive oxygen species.

ROS effects on stem cells



Carolina L. Bigarella et al. Development 2014;141:4206-4218

Development



Reactive oxygen species and cancer paradox: To promote or to suppress?

Free Radical Biology and Medicine Volume 104, March 2017, Pages 144–164

bjh research paper

The oral iron chelator deferasirox inhibits NF-κB mediated gene expression without impacting on proximal activation: implications for myelodysplasia and aplastic anaemia*

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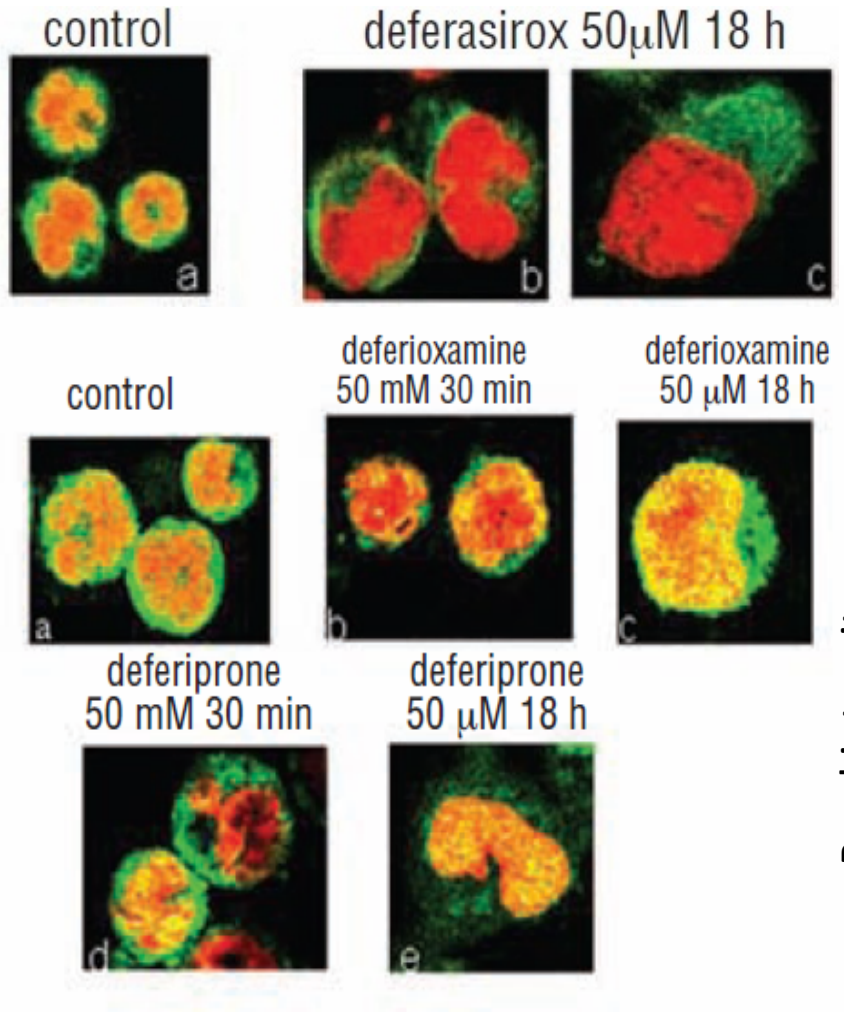
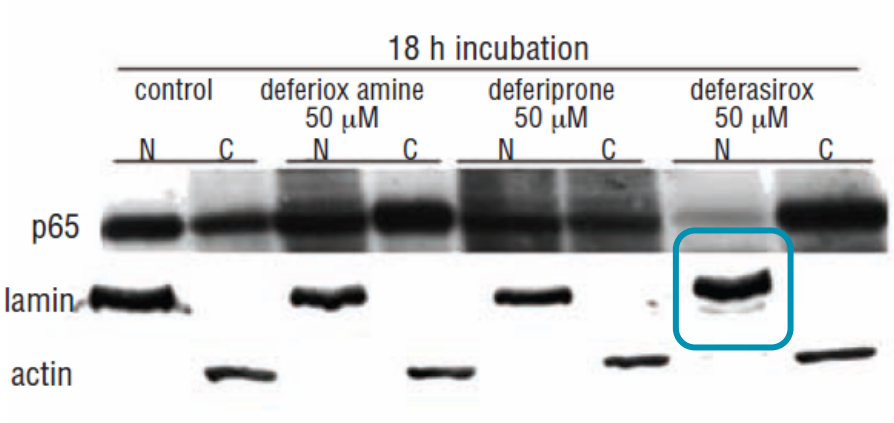
Summary

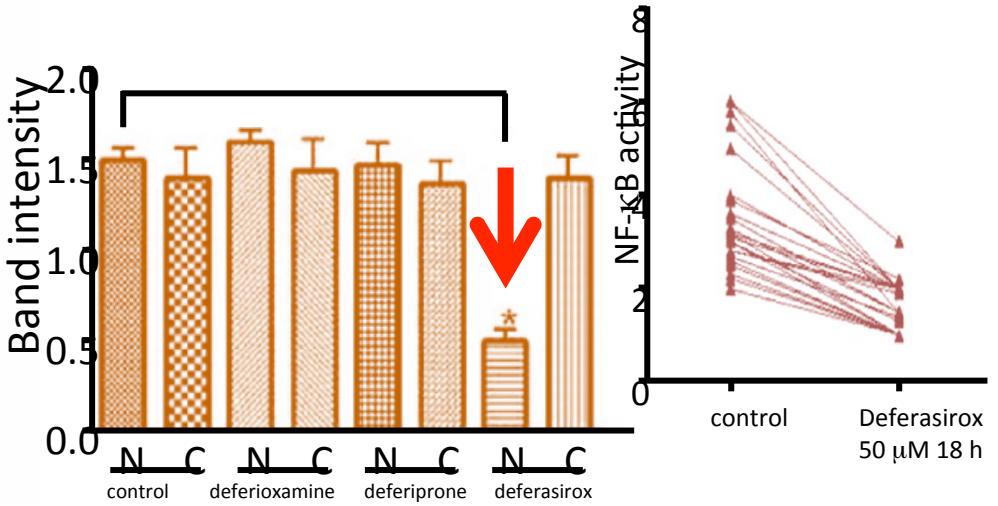
The myelodysplastic syndromes (MDS) are a group of disorders characterized by ineffective haematopoiesis, bone marrow dysplasia and cytopenias. Failure of red cell production often results in transfusion dependency with subsequent iron loading requiring iron chelation in lower risk patients. Consistent with previous reports, we have observed haematopoietic improvement in a cohort of patients treated with the oral iron chelator deferasirox (DFX). It has been postulated that MDS patients have a pro-inflammatory bone marrow environment with increased numbers of activated T cells producing elevated levels of tumour necrosis factor (TNF), which is detrimental to normal haematopoiesis. We demonstrate that DFX inhibits nuclear factor (NF)-κB dependent transcription without affecting its proximal activation, resulting in reduced TNF production from T cells stimulated *in vitro*. These results suggest that the haematopoietic improvement observed in DFX-treated patients may reflect an anti-inflammatory effect, mediated through inhibition of the transcription factor NF-κB and support the therapeutic targeting of this pathway, which is aberrantly activated in a large proportion of haematological malignancies.

Keywords: aplastic anaemia, biochemistry, blood diseases, chelation, myeloid function and development.

Deferasirox inhibits NF-κB in cell lines and MDS; deferoxamine and deferiprone do not







Messa E *et al. Haematologica* 2010;95:1308 - 1316

N°	Title	Purpose
NCT02663752	A Phase II Pilot Study to Assess the Presence of Molecular Factors Predictive for Hematologic Response in Myelodysplastic Syndrome Patients Receiving Deferasirox Therapy. Belgium multicentric study	assess the presence of genetic biomarkers predictive for hematologic response by the use of gene expression profiling of bone marrow aspirates obtained from MDS patients with or without hematological response
NCT02233504	Pilot Study to Assess Hematologic Response in Patients With Acute Myeloid Leukemia or High Risk Myelodysplastic Syndromes Undergoing Monotherapy With Exjade (Deferasirox) Abramson Cancer Center of the University of Pennsylvania	The purpose of this trial is to examine the hematologic response rate of Exjade® in patients with AML and high risk MDS and chronic iron overload from blood transfusions.
NCT01956799	Identification of Mechanism in the Erythroid Response in Patients With Myelodysplasia Undergoing Chelation Therapy (BIOFER12) Fondazione Italiana Sindromi Mielodisplastiche Onlus	The study aims to evaluate the molecular mechanism underlying the erythroid response observed in some patients with myelodysplasia, myelofibrosis and aplastic anemia treated with Deferasirox or Deferoxamina.
NCT02477631	Effect of Deferiprone on Oxidative-Stress and Iron-Overload in Low Risk Transfusion-Dependent MDS Patients Sheba Medical Center, Israel	To evaluate the effect of Deferiprone on oxidative stress parameter - Reactive oxygen species (ROS)

Ongoing studies, http://www.clinicaltrials.gov

My Agenda

- Iron balance and overload
- Clinical results of chelation: reduction of iron overload
- Clinical results of chelation: hematologic improvement
- **Clinical results of chelation: survival**
- Iron chelation in higher risk MDS
- Perspectives

Reference	Country	Study design	Sample size for 2 groups	Population	Age (years)	Male Sex, %	Median OS with ICT (months)	Median OS without ICT (months)	*P* value
Lyons *et al* (2012)	United States	Prospective Non-interventional Cohort	534	Low risk MDS patients (WHO, FAB or IPSS) who received no ICT or ICT ≥6 months	Median age (range): No ICT = 77 (47–99); ICT = 75 (21–94); ICT ≥6 months = 75 (21–94)	Ratio M:F; No emsp;ICT = 1·45:1; emsp;ICT ≥6 months = 1·11:1	ICT = 96·8 ≥6 months ICT = 102·1	50	0·0001
Neukirchen *et al* (2012)	Germany	Retrospective Matched-Pair Analysis	188	Adults with MDS	Median age (range): No ICT = 67·5(33–89) ICT = 64(18–82)	No ICT = 48 emsp;ICT = 42	75	49	0·002
Komrokji *et al* (2011)	United States	Retrospective Cohort	97	Low/Int-1 IPSS MDS patients	Mean age: No ICT = 65·5; ICT = 67	No ICT = 63·5 emsp;ICT = 73·3	59	33·7	0·013
Raptis *et al* (2010)	United States	Retrospective Single arm Descriptive Analysis	78	ICT-eligible Low risk MDS patients (WHO, FAB, or IPSS) (subgroup analysis)	Mean age (SD): No ICT = 70·2(11·6); ICT = 66·1(11·2)	No ICT = 43·5 emsp;ICT = 46·9	Low emsp;Risk = 112·8;	70·8	0·12
Rose *et al* (2010)	France	Prospective Cohort	97	Low/Int-1 IPSS MDS patients	Mean age: All = 72; No ICT = 75; ICT = 70	All = 59·7 No emsp;ICT = 59·1 emsp;ICT = 54·7	124	53	0·0003
Leitch *et al* (2008)	Canada	Prospective Cohort	178	Low/Int-1 IPSS MDS patients	Median age at diagnosis = 69	59	>226	40	0·003
Delforge *et al* (2014)	Belgium	Follow-up, Multicentre, Observational Non-interventional Retrospective	127	Low/Int-1 IPSS MDS patients	Mean age at diagnosis (SD): No ICT = 73(9·0) ICT = 71(9·3)	No ICT = 42 emsp;ICT = 45	122·4	37·2	0·001
Remacha *et al* (2012)	Spain	Retrospective Observational Cohort	263	Transfusion-dependent MDS patients with low/int-1 IPSS who had received ≥10 RBC transfusions during at least 12 months prior to study entry	NA	NA	133	105	0·009

The impact of chelation therapy on survival in transfusional iron overload: a meta-analysis of myelodysplastic syndrome

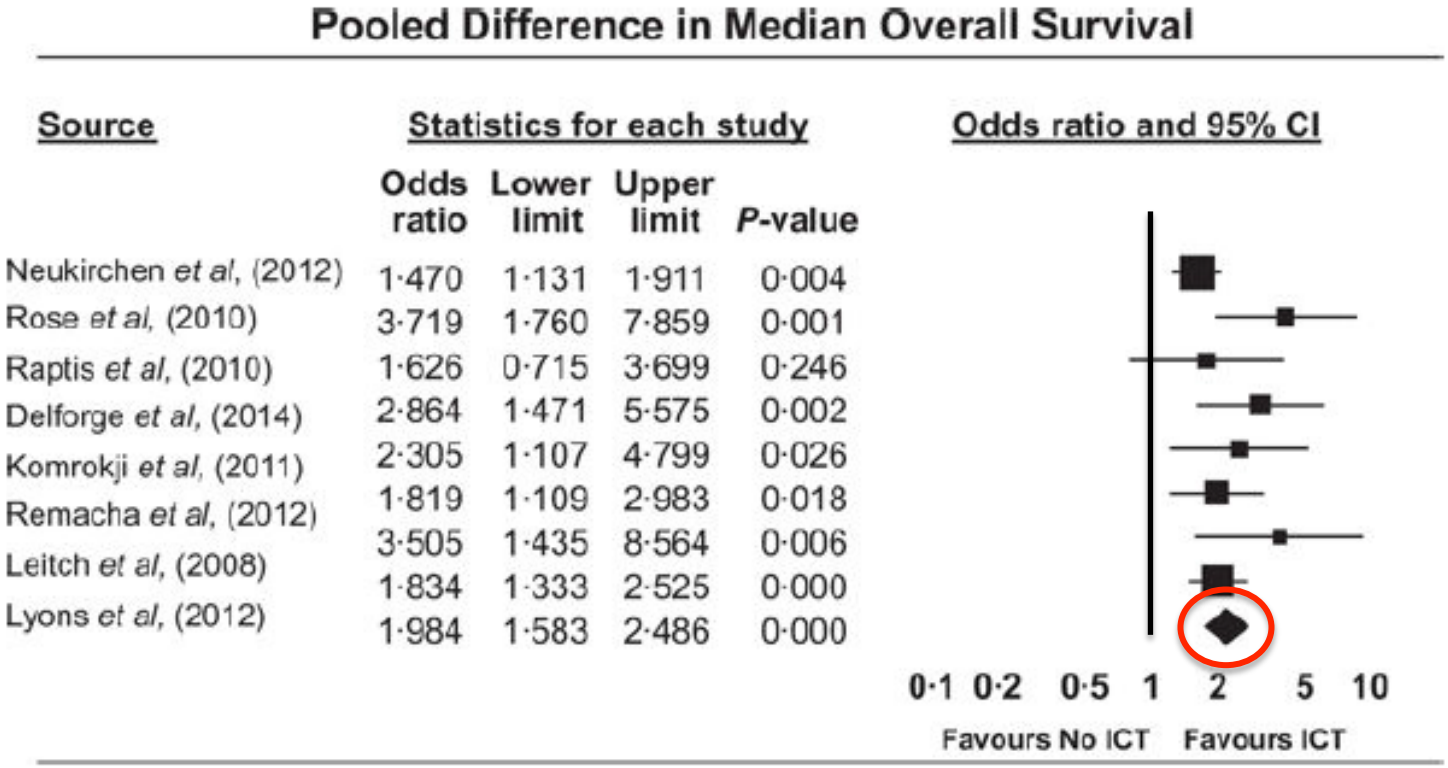


Fig 1.

Pooled differences in median overall survival. Squares represent individual studies; the size of the square represents the weight given to each study in the meta-analysis. Horizontal lines indicate 95% confidence intervals. The diamond represents the pooled results. ICT, iron chelation therapy; 95% CI, 95% confidence interval.

Mainous et a,, Br J Haematol 2014

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Invited review

Relation between chelation and clinical outcomes in lower-risk patients with myelodysplastic syndromes: Registry analysis at 5 years

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ABSTRACT

Prospective data are needed to ascertain the impact of iron chelation therapy in patients with myelodysplastic syndromes. The present 5-year prospective registry analysis was conducted to compare clinical outcomes between chelated and nonchelated patients with lower-risk myelodysplastic syndromes and transfusional iron overload. In an interim analysis at 24 months, we previously reported that chelation therapy was associated with longer median overall survival and a tendency toward longer leukemia-free survival and fewer cardiac events. In the present report, we detail findings from the final analysis at 5 years. We confirm, at the conclusion of this 5-year, prospective, non-interventional study, that overall survival was significantly longer in patients who received iron chelation therapy vs those who did not. Causes of death in the overall population were predominantly myelodysplastic syndromes/acute myeloid leukemia followed by cardiac disease. Time to progression to acute myeloid leukemia was also significantly longer in patients receiving chelation therapy, and significantly fewer patients progressed to leukemia vs those not receiving chelation therapy. Limitations of the study include a potential for clinical bias, as patients with longer predicted survival may have been chosen for chelation therapy, the differences present in concomitant conditions at baseline, and the possibility that some high-risk patients were not identified due to limited cytogenetic classification.

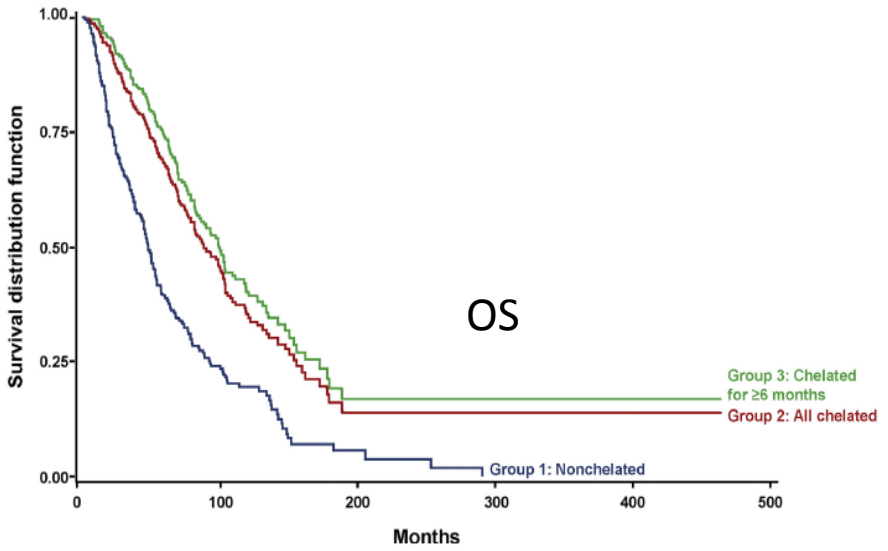


Fig. 1. Overall Survival: All Enrolled Patients. Patients who received iron chelation therapy had longer overall survival compared with nonchelated patients. Kaplan-Meier curves for overall survival show median time to death from myelodysplastic syndrome diagnosis in the nonchelated, chelated, and chelated ≥6 months groups as 47.8, 86.3, and 98.7 months, respectively ($P < 0.0001$ for nonchelated vs both chelated groups).

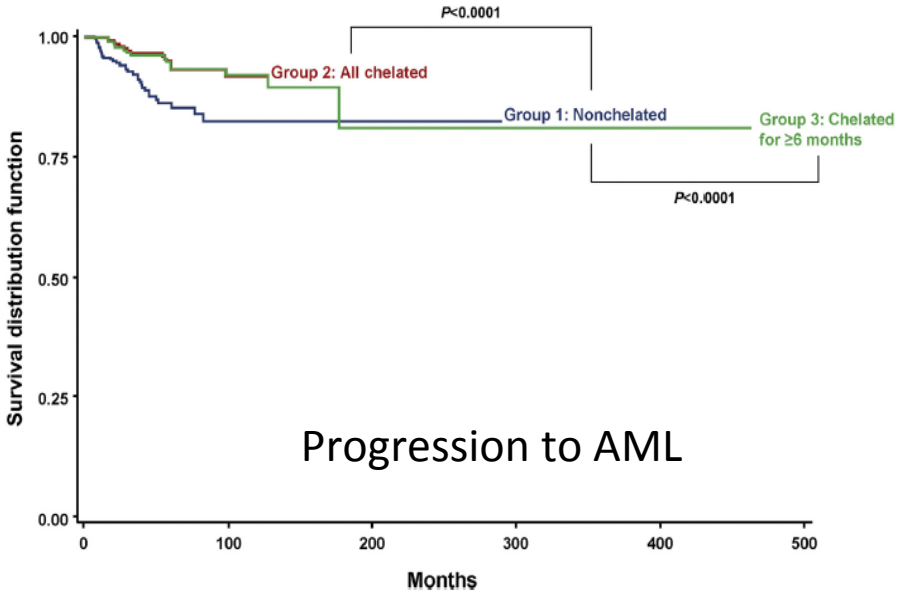
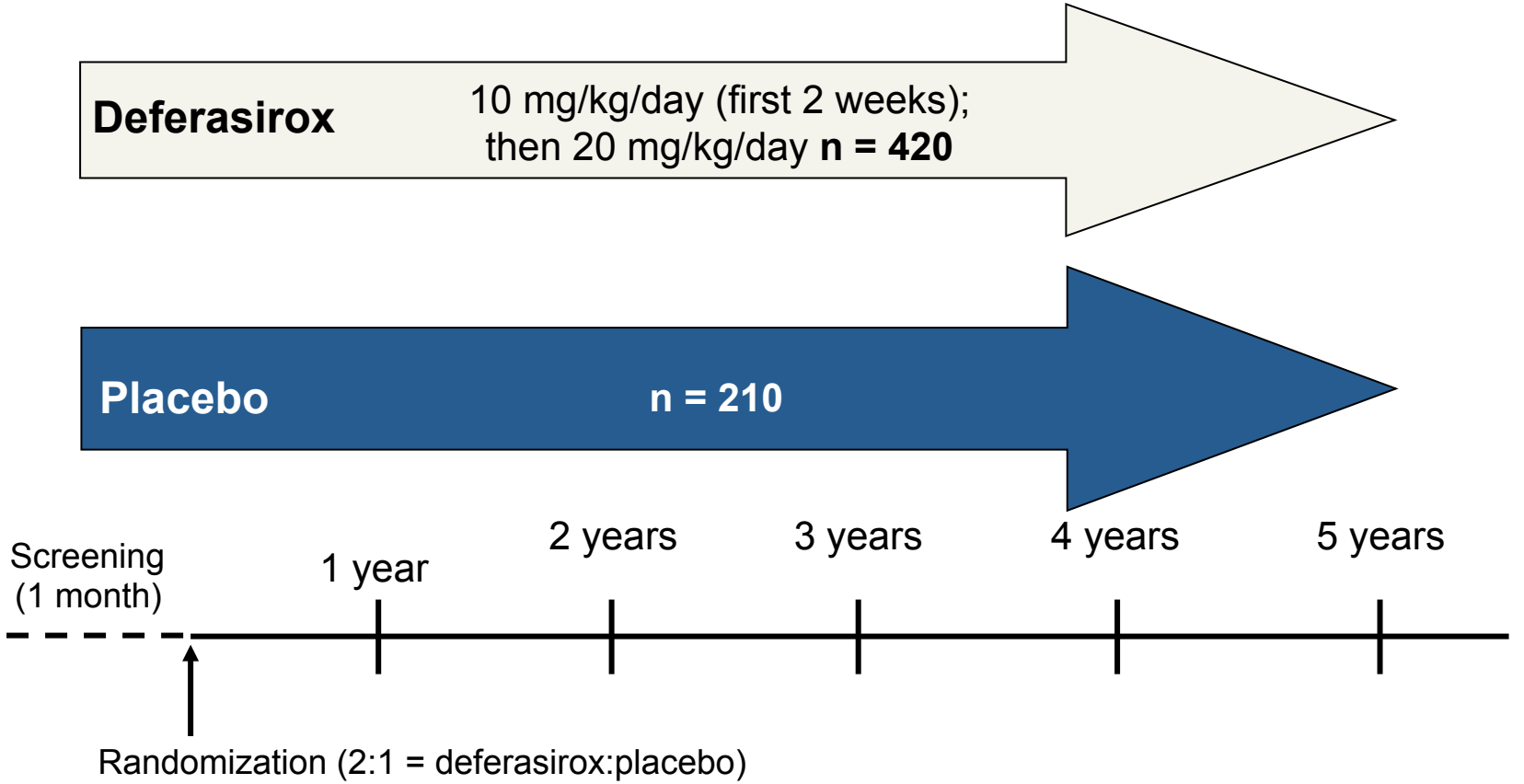


Fig. 3. Progression to Acute Myeloid Leukemia: All Enrolled Patients. Time to progression to acute myeloid leukemia was significantly longer in chelated vs nonchelated patients ($P < 0.0001$). The median time from diagnosis to leukemic progression was 46.7 months in the nonchelated group, 86.3 in the chelated group, and 97.8 in the ≥6 months chelated group.

The “mitic” TELESTO study of deferasirox in MDS

- Prospective, multicentre study to investigate the clinical benefit of chelation therapy with deferasirox in 630 MDS patients
- Primary study (composite) end-point: event-free survival (death, cardiac and hepatic non-fatal events, hospitalization, AML evolution))



Angelucci E, et al. Blood. 2009;114:[abstract 4854].

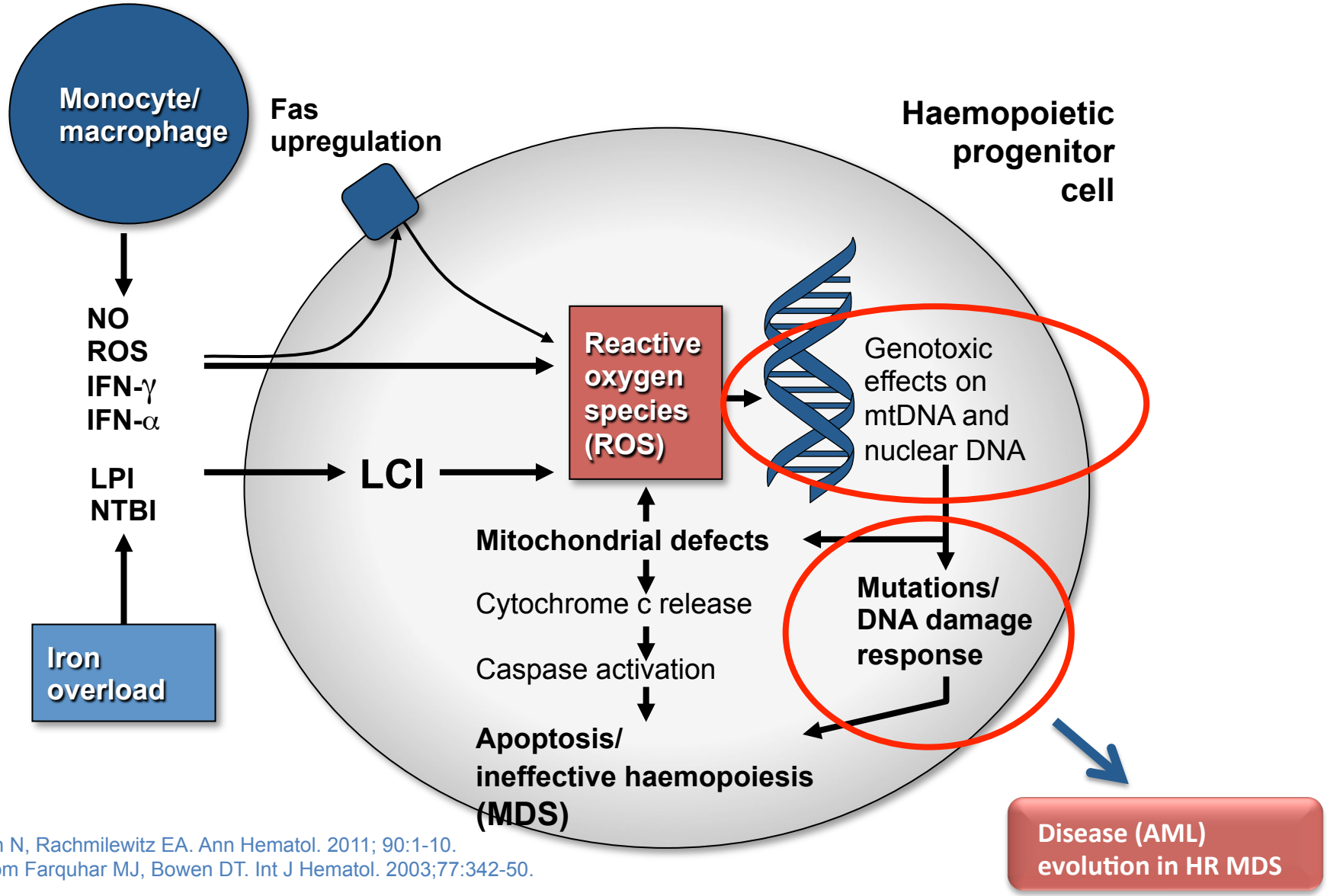
My Agenda

- Iron balance and overload
- Clinical results of chelation: reduction of iron overload
- Clinical results of chelation: hematologic improvement
- Clinical results of chelation: survival
- **Iron chelation in higher risk MDS**
- Perspectives

Which is the current role for ICT in HR-MDS?

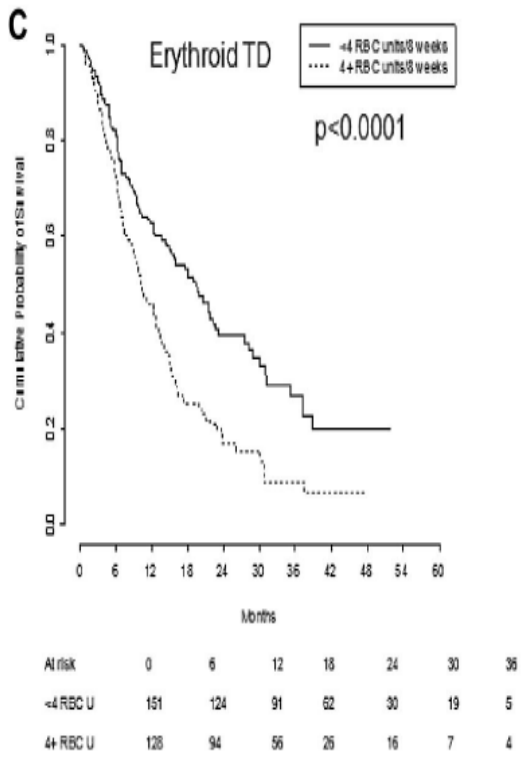
- Although not formally contraindicated, it is not generally recommended outside the setting of AlloSCT
- Main limiting factors are the expected shorter overall survival (OS) of these patients, and the potential increased risk of renal or hepatic impairment/failure and gastro-intestinal bleeding (NCCN, 2017: contraindicated in HR-MDS)
- As a consequence, limited data are currently available on the use of ICT, in particular the oral chelator deferasirox (DFX), in HR-MDS not eligible for transplant

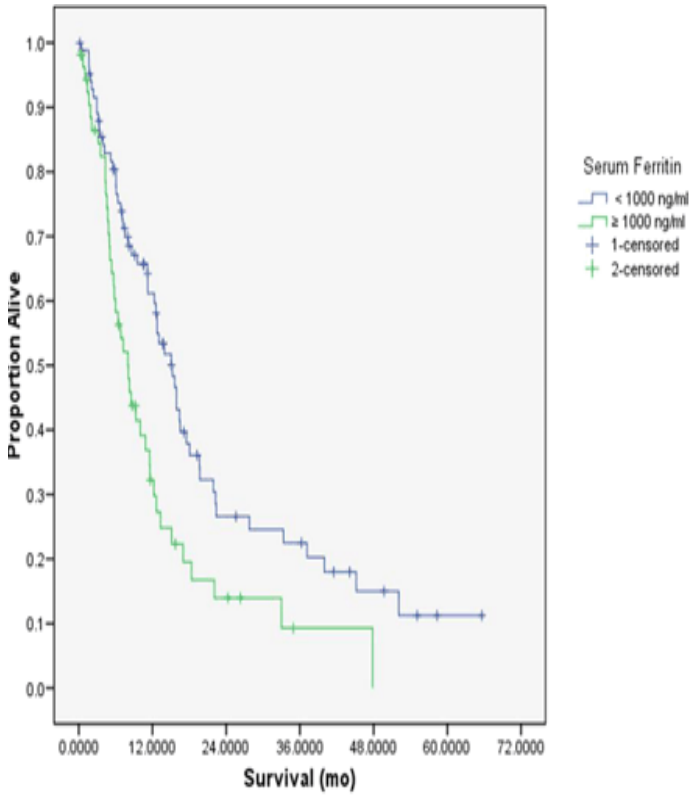
The role of iron overload in inducing oxidative stress in MDS

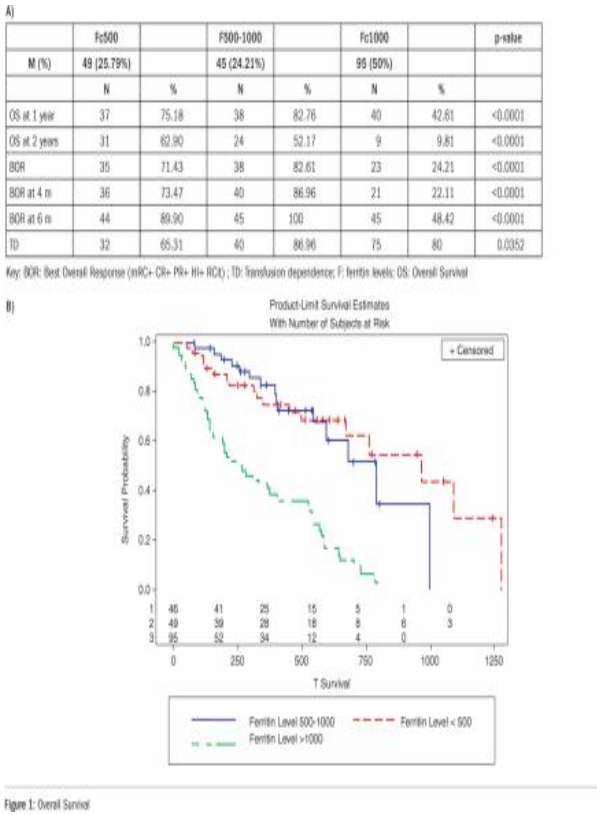


Gattermann N, Rachmilewitz EA. Ann Hematol. 2011; 90:1-10.
Adapted from Farquhar MJ, Bowen DT. Int J Hematol. 2003;77:342-50.

Impact of Iron Overload in Higher Risk MDS treated with azacitidine







	Fc500		F500-1000		Fc1000		p-value
M (%)	49 (25.79%)		45 (24.21%)		95 (50%)		
	N	%	N	%	N	%	
OS at 1 year	37	75.18	38	82.76	40	42.61	<0.0001
OS at 2 years	31	62.90	24	52.17	9	9.81	<0.0001
BOR	35	71.43	38	82.61	23	24.21	<0.0001
BOR at 4 m	36	73.47	40	86.96	21	22.11	<0.0001
BOR at 6 m	44	89.90	45	100	45	48.42	<0.0001
TD	32	65.31	40	86.96	75	80	0.0352

Key: BOR: Best Overall Response (mRC+ CR+ PR+ HI+ RCd) ; TD: Transfusion dependence; F: ferritin levels; OS: Overall Survival

Figure 1: Overall Survival

Itzkiyson et al, Blood 2011

Komrokji et al, ASH Meeting 2011, abs. 2777

Garcia et al, ASH Meeting 2012, Poster 882

- Transfusion-dependence (> 4 RBC units/8 weeks) at baseline negatively affected survival for MDS patients treated with azacitidine (Itzkynson et al, 2011).
- SF > 1,000 ng/ml were independent prognostic factors for both OS and AML transformation at multivariate analysis in 139 intermediate-2 or high risk IPSS MDS, more than half treated with azacitidine (Komrokji et al, 2011).
- High SF at baseline also had a negative impact on response and OS in MDS patients treated with azacitidine in a Spanish experience (Garcia et al, 2012).

LEUKEMIA & LYMPHOMA, 2016
http://dx.doi.org/10.3109/10428194.2016.1157878

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LETTER TO THE EDITOR

Pre- and post-treatment serum ferritin levels in patients with higher risk myelodysplastic syndromes receiving azacitidine

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Table 1. Initial and follow-up ferritin levels in 20 MDS patients receiving azacytidine.

	Median ferritin level [ng/mL] (range)		
AZA response group	Pre-AZA	Post-AZA	*p*
AZA nonresponders	596 (187–1714)	7869 (1175–25,544)	0.02
AZA responders	583 (79–12,860)	763 (96–4430)	NS

AZA, azacitidine; NS, not significant.

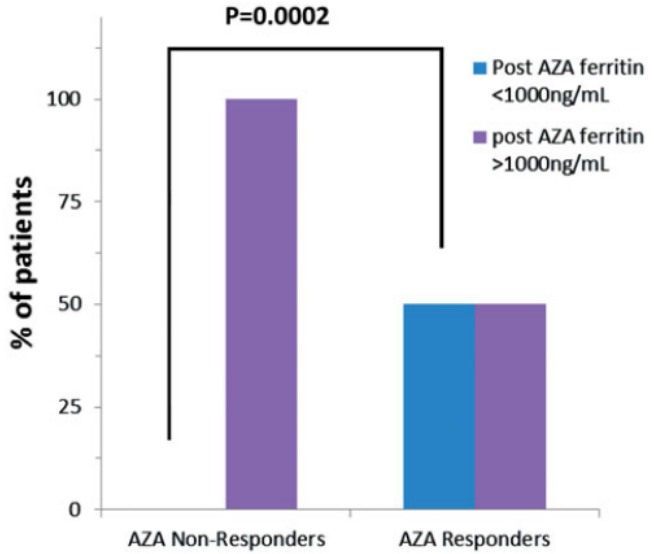

Figure 1. Percent of patients with post-AZA ferritin level $<$ or $\geq$ 1000 ng/mL by response to AZA.

Time-dependent changes in mortality and transformation risk in MDS

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Key Points

- Hazards regarding mortality and leukemic transformation in MDS diminish over time in higher-risk but remain stable in lower-risk patients.
- This change of hazard indicates time-dependent attenuation of power of basal risk scores, which is relevant for clinical decision making.

In myelodysplastic syndromes (MDSs), the evolution of risk for disease progression or death has not been systematically investigated despite being crucial for correct interpretation of prognostic risk scores. In a multicenter retrospective study, we described changes in risk over time, the consequences for basal prognostic scores, and their potential clinical implications. Major MDS prognostic risk scoring systems and their constituent individual predictors were analyzed in 7212 primary untreated MDS patients from the International Working Group for Prognosis in MDS database. Changes in risk of mortality and of leukemic transformation over time from diagnosis were described. Hazards regarding mortality and acute myeloid leukemia transformation diminished over time from diagnosis in higher-risk MDS patients, whereas they remained stable in lower-risk patients. After approximately 3.5 years, hazards in the separate risk groups became similar and were essentially equivalent after 5 years. This fact led to loss of prognostic power of different scoring systems considered, which was more pronounced for survival. Inclusion of age resulted in increased initial prognostic power for survival and less attenuation in hazards. If needed for practicability in clinical management, the differing development of risks suggested a reasonable division into lower- and higher-risk MDS based on the IPSS-R at a cutoff of 3.5 points. Our data regarding time-dependent performance of prognostic scores reflect the disparate change of risks in MDS subpopulations. Lower-risk patients at diagnosis remain lower risk whereas initially high-risk patients demonstrate decreasing risk over time. This change of risk should be considered in clinical decision making. (*Blood*. 2016;128(7):902-910)

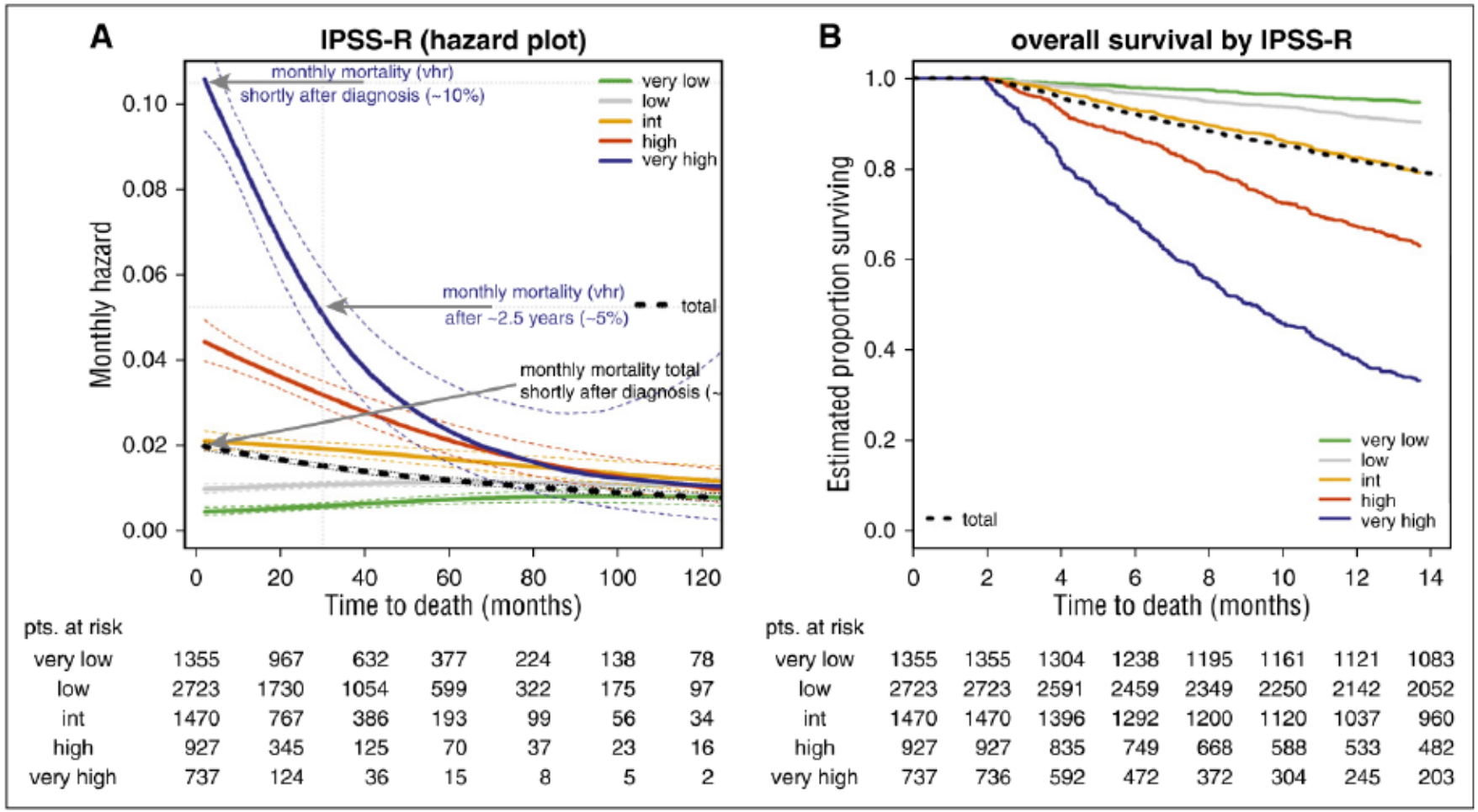

Figure 1. Survival of IPSS-R–classified patient subgroups using smoothed hazard plots and corresponding Kaplan-Meier curves (representative example). (A) Smoothed hazard plots more clearly demonstrate changes in risk at different time intervals than do (B) Kaplan-Meier plots. The smoothed hazard for very high risk indicates 10% monthly mortality risk in the beginning (A, top arrow) in agreement with the Kaplan-Meier curve. After approximately 30 months (A, middle arrow), 5% monthly mortality for the very-high-risk group is shown, which is not clearly visible in the Kaplan-Meier curve. The mortality risks of the remaining patients for all risk groups are similar after approximately 60 months. Note that the time scale in (B) is expanded to improve visibility of the decline in the first year. The bold black dotted line represents all patients. int, intermediate; pts, patients; vhr, very high-risk.

bjh research paper

Iron-chelating therapy with deferasirox in transfusion-dependent, higher risk myelodysplastic syndromes: a retrospective, multicentre study

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Summary

Iron chelation is controversial in higher risk myelodysplastic syndromes (HR-MDS), outside the allogeneic transplant setting. We conducted a retrospective, multicentre study in 51 patients with transfusion-dependent, intermediate-to-very high risk MDS, according to the revised international prognostic scoring system, treated with the oral iron chelating agent deferasirox (DFX). Thirty-six patients (71%) received azacitidine concomitantly. DFX was given at a median dose of 1000 mg/day (range 375–2500 mg) for a median of 11 months (range 0·4–75). Eight patients (16%) showed grade 2–3 toxicities (renal or gastrointestinal), 4 of whom (8%) required drug interruption. Median ferritin levels decreased from 1709 μg/l at baseline to 1100 μg/l after 12 months of treatment ($P = 0·02$). Seventeen patients showed abnormal transaminase levels at baseline, which improved or normalized under DFX treatment in eight cases. One patient showed a remarkable haematological improvement. At a median follow up of 35·3 months, median overall survival was 37·5 months. The results of this first survey of DFX in HR-MDS are comparable, in terms of safety and efficacy, with those observed in lower-risk MDS. Though larger, prospective studies are required to demonstrate real clinical benefits, our data suggest that DFX is feasible and might be considered in a selected cohort of HR-MDS patients.

doi: 10.1111/bjh.14621

DFX in HR-MDS: the Italian study

- Initial enrollment: 58 patients, representing 13.7% (range 4.5-33%) of 423 HR-MDS patients observed in the participating Centres during the study period
- Analysis restricted to 51 patients with a complete dataset of clinical information
- The reasons why the investigators chose to treat their patients with DFX were:

  a) Candidates for AlloSCT (n. 8, 16%)

  b) Very high transfusion burden (n. 17, 33%)

  c) Stable or responsive disease under life-extending therapies (life expectancy > 1 year) (n. 24, 47%)

  d) Other or unspecified reasons (n. 2, 4%)

Musto et al, Br J Haematol, 2017

Table I. Clinical characteristic of patients.

Patients	
Male/Female	34/17
Median age (range), years	65 (36–83)
WHO 2016 classification (Arber *et al*, 2016)	
MDS-SLD	1
MDS-MLD	2
MDS-EB-1	11
MDS-EB-2	30
MDS-U*	7
R-IPSS	
Intermediate risk	7
High-risk	29
Very high-risk	15
Other characteristics at start of DFX	
Median time from diagnosis (range), months	11·1 (0–84·9)
Median number of RBC transfusions received (range)	23 (2–60)
Median serum ferritin level (range), µg/l	1·709 (460–7·293)
Median Hb (g/l) levels (range)	82 (65–108)
Median serum creatinine levels (range), µmol/l	75·14 (73·38–131·72)
Normal/abnormal AST/ALT	34/17
Previous treatments	
Recombinant erythropoietin	6
Azacitidine	16
Recombinant erythropoietin and azacitidine	13

- **DFX median dose:** 1,000 mg per day (range 375- 2,500 mg), for a median time of 11 months (range 0.4-75)
- **Initial daily dose/kg**: 5 mg (8%,) 10 mg (42.%), 20 mg (48%) 30 mg (2%) (mean dose: 14.8 +/- 5.9 mg/kg/d)
- **Dose reduction/increase:** 10/4 patients, due to intolerance or inefficacy, respectively
- **Toxicity**:Seven patients (13.7%) showed grade 2 (5 renal, 2 GI) and one patient (1.9%) developed grade 3 GI toxicity
- **Definitive DFX interruption:** 7 patients (three renal and one GI toxicities, three because of leukaemic evolution). One patient stopped DFX after reaching normal SF values
- **Effects on liver**: Under DFX treatment, eight out of 17 patients (47%) improved or normalized ALT/AST levels, increased at baseline
- **Concomitant treatments received:** Thirty-nine pts. continued or started concomitant therapies with lenalidomide (n. 1, 1.9%), r-EPO (n. 2, 3.9 %), azacitidine (n. 25, 49%), or both (n. 11, 21.6%) during DFX therapy; 22 pts. experienced clinical benefits from these treatments and 4 successfully received Allo-SCT after DFX therapy

Musto et al, Br J Haematol, 2017

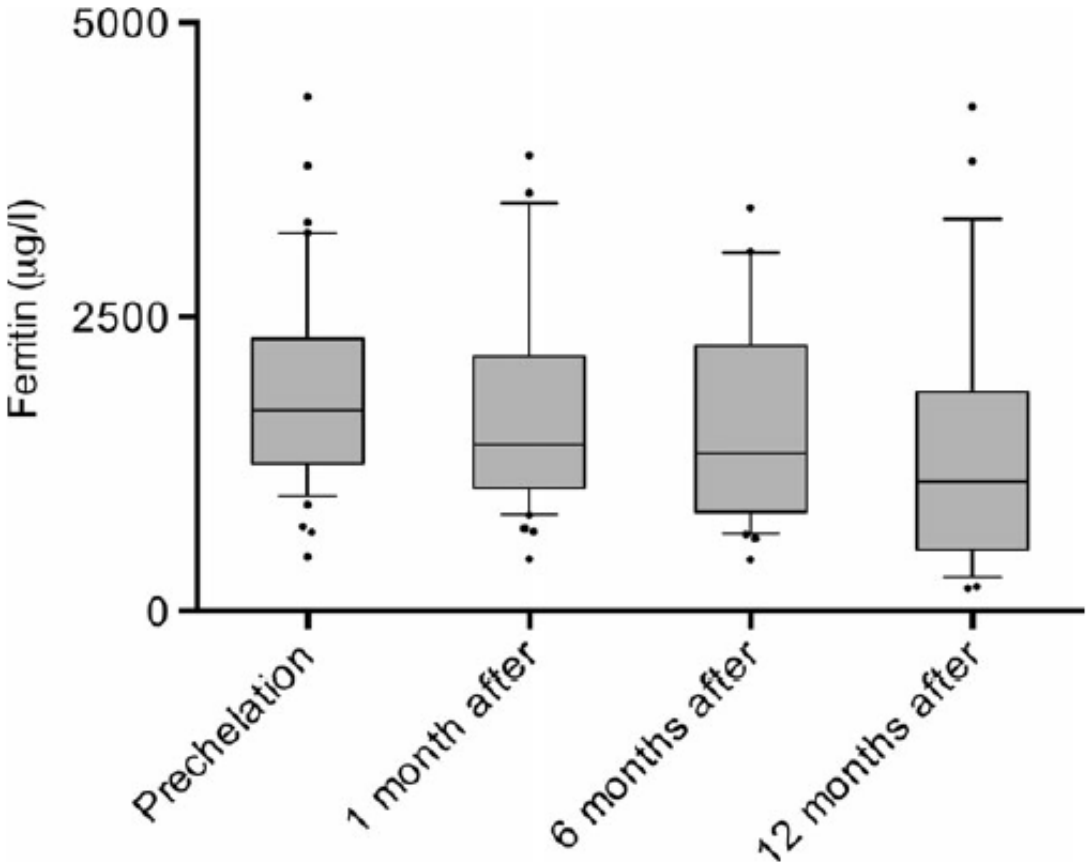
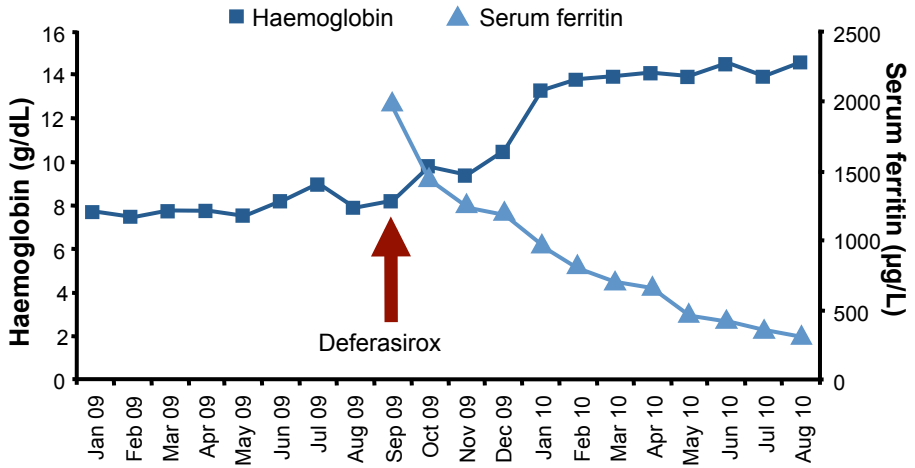


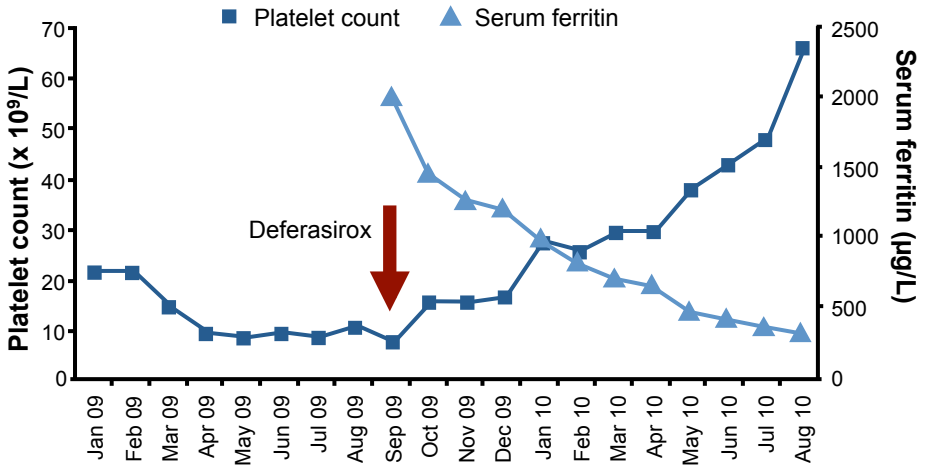
Fig 1. Monitoring of ferritin serum levels (µg/l) during deferasirox therapy in 51 higher risk myelodysplastic syndromes (HR-MDS) patients. Kruskall–Wallis test: $P = 0{\cdot}0478$; Dunn's multiple comparison test: $P = 0{\cdot}0205$, in the comparison between pre-chelation and after 12 months of treatment levels.

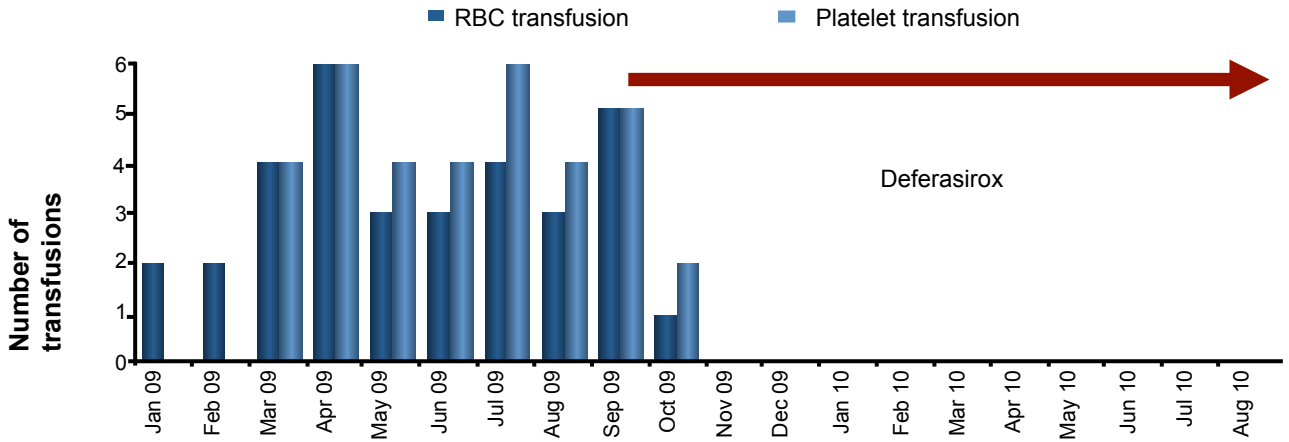
In evaluable patients, median ferritin levels decreased from 1,709 ng/ml at baseline (n. 51, range 460-7,293), to 1,421 ng/ml after one month of DFX treatment (n.42, 443-8513), to 1,382 ng/ml at 6 months (n.32, 439-10.112) and to 1,100 ng/ml at 12 months (n.22, 198-4.282)

Musto et al, Br J Haematol, 2017

Transfusion independence following deferasirox in a low-to-high WPSS risk transformed MDS with complete hematologic response







Guariglia R, et al. Leuk Res. 2011;35:566-70.

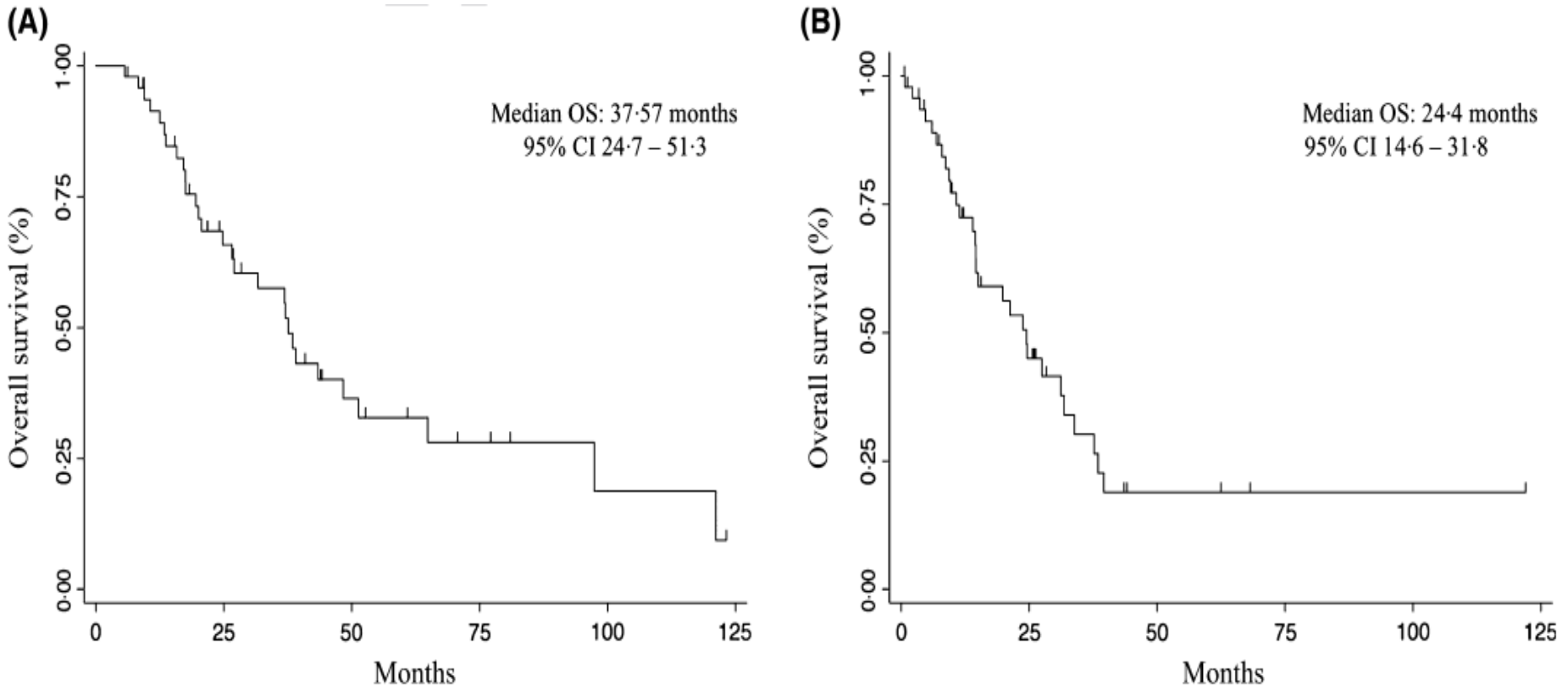


Fig 2. Overall survival curves of 51 higher risk myelodysplastic syndromes patients treated with deferasirox: (A) from diagnosis; (B) from the start of defereasirox. 95% CI, 95% confidence interval; OS, overall survival.

At a median follow up of 35.3 months from diagnosis and 21.4 months after the start of ICT, 19 patients (37%) evolved into AML.

Musto et al, Br J Haematol, 2017

My Agenda

- Iron balance and overload
- Clinical results of chelation: reduction of iron overload
- Clinical results of chelation: hematologic improvement
- Clinical results of chelation: survival
- Iron chelation in higher risk MDS
- **Perspectives**

La ferrochelazione delle SMD: che cosa è cambiato negli ultimi anni?

- Miglior comprensione dei meccanismi fisiopatologici dell'Iron toxicity/Iron overload
- Aumentata sensibilità alla valutazione e presa in carico dell'Iron toxicity/Iron overload nelle MDS
- Riconoscimento del valore prognostico negativo (possibile impatto sulla OS) dell'Iron toxicity/Iron overload nelle MDS
- Opzione molto pratica e fattibile dopo l'introduzione dei chelanti orali
- Migliore gestione della terapia ferrochelante

“What’s next” per la ferro-chelazione nelle Sindromi Mielodsplastiche?

- Early marker(s) della tossicità da ferro
- Marker(s) di risposta al trattamento ferrochelante
- Studi prospettici sulla sopravvivenza
- Valutazione di un trattamento chelante precoce
- Meccanismi biologici alla base della risposta ematologica
- Definire/consolidare il ruolo nelle forme ad alto rischio
- Nuove formulazioni
- Osso e sovraccarico marziale

DFX in HR-MDS: prospective trials

Two randomized, ongoing phase 2 trials comparing azacitidine alone vs azacitidine plus DFX (NCT02159040 and NCT02038816) and one non-randomized phase 1/2 study which evaluates the addition of vitamin D to the two-drug combination (NCT01718366) will better address:

a. whether azacitidine and DFX combination is safe (mainly in terms of infections) and able to improve, along with serum ferritin and labile plasma iron levels, response rate, time to leukaemic evolution and survival

b. The role of intracellular reactive oxygen species (ROS), erythroid colony forming units, markers of DNA damage, and specific signaling pathways will be also investigated

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RESEARCH ARTICLE

New film-coated tablet formulation of deferasirox is well tolerated in patients with thalassemia or lower-risk MDS: Results of the randomized, phase II ECLIPSE study

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Novartis Pharma AG, Novartis Pharmaceuticals Corporation.

Abstract

Once-daily deferasirox dispersible tablets (DT) have a well-defined safety and efficacy profile and, compared with parenteral deferoxamine, provide greater patient adherence, satisfaction, and quality of life. However, barriers still exist to optimal adherence, including gastrointestinal tolerability and palatability, leading to development of a new film-coated tablet (FCT) formulation that can be swallowed with a light meal, without the need to disperse into a suspension prior to consumption. The randomized, open-label, phase II ECLIPSE study evaluated the safety of deferasirox DT and FCT formulations over 24 weeks in chelation-naïve or pre-treated patients aged ≥10 years, with transfusion-dependent thalassemia or IPSS-R very-low-, low-, or intermediate-risk myelodysplastic syndromes. One hundred seventy-three patients were randomized 1:1 to DT (n = 86) or FCT (n = 87). Adverse events (overall), consistent with the known deferasirox safety profile, were reported in similar proportions of patients for each formulation (DT 89.5%; FCT 89.7%), with a lower frequency of severe events observed in patients receiving FCT (19.5% vs. 25.6% DT). Laboratory parameters (serum creatinine, creatinine clearance, alanine aminotransferase, aspartate aminotransferase and urine protein/creatinine ratio) generally remained stable throughout the study. Patient-reported outcomes showed greater adherence and satisfaction, better palatability and fewer concerns with FCT than DT. Treatment compliance by pill count was higher with FCT (92.9%) than with DT (85.3%). This analysis suggests deferasirox FCT offers an improved formulation with enhanced patient satisfaction, which may improve adherence, thereby reducing frequency and severity of iron overload-related complications.

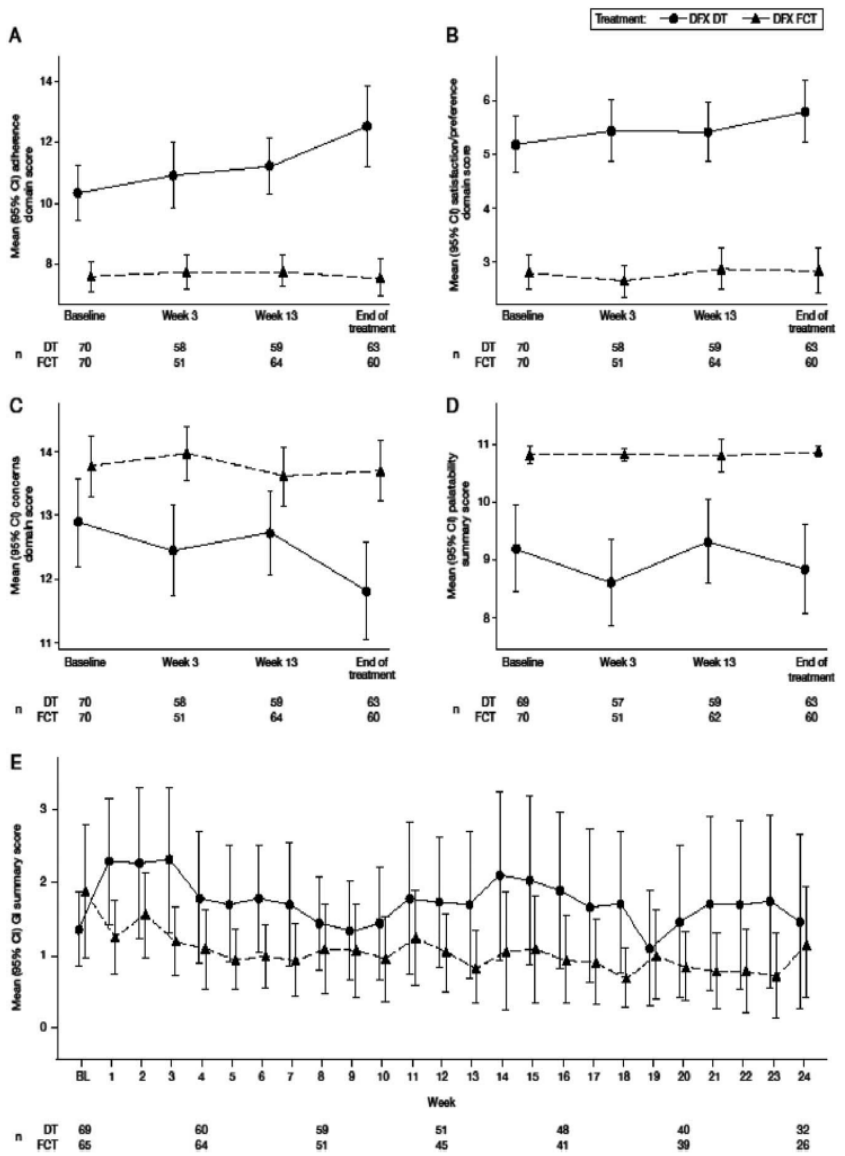


FIGURE 1 Mean domain scores for patient-reported outcomes (adherence, satisfaction/preference, and concern) (A-C), mean palatability score (D), and mean gastrointestinal symptom scores (E). For adherence (A; scale 6-30), satisfaction/preference (B; scale 2-10), and GI symptoms (E; scale 0-50), higher scores indicate worse outcomes/symptoms. For concern (C; scale 3-15) and palatability (D; scale 0-11), higher scores indicate fewer concerns and better palatability. A-D, baseline was defined as week 2 assessment. If missing, then the week 3 assessment was considered baseline; E, baseline was defined as week 1 score. If missing, then the week 2 score was considered baseline. BL, baseline.

TABLE 3 Most common AEs (overall and severe; >10% in any group) regardless of study drug relationship by preferred term and treatment

AE	Deferasirox DT, *N* = 86		Deferasirox FCT, *N* = 87	
	All AEs *n* (%)	Severe AEs *n* (%)	All AEs *n* (%)	Severe AEs *n* (%)
Total	77 (89.5)	22 (25.6)	78 (89.7)	17 (19.5)
Diarrhea	30 (34.9)	6 (7.0)	29 (33.3)	1 (1.1)
Nausea	23 (26.7)	2 (2.3)	24 (27.6)	1 (1.1)
Abdominal pain	23 (26.7)	4 (4.7)	23 (26.4)	2 (2.3)
Increased UPCR (>0.5)	11 (12.8)	2 (2.3)	18 (20.7)	0 (0.0)
Vomiting	19 (22.1)	1 (1.2)	15 (17.2)	0 (0.0)
Abdominal pain upper	6 (7.0)	1 (1.2)	10 (11.5)	0 (0.0)
Constipation	13 (15.1)	2 (2.3)	7 (8.0)	0 (0.0)
Headache	12 (14.0)	2 (2.3)	5 (5.7)	0 (0.0)

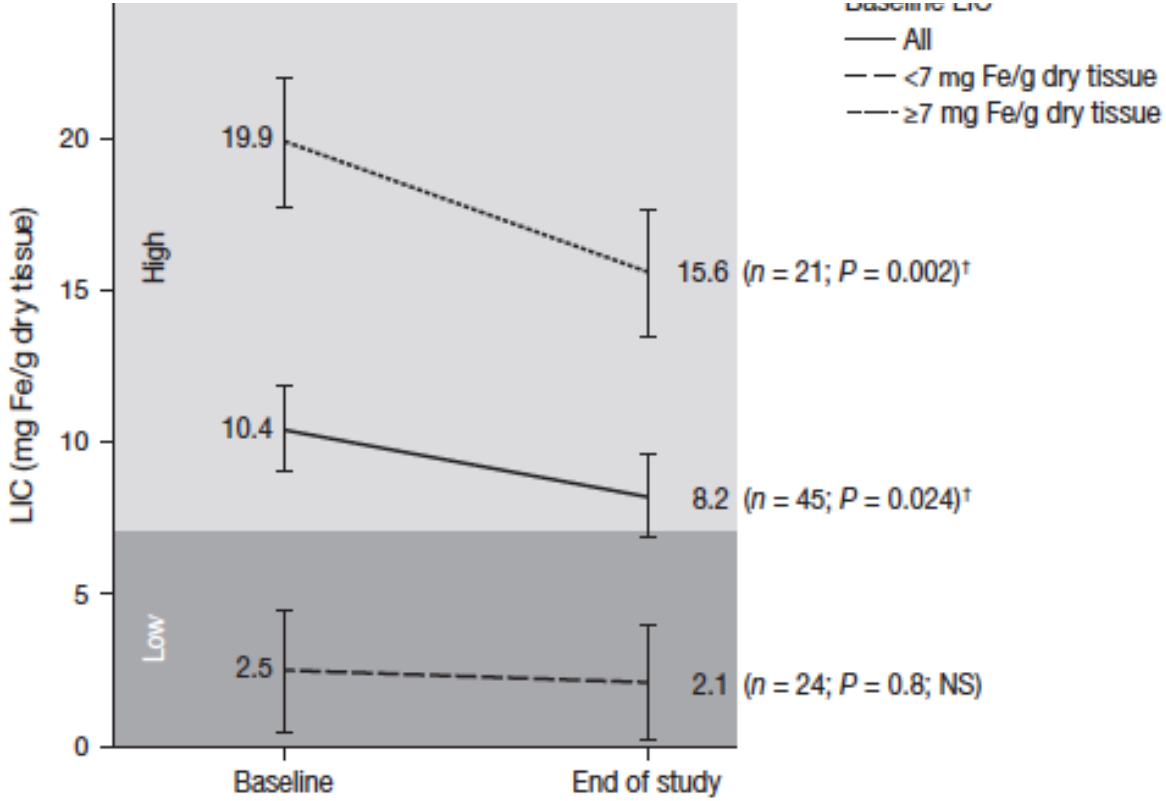
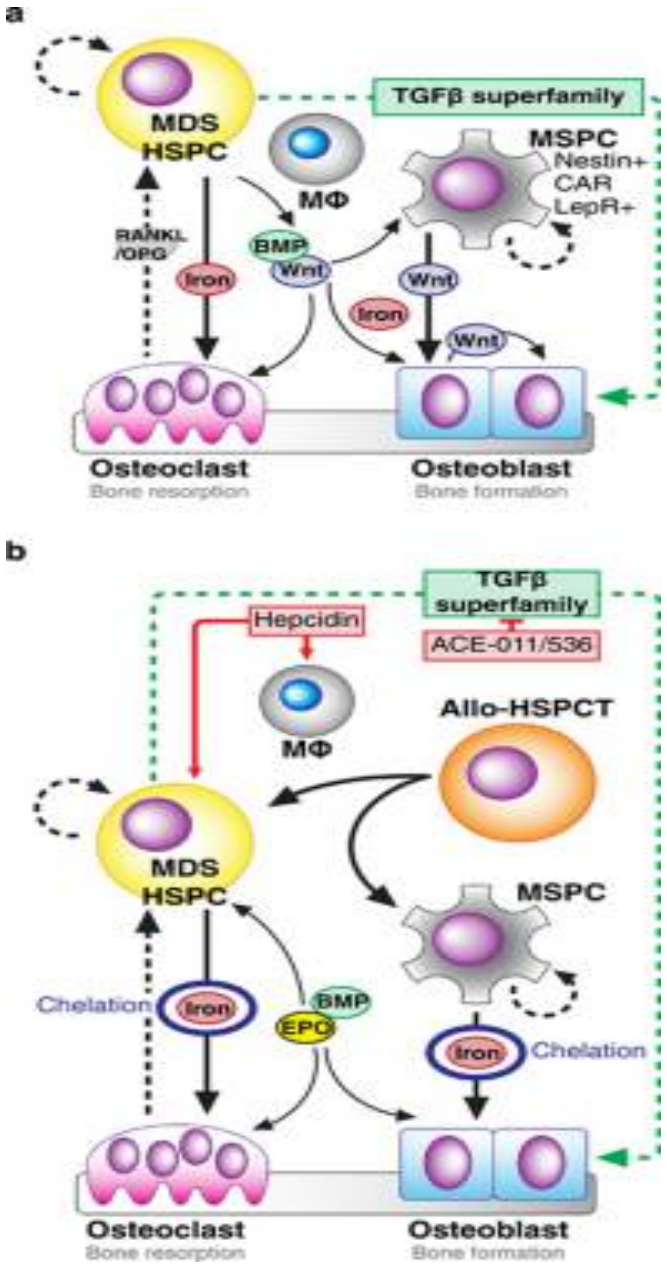


Figure 2 Change in liver iron concentration after 12 months. Results are presented as the adjusted means ± standard error of the mean after the analysis model. †Statistically significant. LIC, liver iron concentration; NS, nonsignificant.

The new scientific rationale of osteo-hematology as emerging research field in MDS



- The niche simultaneously contains stem cells, precursors cells and terminally differentiated cells
- Stem cells live in a specialized microenvironment or niche and depend on it for self-renewal and regulated differentiation
- Hematopoietic stem and progenitor cells (HSPCs) represent precursors for osteoclasts (OCs) responsible for bone resorption, whereas mesenchymal stem and progenitor cells (MSPCs) are precursors for osteoblasts (OBs) that produce the bone matrix
- **In MDS model has reported decreased OBs and OCs number and bone formation rate**
- **Iron overload inhibit OBs and increase OCs**
- **Oxidative stress is involved in the pathogenesis of the bone loss during iron excess**

Bulycheva E et al. Leukemia (2015) 29, 259-268

Registro Sindromi Mielodisplastiche della Basilicata

FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

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Alla cortese attenzione del
Presidente
Comitato Etico Unico Regionale (CEUR) della Basilicata

Alla cortese attenzione del
Direttore Generale
ASL di Matera

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Alla cortese attenzione dello
Sperimentatore Principale
Dr. Alberto Fragasso

Alla cortese attenzione del
Direttore Generale
Ospedale San Carlo

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Dr. Attilio Olivieri

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Alla cortese attenzione dello
Sperimentatore Principale
Dr. Pellegrino Musto

Alessandria, 24/03/2014

Oggetto: **Lettera Intenti** ***studio FISM-Rete Italiana MDS "Rete Italiana dei registri regionali delle sindromi mielodisplastiche (MDS)"***

Codice identificativo studio: ***FISM-Rete Italiana MDS***

Con la presente la Fondazione Italiana Sindromi Mielodisplastiche Onlus (FISM) con sede legale in Alessandria, Piazza Turati, 5, codice fiscale 96039720063, rappresentata dal Presidente Prof. Giuseppe Saglio, intende proporre lo svolgimento del protocollo sperimentale ***FISM-Rete Italiana MDS*** dal titolo: "Rete Italiana dei **Registri Regionali** delle sindromi mielodisplastiche (MDS)".