SESSIONE I:
PARLIAMO DI FERRO

La ferrochelazione oggi e nel prossimo futuro

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TERAPIA CHELANTE NELLE MDS: INDICAZIONI

- 1 unità di eritrociti: 200 mg di Ferro
- **1 anno di trasfusioni = 4-8 g di Ferro**
- **emosiderosi clinicamente manifesta quando Ferro corporeo > 100-200 mg/ Kg (= 7-14 g)**
- chelazione indicata nelle MDS a basso rischio (***LOW o INT-1: aspettativa di vita > 1 aa***) dopo > 20-25 unità GRC, e/o se ferritina > 1.000 ng/ml

GUIDELINES FOR TREATMENT OF MDS: IRON CHELATION

	SIE Italy 2010	ELN 2013	NHS UK 2014	NCCN 2016
Patient profile	-IPSS L or Int-1 **-IPSS H or Int-2** candidates to HSCT or **responding to Tx (HMA)**	**-WHO: RA, RARS, or MDS with isolated del(5q)** - potentially candidates to HSCT	**-WHO: RA, RARS, or MDS with isolated del(5q)**	-IPSS L or Int-1, transf-dependent **or ongoing RBC anticipated**)
Transf. status	≥ 20 RBC	≥ 25 RBC	> 20 RBC	> 20 RBC
Ferritin		>1000	>1000	**>2500**
Tx	**DFX (1° choice)**		**-DFO (1° choice)** **-DFX (if DFO intolerance)** **-Deferiprone (?) (if normal PMN)**	
dose	10-30 mg/Kg/d			
Parameters	**transf. regimen**, ferritin, organ damage			ferritin, creatinine, VFG, liver function

Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet
(Malcovati L et al, Blood 2013)

- The Expert Panel agreed that iron chelation should be considered in transfusion-dependent patients with RA, RARS, or MDS with isolated 5q deletion and a serum ferritin level higher than 1000 ng/mL after approximately 25 units of red cells **(recommendation level D)**.

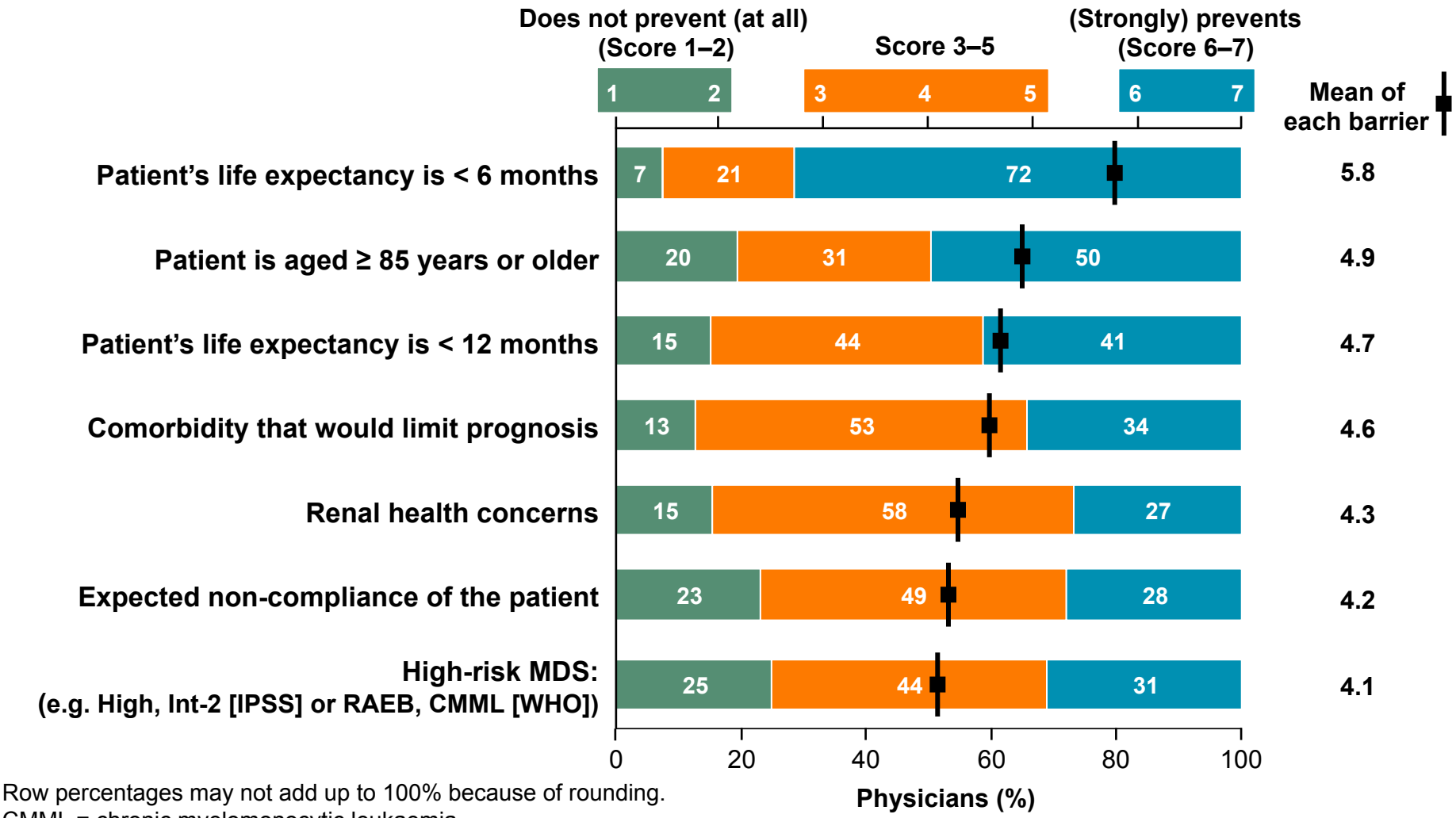
- MDS patients who are potentially candidates for allo-SCT can be considered for appropriate iron chelation therapy prior to the conditioning regimen for transplantation **(recommendation level D)**.

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Myelodysplastic Syndromes Version 1.2016 (1)

For patients with chronic RBC transfusion need, serum ferritin levels and associated organ dysfunction (heart, liver, and pancreas) should be monitored. The NCCN Panel Members recommend **monitoring serum ferritin levels and number of RBC transfusions** received as a practical means to determine iron stores and assess iron overload. Monitoring serum ferritin may be useful, **aiming to decrease ferritin levels to less than 1000 mcg/L**. It is recognized that such measurements, though useful, are less precise than SQUID (Superconducting Quantum Interference Device), or more recently **T2* MRI**, to provide a specific measurement of hepatic iron content.

MIDIS: strongest barriers to initiation of iron chelation therapy



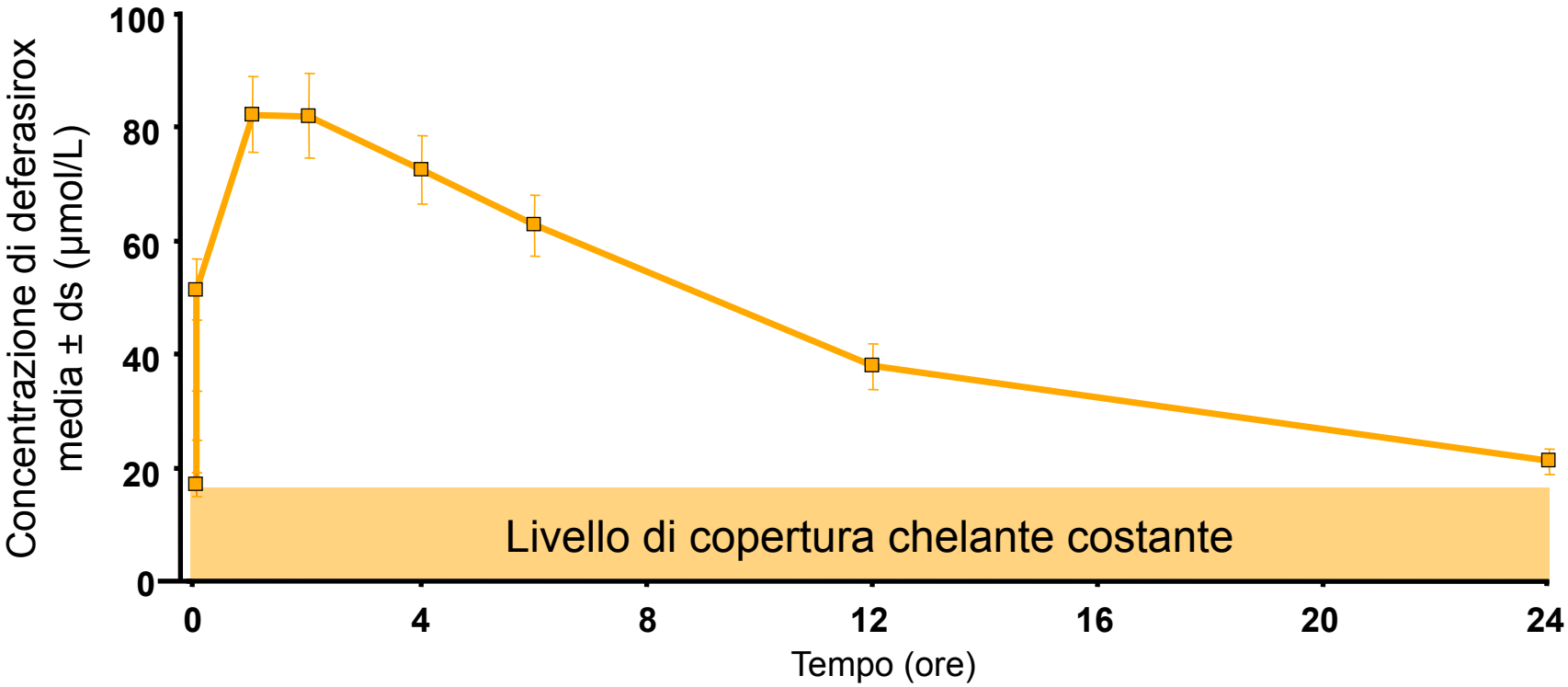
Row percentages may not add up to 100% because of rounding.
CMML = chronic myelomonocytic leukaemia.

Giagounidis A, et al. Ann Hematol. [Epub ahead of print 2011 Feb 16].

Comparison of chelators

Property	DFO	Deferiprone	Deferasirox
Usual dose (mg/kg/day)	25–60	75–100	20–30
Route	Sc, iv (8–12 hours, 5 days/week)	Oral 3 times daily	Oral Once daily
Half-life	20–30 minutes	3–4 hours	8–16 hours
Excretion	Urinary, fecal	Urinary	Fecal
Main adverse effects in prescribing information	Local reactions, ophthalmologic, auditory, growth retardation, allergic	Gastrointestinal disturbances, agranulocytosis/ neutropenia, arthralgia, elevated liver enzymes	Gastrointestinal disturbances, rash, renal impairment, hepatic impairment, ophthalmologic, auditory
Status	Licensed	Licensed	Licensed

Lunga emivita del farmaco: copertura per 24 ore con una monosomministrazione giornaliera

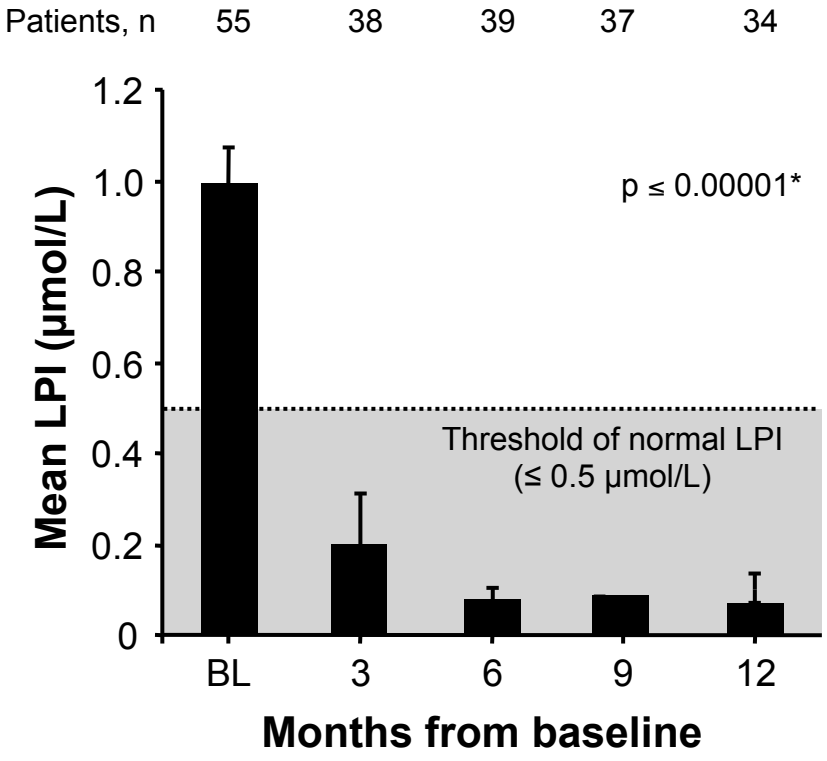


AUC dopo monosomministrazioni giornaliere ripetute di 20 mg/kg/die

Study 105 : Piga et al Haematologica 2006; 91:873-880

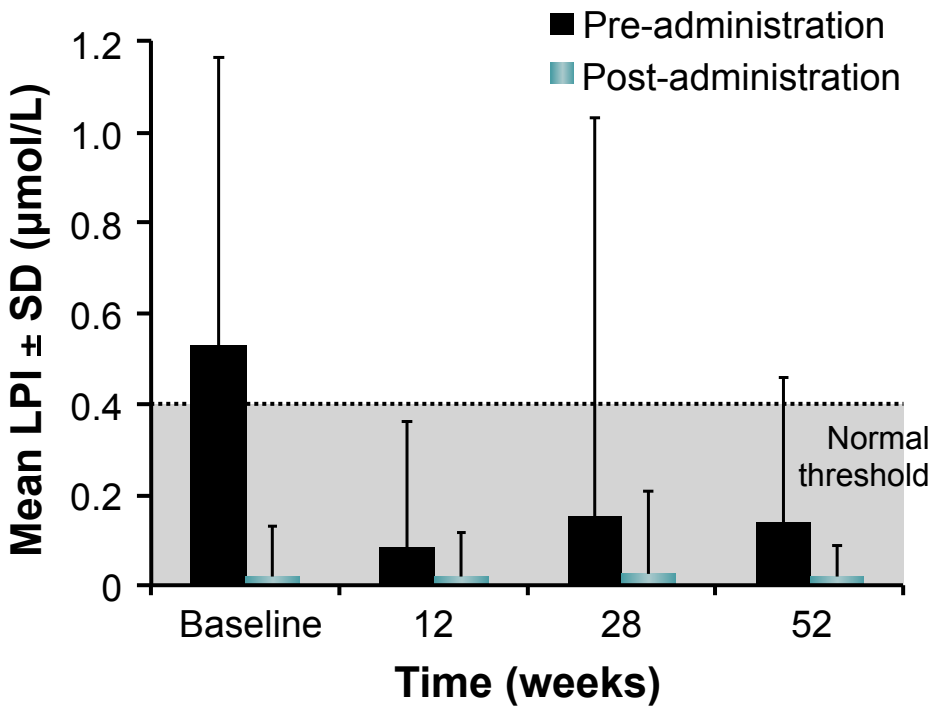
Effect of deferasirox on LPI in MDS

US03 study[1]



Patients with baseline LPI ≥ 0.5 µmol/L = 41%

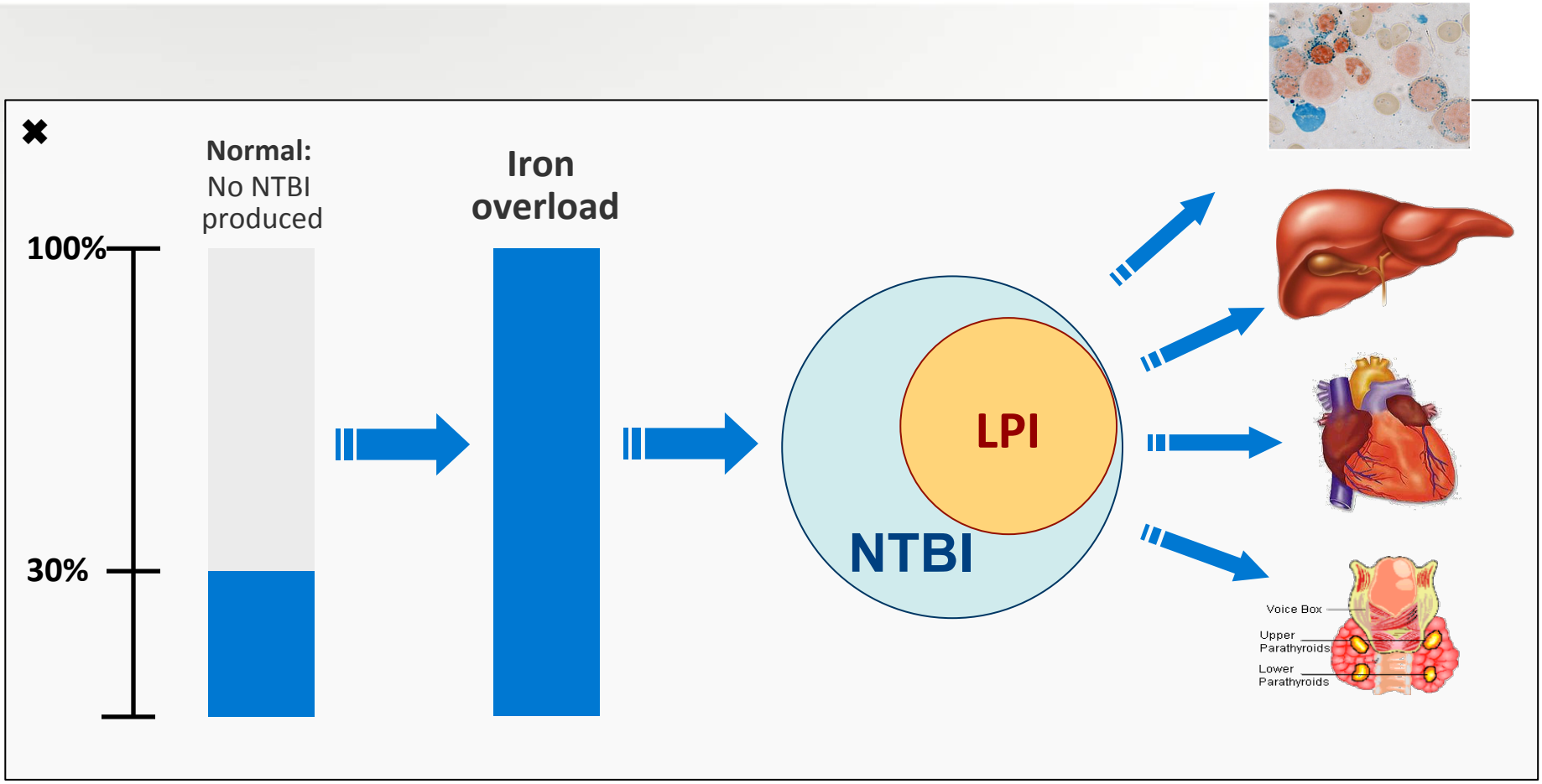
EPIC study – MDS cohort [2]



LPI = labile plasma iron.

1. Data from List AF, et al. Blood. 2008;112:[abstract 634].
2. Data from Gattermann N, et al. Leuk Res 2010;34:1143-50.

Non-Transferrin-Bound Iron (NTBI)



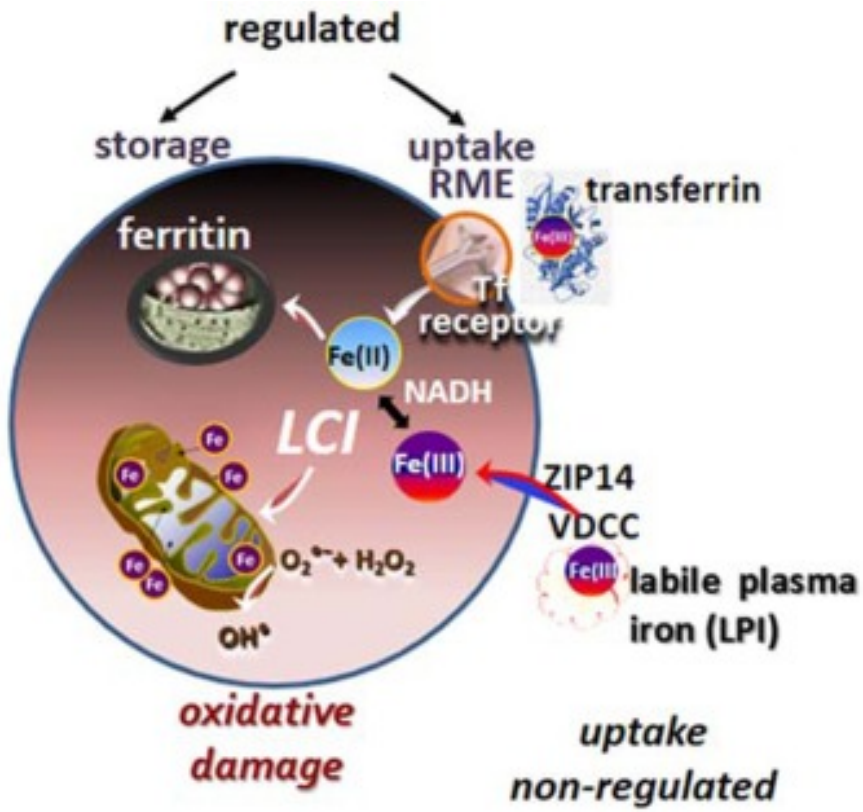
NTBI appears when plasma iron exceeds transferrin binding capacity (saturation > 60–70%)

LPI = labile plasma iron:

- **redox-active**
- **chelatable**
- **membrane-permeant**

The dark side of iron – NTBI and LPI

- **The labile iron pool (LIP, LCI) - redox active, exchangeable and chelatable**
- LIP levels are maintained within a 0.5–1.5 μM physiological range by an iron-sensing-transducing machinery that coordinately regulates **uptake vs storage** so as to support **Fe utilization** and minimize **Fe-O-driven oxidations**
- **LIP rises following prolonged exposure of cells to labile plasma iron (LPI)** or when faulty cell iron-utilizing machineries lead to maldistribution of the metal (e.g. excessive iron accumulation in mitochondria)
- **An excessive rise in LIP can promote the generation of reactive-O species (ROS)** by reacting with respiratory O intermediates and thereby override the cellular antioxidant defences **and chemically damage cell components and associated functions**



LIP, labile iron pool.

Cabantchik ZI. Front Pharmacol. 2014;5:45.

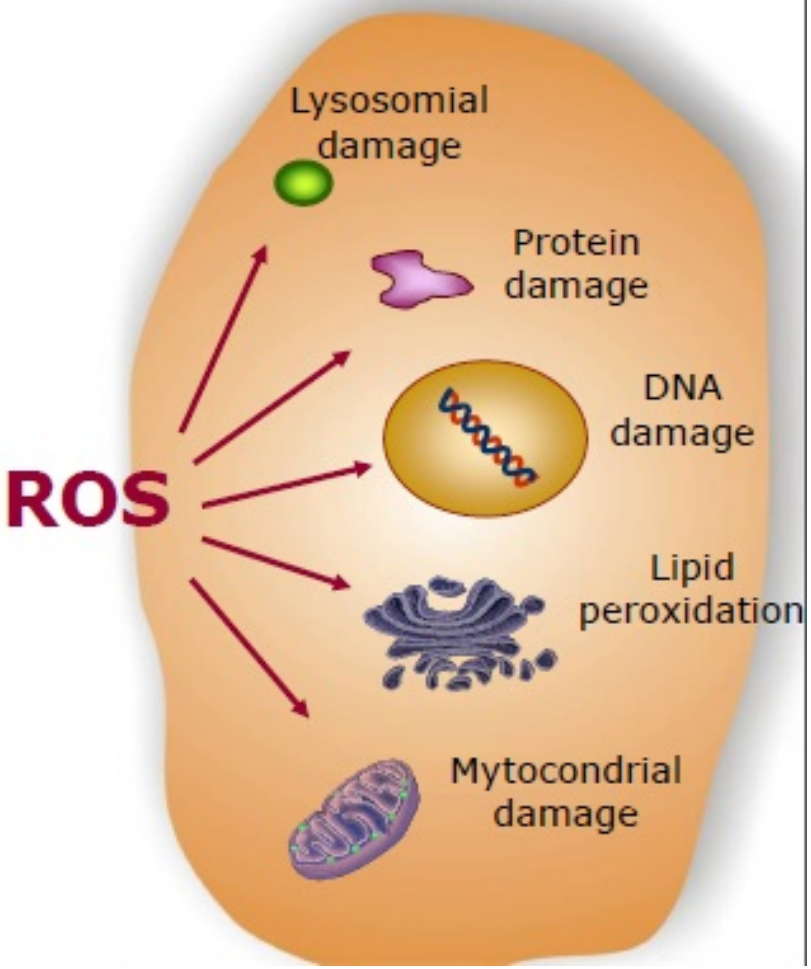
Fe toxicity tissue =

Σ Tissue Reactive Iron **x** Genetics **x** Environmental Factors **x** Time

Fenton reaction

$$O_2^{\cdot -} + Fe^{3+} \longrightarrow O_2 + Fe^{2+}$$

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



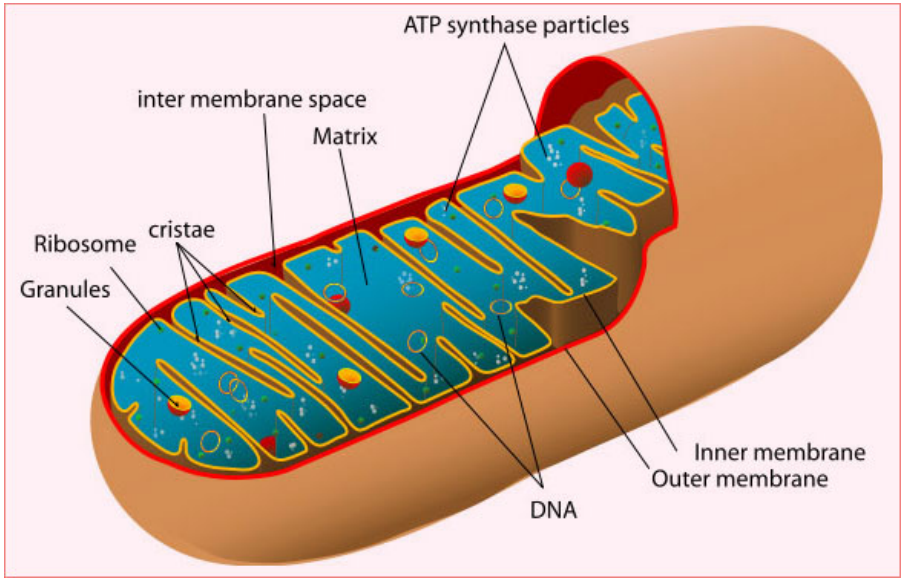
Coates TD. Free Radic Biol Med 2014

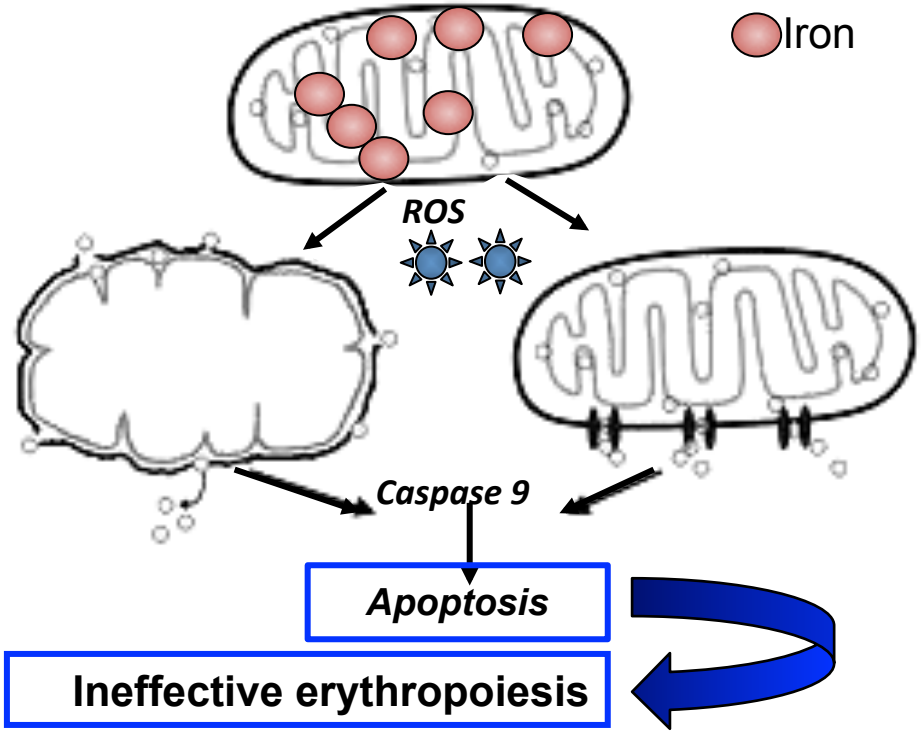
Figure adapted by Jomova et al. Toxicology. 2011:283:65

ROS Promote Apoptosis through Activation of the Caspase Cascade

Iron is also a potentially toxic metal
Labile iron can catalyze the production of toxic radicals:

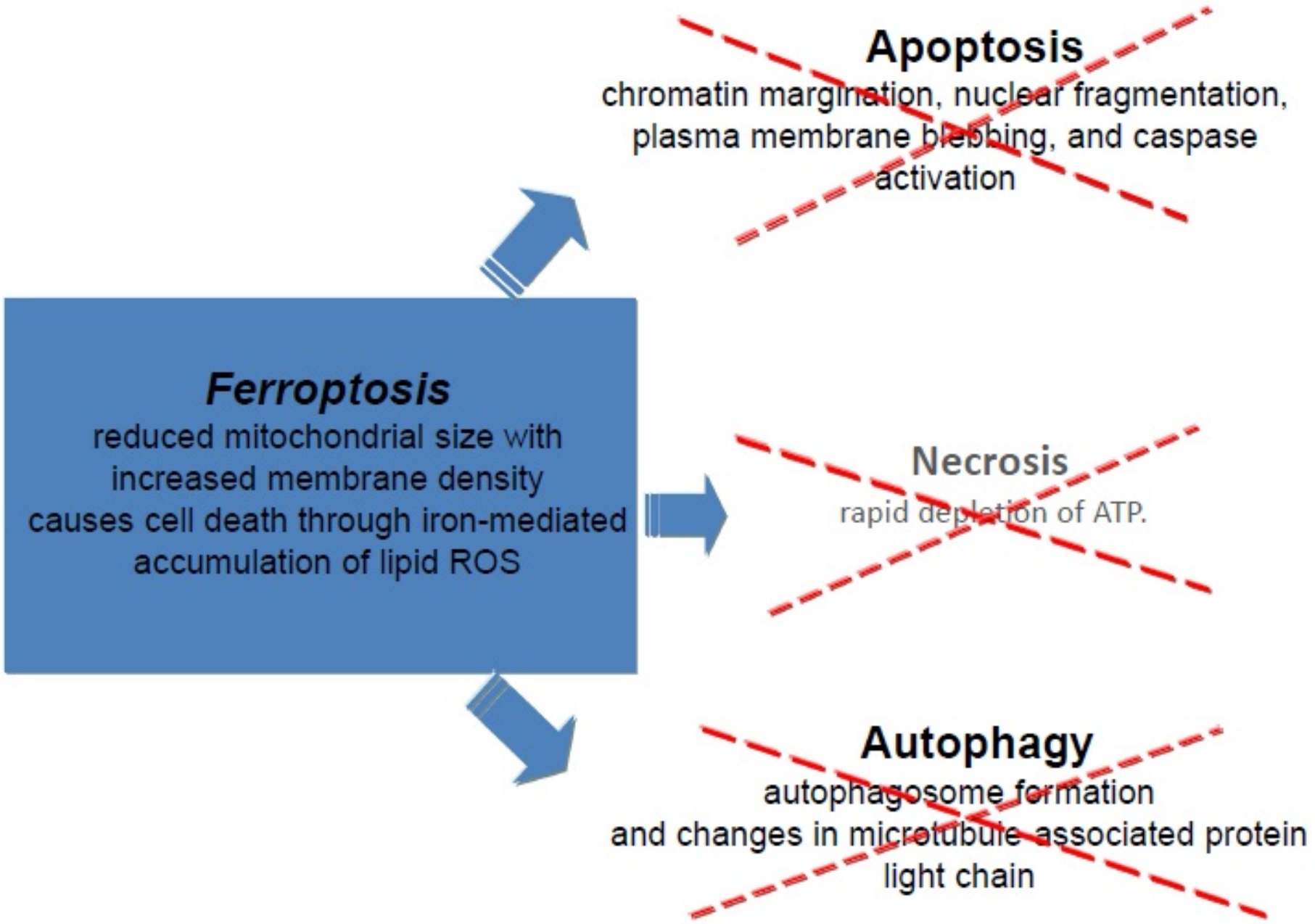
$$O_2^{\bullet -} + H_2O_2 \xrightarrow{Fe(II)} O_2 + OH^- + OH^{\bullet}$$ that can damage the cells





Zuo Y, *et al. Cell Res*. 2009;19:449-57.

Manz DH et al; Ann.N.Y.Acad.Sci Feb 2016



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Atherogenesis and iron: from epidemiology to cellular level

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Iron accumulates in human atherosclerotic lesions but whether it is a cause or simply a downstream consequence of the atheroma formation has been an open question for decades. According to the so called "iron hypothesis," iron is believed to be detrimental for the cardiovascular system, thus promoting atherosclerosis development and progression. Iron, in its catalytically active form, can participate in the generation of reactive oxygen species and induce lipid-peroxidation, triggering endothelial activation, smooth muscle cell proliferation and macrophage activation; all of these processes are considered to be proatherogenic. On the other hand, the observation that hemochromatotic patients, affected by life-long iron overload, do not show any increased incidence of atherosclerosis is perceived as the most convincing evidence against the "iron hypothesis." Epidemiological studies and data from animal models provided conflicting evidences about the role of iron in atherogenesis. Therefore, more careful studies are needed in which issues like the source and the compartmentalization of iron will be addressed. This review article summarizes what we have learnt about iron and atherosclerosis from epidemiological studies, animal models and cellular systems and highlights the rather contributory than innocent role of iron in atherogenesis.

Keywords: atherosclerosis, iron, hemoglobin, heme, intraplaque hemorrhage, LDL, oxidative stress, macrophages

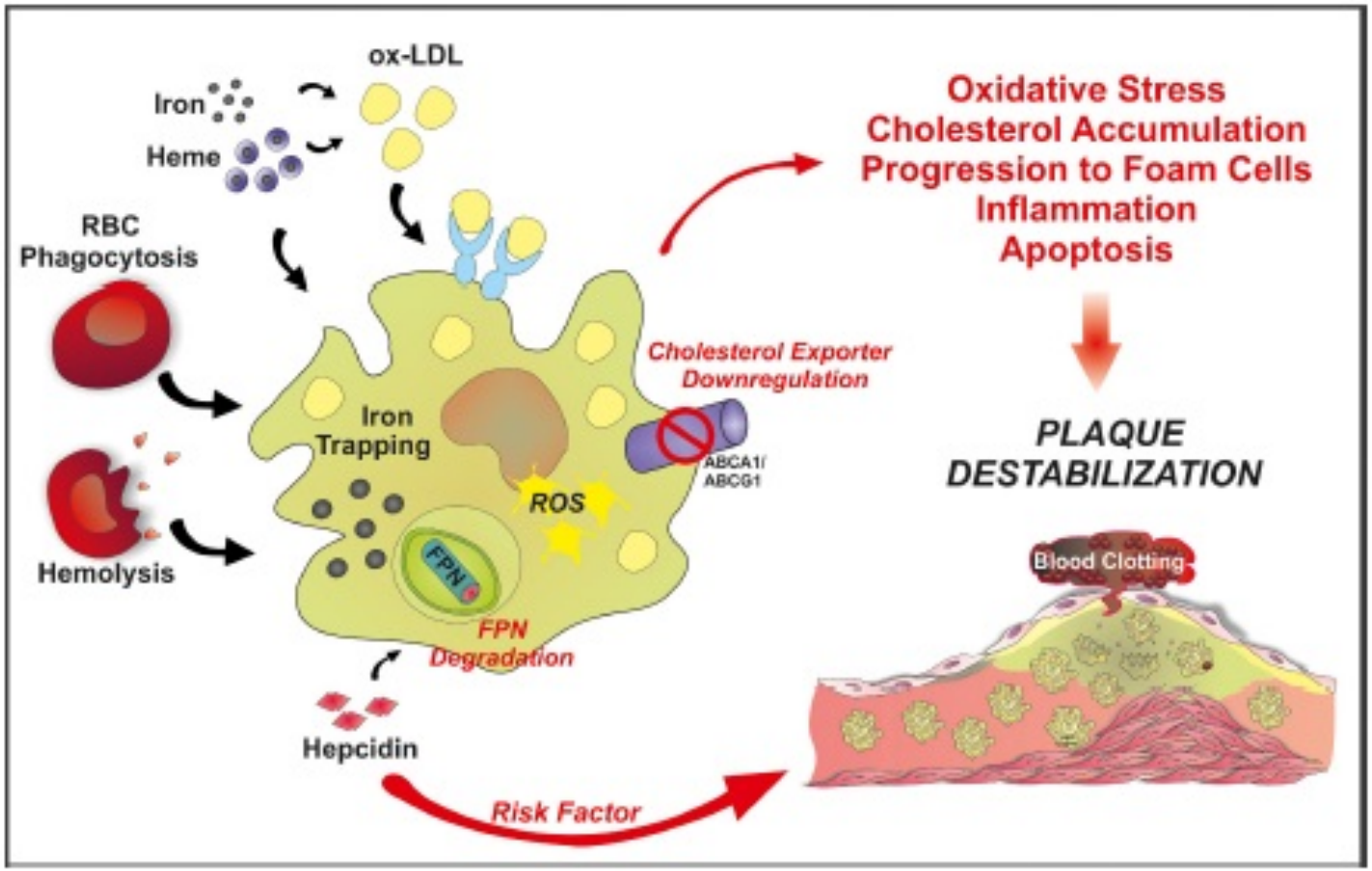

FIGURE 2 | Schematic overview of the "refined iron hypothesis": a role for macrophage-retained iron in atherosclerosis. Iron can accumulate in macrophages as inorganic iron and Hb-iron, upon erytrophagocytosis or hemolysis. Once stored in the cell, iron can be made available to the bloodstream via FPN-mediated export. According to the refined iron hypothesis, high hepcidin levels are considered a risk factor for plaque progression and destabilization. Hepcidin is known to bind to FPN, thus promoting its degradation and blocking iron export. This increases intracellular ROS levels and decreases cholesterol efflux. As a result, the oxidative status alters and LDL accumulation occurs, promoting foam cell formation, inflammation and eventually plaque instability.

Iron Chelation Improves Endothelial Function in Patients With Coronary Artery Disease

Stephen J. Duffy, MB, BS, PhD; Elizabeth S. Biegelsen, MD; Monika Holbrook, MS; Judson D. Russell, BS; Noyan Gokce, MD; John F. Keaney, Jr, MD; Joseph A. Vita, MD

Background—Some epidemiological studies have shown that increased iron stores are associated with increased cardiovascular events. Redox-active iron may contribute to lipid peroxidation, endothelial cell activation, and generation of reactive oxygen species (especially hydroxyl radical, via Fenton chemistry). Increased oxidative stress is associated with impaired action of endothelium-derived nitric oxide in patients with atherosclerosis.

Methods and Results—To test the hypothesis that reducing vascular iron stores would reverse endothelial dysfunction, we examined the effects of the iron chelator deferoxamine (500 mg intra-arterially over 1 hour) on vasomotor function in forearm resistance vessels of patients with coronary artery disease by venous occlusion plethysmography. Patients with coronary artery disease had impaired endothelium-dependent vasodilation in response to methacholine compared with healthy control subjects ($P<0.001$). Deferoxamine infusion decreased serum iron levels ($P<0.001$). Deferoxamine improved the blood flow response to methacholine in patients with coronary artery disease ($P<0.01$ by 2-way repeated-measures ANOVA) but had no effect on the response to sodium nitroprusside. In normal volunteers, deferoxamine had no effect on the response to methacholine. The nitric oxide synthase inhibitor N^{G}-monomethyl-L-arginine abolished augmentation of the methacholine response associated with deferoxamine. The hydroxyl radical scavenger mannitol had no effect on the methacholine response.

Conclusions—Deferoxamine improved nitric oxide–mediated, endothelium-dependent vasodilation in patients with coronary artery disease. These results suggest that iron availability contributes to impaired nitric oxide action in atherosclerosis. (*Circulation*. 2001;103:2799-2804.)

Key Words: iron ■ nitric oxide ■ endothelium ■ coronary disease

bjh research paper

Effect of deferasirox (ICL670) on arterial function in patients with beta-thalassaemia major

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Summary

Deferasirox (ICL670) has been shown to have rapid accessibility to intracellular labile iron. We tested the hypothesis that oral deferasirox improves arterial dysfunction in patients with beta-thalassaemia major. Nineteen thalassaemia patients, aged 23 ± 7 years, with normal left ventricular (LV) function were treated with deferasirox at 25–35 mg/kg/d for 12 months. LV function, brachial arterial flow-mediated dilation (FMD), carotid arterial stiffness, and serum ferritin levels were determined at baseline prior to initiation, after 6 months and after 12 months of therapy. The baseline cardiovascular indices were compared with those of 17 age-matched controls. Longitudinal changes in patients during the treatment period were also determined. Compared with controls, patients had similar echocardiographic indices of LV function (all $P > 0{\cdot}05$), while their baseline brachial FMD was reduced ($P < 0{\cdot}001$) and carotid stiffness increased ($P = 0{\cdot}019$). An increase in FMD ($P < 0{\cdot}001$) and a decrease in carotid stiffness ($P = 0{\cdot}007$) were found at 6 and 12 months follow-up. The stiffness index correlated inversely with FMD ($r = -0{\cdot}42$, $P = 0{\cdot}001$). Although there was an increase in ferritin level at 12 months (3303 ± 1185 ng/ml vs. 2714 ± 780 ng/ml at baseline, $P = 0{\cdot}006$), no significant correlation existed between ferritin level and FMD or carotid stiffness. In conclusion, deferasirox therapy in thalassaemia patients is associated with improved arterial function.

Keywords: deferasirox, arterial function, beta-thalassaemia major.

Principal clinical studies on DFX in MDS patients

	Study Type	No. pts	Inclusion criteria	Dose (mg/ kg/d)	Adverse effects	Efficacy
Porter, 2008	Phase II prospective multicenter	47	life expect >1 yr ≥8 transf/yr LIC[1]≥2 mg Fe/g dw	5-30	GI[5] events skin rash ↑ creatinine	↓ IOL[6] (SF[2],LIC[1])
List, 2009 (US03)	Phase II prospective multicenter open-label single-arm	176	IPSS[4] low/INT-1 ≥20 transfusions SF[2]≥1000 ng/mL	20	GI[5] events, ↑ creatinine	↓ IOL[6] (SF[2]) ↓ LPI[6] HI[9] (15-22%)
Gattermann, 2010 (EPIC)	Phase IIIb prospective multicenter open-label single-arm	341	life expect>1 yr >20 transfusions, SF[2]1000 ng/mL LIC[1]≥2 mg Fe/g dw	10-30	GI[5] events skin rash	↓ IOL[6] (SF[2]) ↓ LPI[8] HI[9] (13-22%)
Greenberg, 2010 (US02)	Prospective multicenter open-label single-arm	24	IPSS[4] low/INT-1 ≥20 transfusions SF[2]≥1000 ng/mL	20	GI[5] events ↑ creatinine skin rash	↓ IOL[6] (SF[2], LIC[1]) ↓ LPI[8]
Gattermann, 2012 (eXtend, eXjange)	Prospective observational multicenter open-label	167	SF[2]>1000 ng/mL ≥20 transfusions	10-30	GI[5] events ↑ creatinine skin rash	↓ IOL[6] (SF[2])
Angelucci, 2014 (GIMEMA MDS0306)	Prospective multicenter open-label single arm	150	IPSS[4] low/INT-1 ≥20 transfusions SF[2]≥1000 ng/mL	10-30	GI[5] events ↑ creatinine skin rash	↓ IOL[6] (SF[2)] HI[9] (13-22%)

bjh research paper

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

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Summary

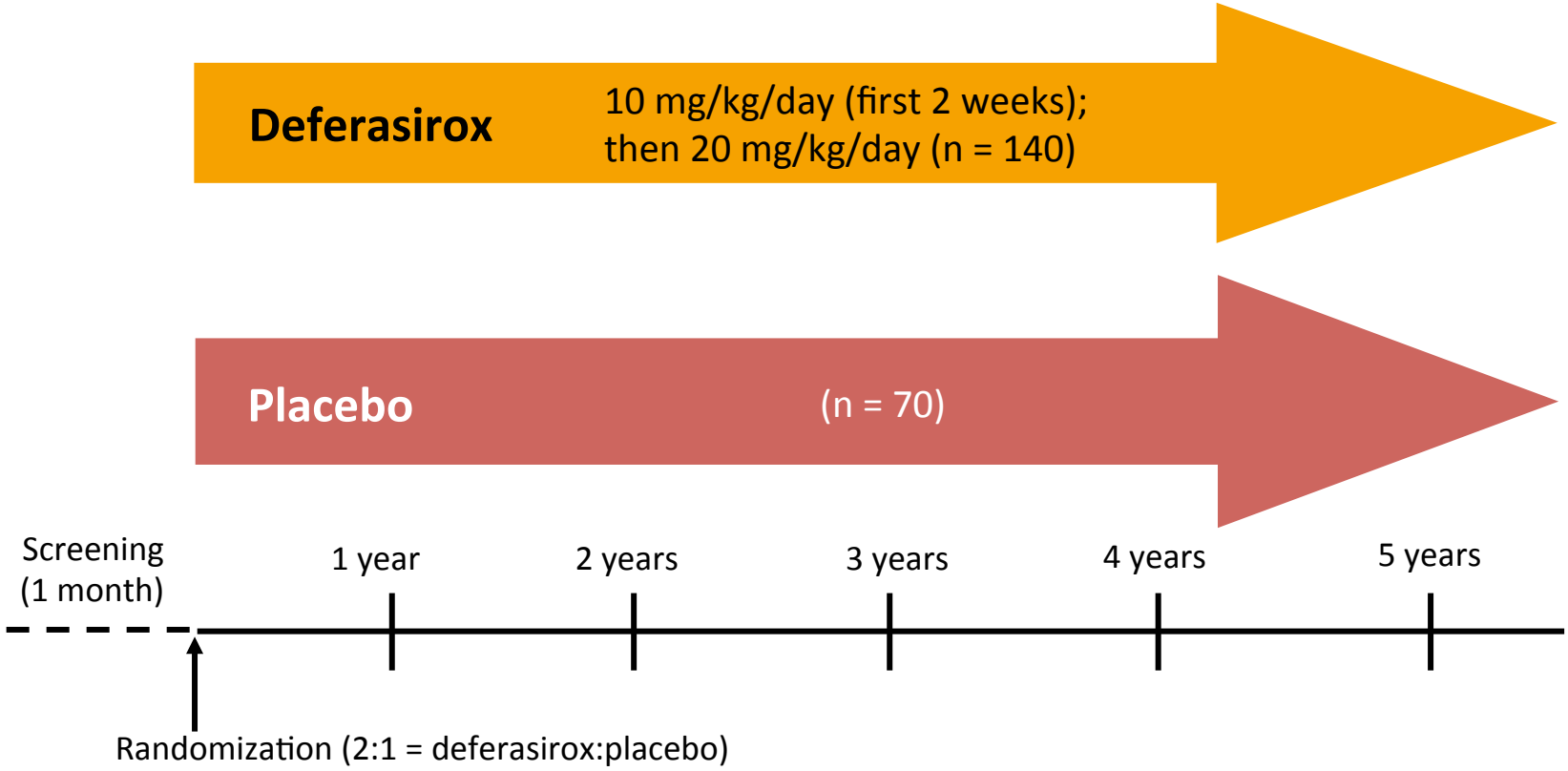
Iron chelation is controversial in higher risk myelodysplastic syndromes (HR-MDS), outside the allogeneic transplant setting. We conducted a retrospective, multicentre study in 51 patients with transfusion-dependent, intermediate-to-very high risk MDS, according to the revised international prognostic 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.

Summary

The use of iron chelation outside the setting of preparation to allogeneic transplantation is controversial in higher risk myelodysplastic syndromes (HR-MDS). We conducted a retrospective, multicenter study in 51 patients with transfusion dependent, intermediate-to-very high R-IPSS risk MDS treated with the oral iron chelating agent deferasirox (DFX). Thirty-six patients (71%) received azacitidine concomitantly. DFX was given at a median dose of 1.000 mg per 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) and 4 of them (8%) interrupted the treatment. Median ferritin levels progressively decreased from 1.709 ng/ml at baseline to 1.100 ng/ml after 12 months of treatment (p=0.02). In 8 of 17 patients (47%) initially abnormal ALT/AST levels improved or normalized under DFX. One patient showed a remarkable hematological improvement. At a median follow up of 35.3 months, median overall survival was 37.5 months. The results of this first real-life survey of DFX in HR-MDS are comparable, in terms of safety and efficacy, with those observed in lower-risk MDS. Though larger and prospective studies are required to demonstrate real clinical benefits, our data suggest that DFX might be considered for selected patients with HR-MDS.

TELESTO: ongoing prospective study of deferasirox in MDS

- Prospective, multicentre study to investigate the clinical benefit of chelation therapy with deferasirox in **210** MDS patients
- Primary study end-point: EFS (death, cardiac, and hepatic non-fatal events)



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

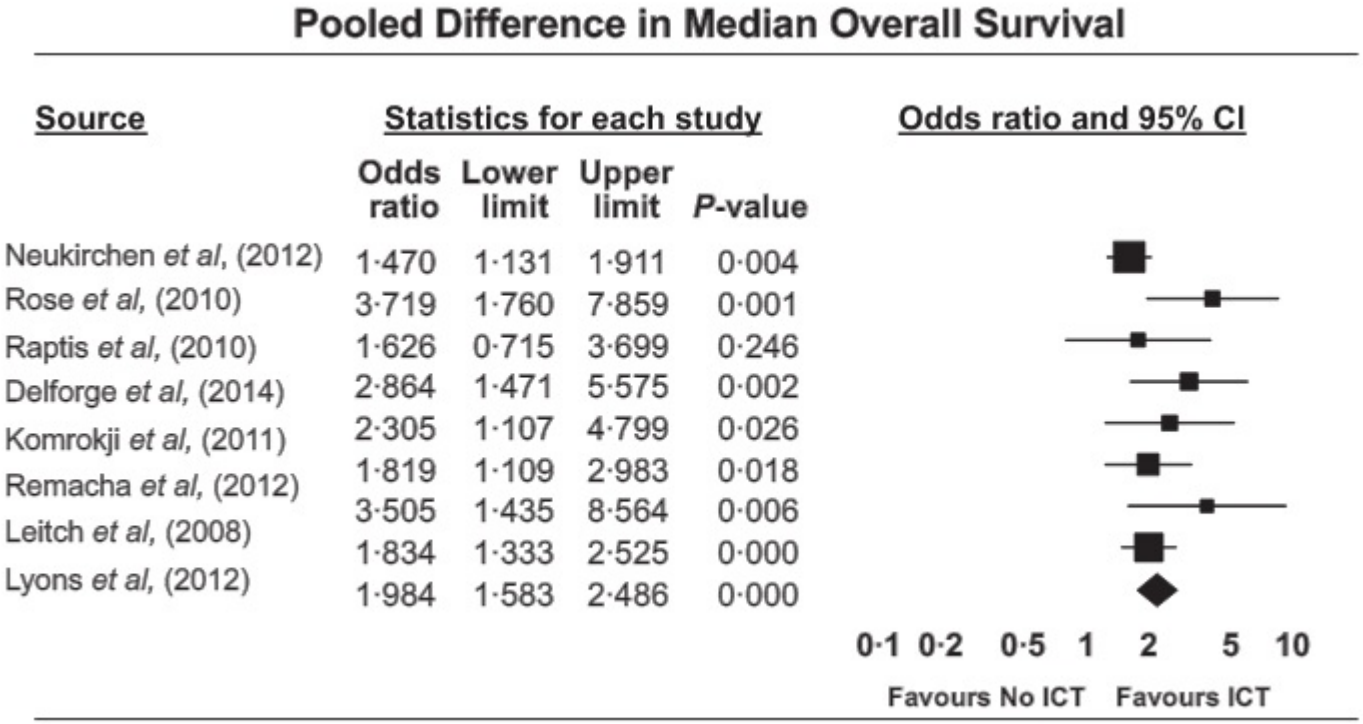
Multiple lines of evidence suggest ICT may improve OS in transfusion-dependent MDS

Study	N	Design	Survival	Non-chelated patients	Chelated patients	p value
Leitch 2008	36	Retrospective	Median OS	40 mo	Not reached	0.003
			4-year survival rate	43%	64%	0.003
Rose 2010	97	Prospective follow-up	Median OS from diagnosis	53 mo	124 mo	< 0.0003
			Median OS with adequate vs weak chelation	NA	124 vs. 85 mo	< 0.001
Neukirchen 2012[a]	188	Matched pair analysis	Median OS	49 mo	75 mo	0.002
Neukirchen 2012[b]	417	Retrospective, registry	Median time to death in TD patients	30 mo	67 mo	NR
Komrokji 2011	97	Retrospective	Median OS	34 mo	59 mo	0.013
Delforge 2012	186	Retrospective	Median OS in Low/Int-1	37 mo	126 mo	< 0.001
Zeidan 2012	4,226	Retrospective, registry	Median survival	47 wk	110 wk	0.003
			HR for 27-52 wks on DFX	1	0.77	NR
			HR for ≥ 53 wk on DFX	1	0.34	NR
Remacha 2012	228	Retrospective	Median OS	105 mo	133 mo	0.009
Lyons 2013	600	Prospective, registry	Median OS from diagnosis	48.7 mo	All 96.8 mo ICT > 6 mo 102.5 mo	< 0.0001
de Witte T 2012	1,000	Prospective, registry	Adjusted HR	1	0.51 (0.19-1.32)	NS

Delforge M, et al. Haematologica. 2012;97 Suppl 1:abstract 0898. Komorokji RS, et al. Blood. 2011;118:abstract 2776. Leitch H, et al. Clin Leuk. 2008;2:205-11. Lyons RM, et al. Blood. 2013;122:abstract 2775. [a] Neukirchen J, et al. Leuk Res. 2012;36:1067-70. [b] Neukirchen J, et al. Haematologica. 2012;97 Suppl 1: abstract 0359. Remacha A, et al. Blood. 2012;120:abstract 1723. Rose C, et al. Leuk Res. 2010;34:864-70. de Witte T, et al. EUMDS Registry. Presented at ELN 2012. Zeidan AM, et al. Blood. 2012;120:abstract 426.

THE IMPACT OF CHELATION THERAPY ON SURVIVAL IN TRANSFUSIONAL IRON OVERLOAD: A META-ANALYSIS OF MDS (Mainous A et al, Br J Hematol, 2014, 167, 697-726)

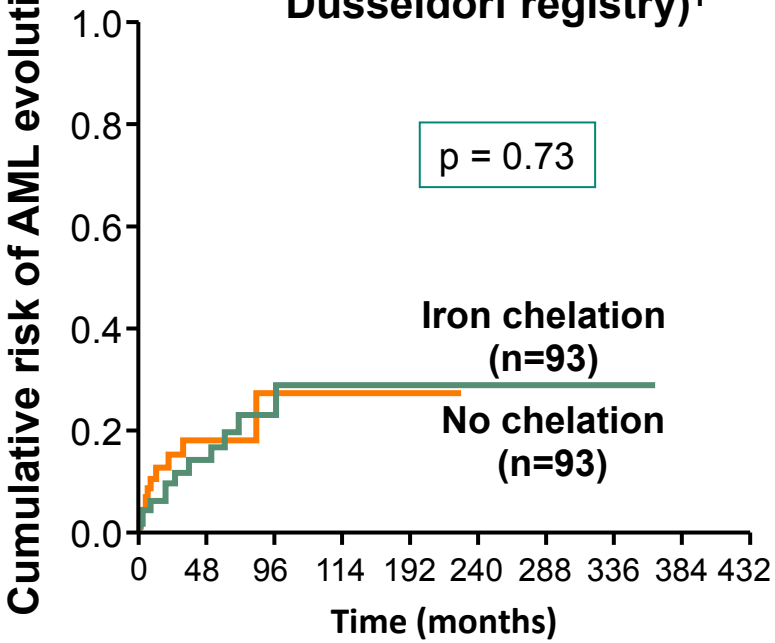
- **Methods:** 8 observational studies, , 1562 pts, median sample size: 153 (78-534)
- **Results:** ICT associated with longer survival (mean difference: 61.2 months)



Mainous A et al, Br J Hematol 2014, 167, 697-726

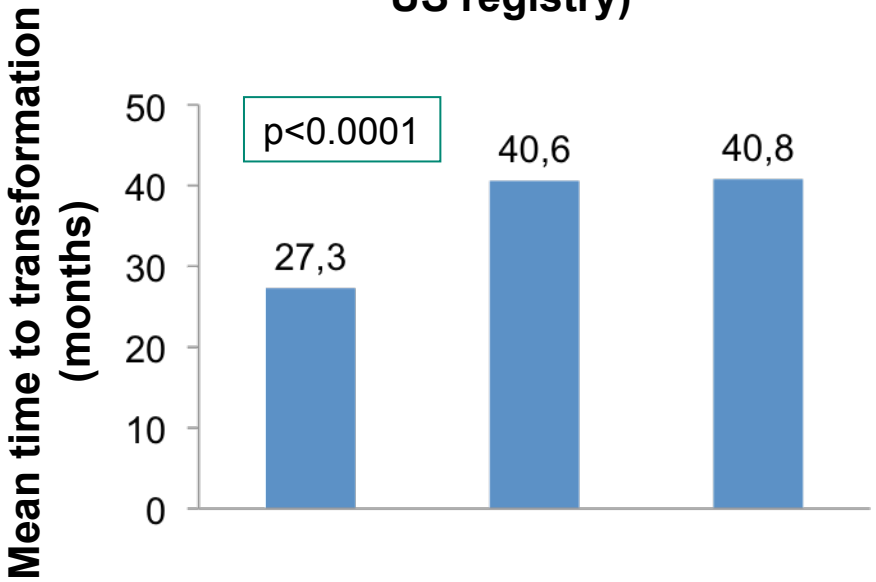
Iron Chelation and AML Transformation: Clinical Data

Iron chelation does not delay AML transformation (Matched-pair analysis from Dusseldorf registry)[1]



AML risk	2 years	5 years
Chelation	10%	19%
No chelation	12%	18%

Iron chelation delays AML transformation (Multi-center analysis from US registry)[2]



	Non-chelated n=337	All Chelated n=263	Chelated ≥6 months n=191
AML transformation n (%)	30 (8.9)	12 (4.6)	10 (5.2)

[1]Fox *et al. Blood*. 2009;114:[abstract 1747]. [2]Lyons *et al. Blood*. 2011;118:[abstract 2800].

Summary of the mouse model data

- Iron is mutagenic in haemopoietic cells (through increased intracellular ROS)
- Iron is not itself leukaemogenic; but in the context of the genomic instability of the MDS clone, iron overload may promote clonal evolution and thus accelerate progression of MDS to AML
- Further evaluation in animal models and in clinical trials is necessary to elucidate the clinical implications of these observations, especially in regard to the deployment of iron chelation therapy

Chan L, et al. Presented at ASH 2010. Blood. 2010;116:[abstract 122].

bjh research paper

Overall survival in lower IPSS risk MDS by receipt of iron chelation therapy, adjusting for patient-related factors and measuring from time of first red blood cell transfusion dependence: an MDS-CAN analysis

Heather A. Leitch,[1] Ambica Parmar,[2] Richard A. Wells,[3] Lisa Chodirker,[3] Nancy Zhu,[4] Thomas J. Nevill,[5] Karen W. L. Yee,[6] Brian Leber,[7] Mary-Margaret Keating,[8] Mitchell Sabloff,[9] Eve St. Hilaire,[10] Rajat Kumar,[11] Robert Delage,[12] Michelle Geddes,[13] John M. Storring,[14] Andrea Kew,[8] April Shamy,[15] Mohamed Elemary,[16] Martha Lenis,[3] Alexandre Mamedov,[3] Jessica Ivo,[3] Janika Francis,[3] Liying Zhang[3] and Rena Buckstein[3]

Received 18 March 2017; accepted for publication 25 May 2017

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Summary

Analyses suggest iron overload in red blood cell (RBC) transfusion-dependent (TD) patients with myleodysplastic syndrome (MDS) portends inferior overall survival (OS) that is attenuated by iron chelation therapy (ICT) but may be biassed by unbalanced patient-related factors. The Canadian MDS Registry prospectively measures frailty, comorbidity and disability. We analysed OS by receipt of ICT, adjusting for these patient-related factors. TD International Prognostic Scoring System (IPSS) low and intermediate-1 risk MDS, at RBC TD, were included. Predictive factors for OS were determined. A matched pair analysis considering age, revised IPSS, TD severity, time from MDS diagnosis to TD, and receipt of disease-modifying agents was conducted. Of 239 patients, 83 received ICT; frailty, comorbidity and disability did not differ from non-ICT patients. Median OS from TD was superior in ICT patients (5·2 vs. 2·1 years; $P < 0·0001$). By multivariate analysis, not receiving ICT independently predicted inferior OS, (hazard ratio for death 2·0, $P = 0·03$). In matched pair analysis, OS remained superior for ICT patients ($P = 0·02$). In this prospective, non-randomized analysis, receiving ICT was associated with superior OS in lower IPSS risk MDS, adjusting for age, frailty, comorbidity, disability, revised IPSS, TD severity, time to TD and receiving disease-modifying agents. This provides additional evidence that ICT may confer clinical benefit.

Keywords: iron chelation therapy, myelodysplastic syndromes, patient-related factors, transfusion dependence.

Pre-transplantation SF level and outcome after allo-SCT (selected trials)

Author	n	HSCT	Results
Armand et al. 2007	590 (AML,CML, MDS)	Myeloablative allogeneic	SF ↑ → NRM ↑ (OS and DFS ↓)
Pullarkat et al. 2008	190 (myeloid and lymphoid)	Myeloablative allogeneic	SF ↑ (≥ 1,000 µg/L) NRM ↑ → DFS/ OS ↓ + GVHD ↑; blood stream infection ↑
Platzbecker et al. 2008	172 (MDS)	Myeloablative allogeneic	OS↓ (SF ↑) acute GVHD ↑ (SF ↑)
Kataoka et al. 2009	264 (haematological disease)	Myeloablative allogeneic	SF ≥ 599 µg/L: NRM ↑; OS↓, no impact on GVHD
Lee et al. 2009	101 (paediatric patients)	Myeloablative allogeneic	SF ≥ 1,000 µg/L OS ↑; DFS↓
Alessandrino et al. 2010	357 MDS	RIC/ myeloablative allogeneic	Transfusion dependence and SF ↑: NRM ↑; OS↓; DFS↓ (only myeloablative)

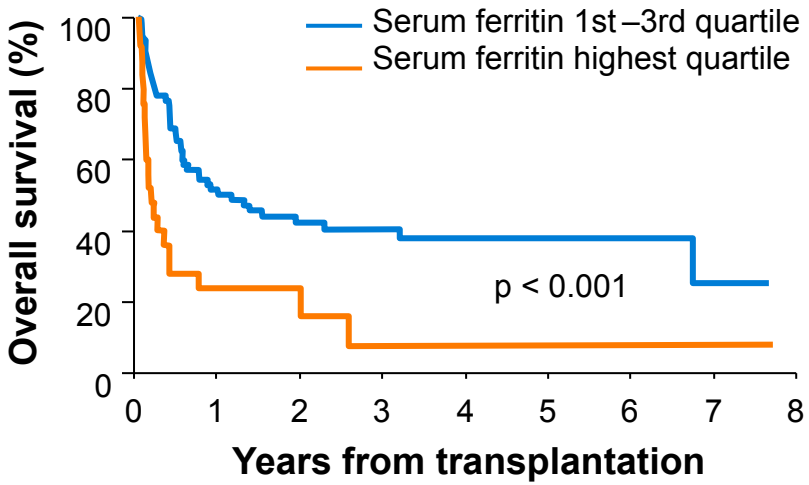
AML, acute myeloid leukaemia; CML, chronic myeloid leukaemia; RIC, reduced-intensity conditioning.

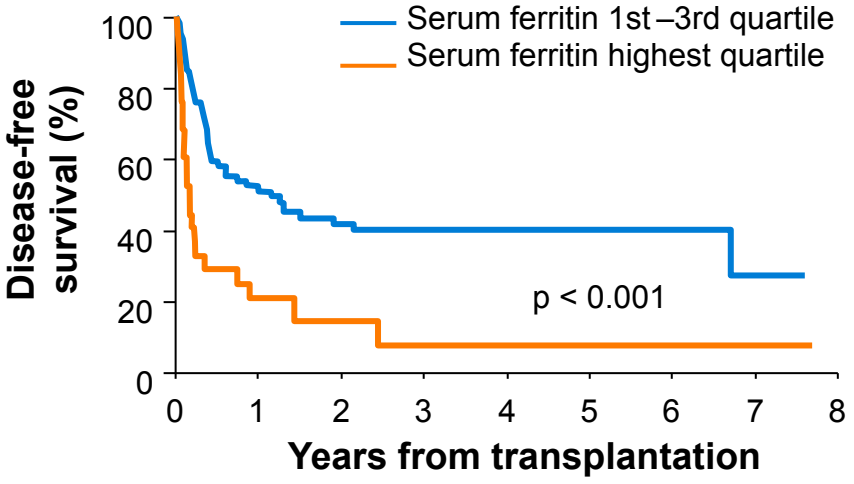
Alessandrino EP, et al. Haematologica. 2010;95:476-84. Armand P, et al. Biol Blood Marrow Transplant. 2007;13:655-64. Kataoka K, et al. Biol Blood Marrow Transplant. 2009;15:195-204. Lee JW, et al. Bone Marrow Transplant. 2009;44:793-7.Platzbecker U, et al. Biol Blood Marrow Transplant. 2008;14:1217-25. Pullarkat V, et al. Bone Marrow Transplant. 2008;42:799-805.

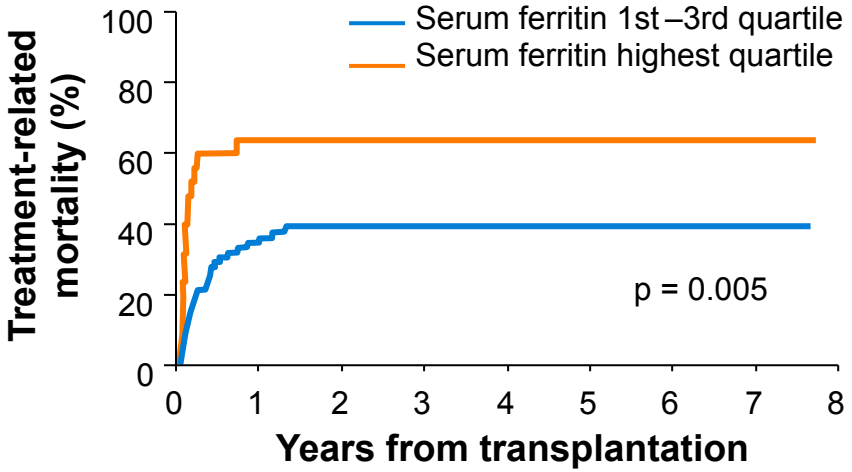
Outcome according to serum ferritin level

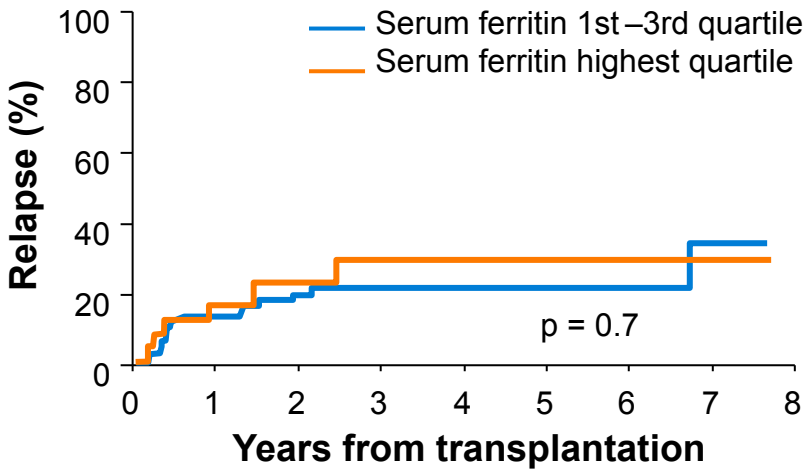
(590 pts: 154 CML, 144 AML, 103 MDS, 74 ALL, 115 other)

Armand P, et al. Blood. 2007;109:4586-8.

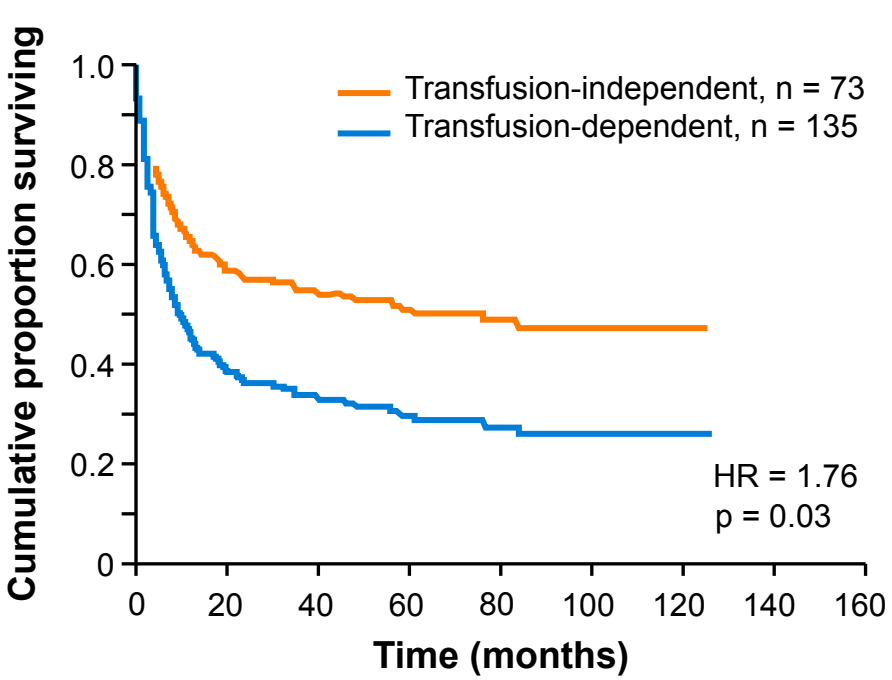


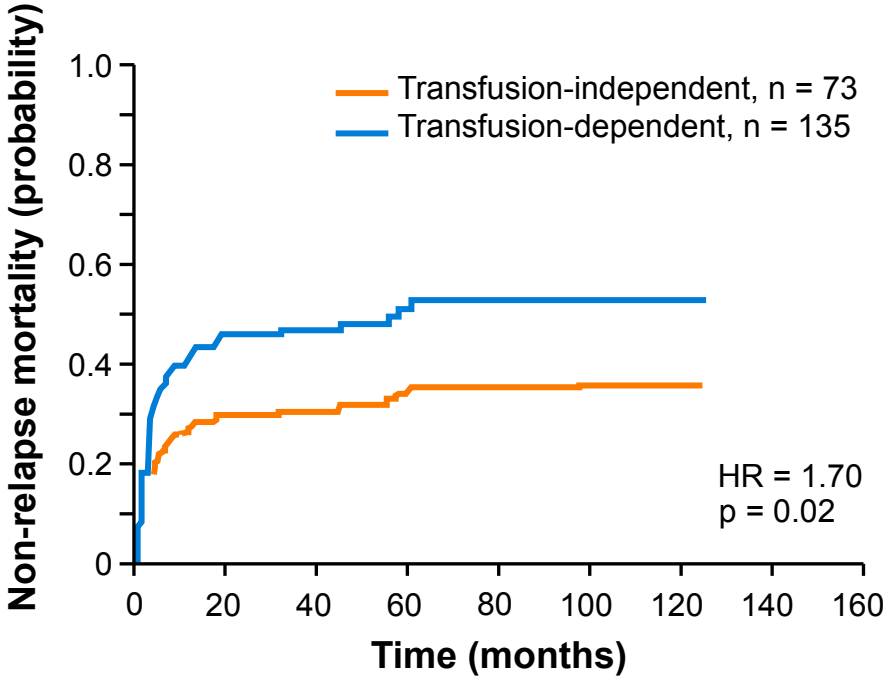






Impact of transfusion dependence on overall survival and non-relapse mortality in myeloablative SCT*





Lower overall survival in transfusion-dependent patients

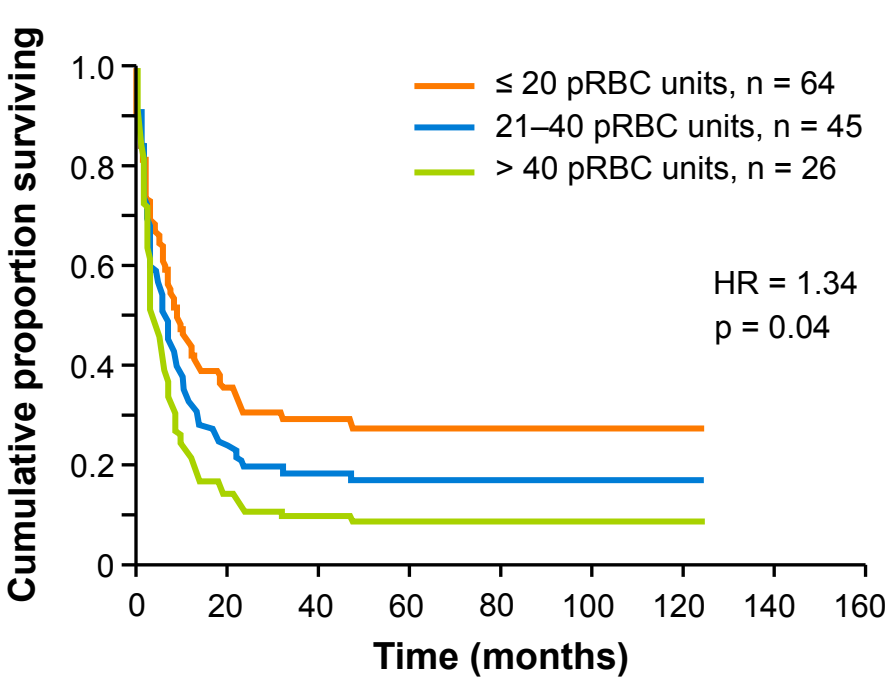
Higher non-relapse mortality in transfusion-dependent patients

*Multivariate analysis adjusted for other prognostic factors

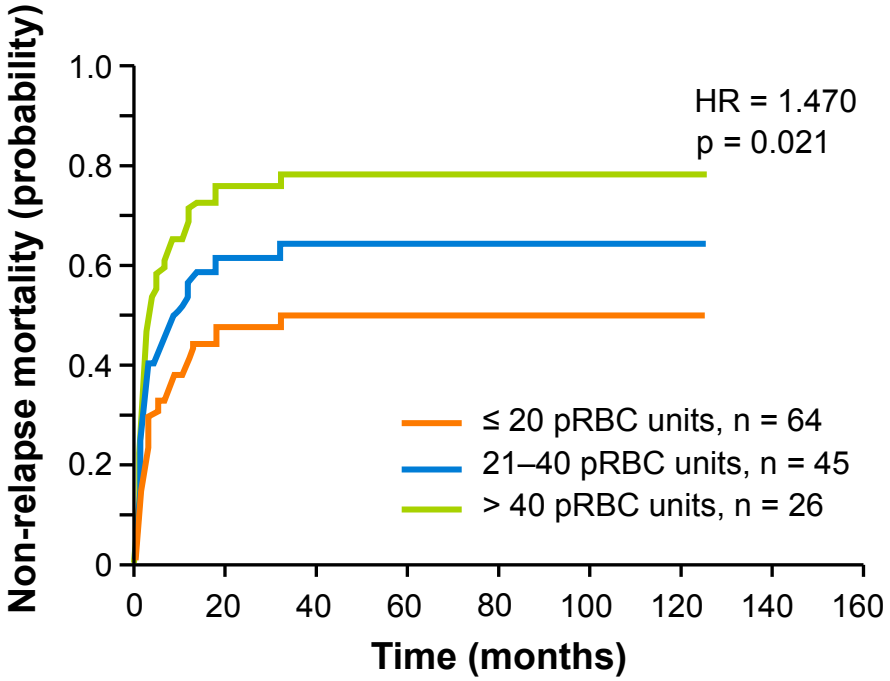
HR = hazard ratio;
SCT = stem cell transplantation.

Alessandrino EP, et al. Haematologica. 2010;95:476-84.

Impact of transfusion burden prior to SCT on overall survival and non-relapse mortality post-SCT



Overall survival by transfusion burden prior to SCT



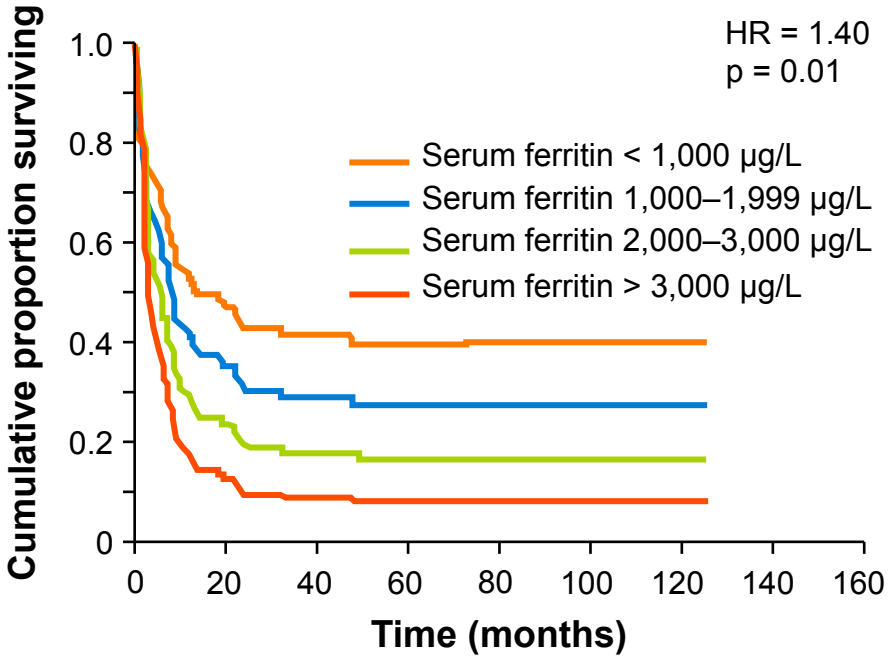
Non-relapse mortality by transfusion burden prior to SCT

Overall survival and non-relapse mortality for < 20 units were not significantly different compared with transfusion-independent patients

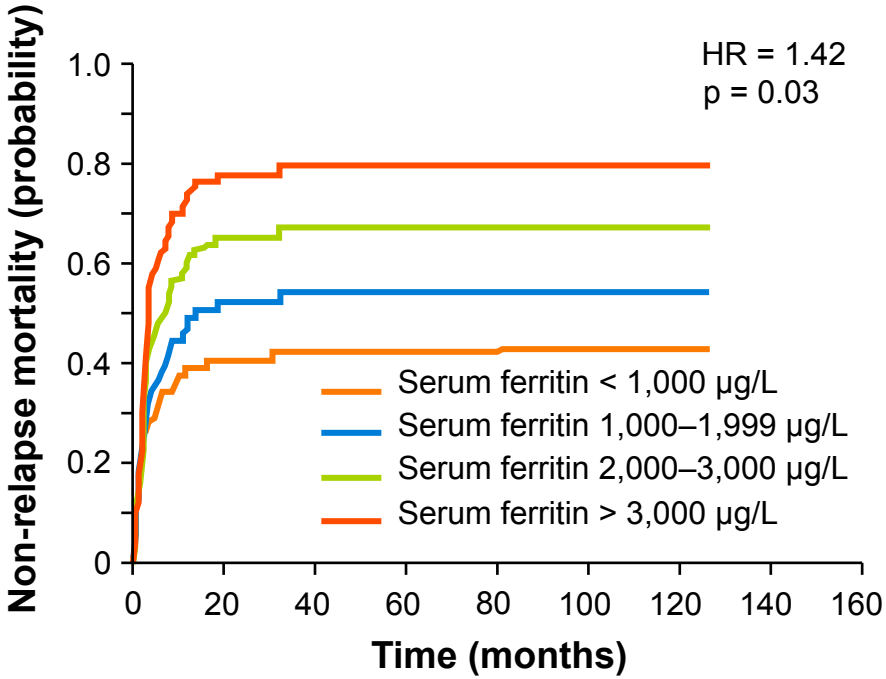
pRBC = packed red blood cells.

Alessandrino EP, et al. Haematologica. 2010;95:476-84.

Impact of serum ferritin level prior to SCT on overall survival and non-relapse mortality post-SCT (n = 129)



Overall survival by serum ferritin level prior to SCT



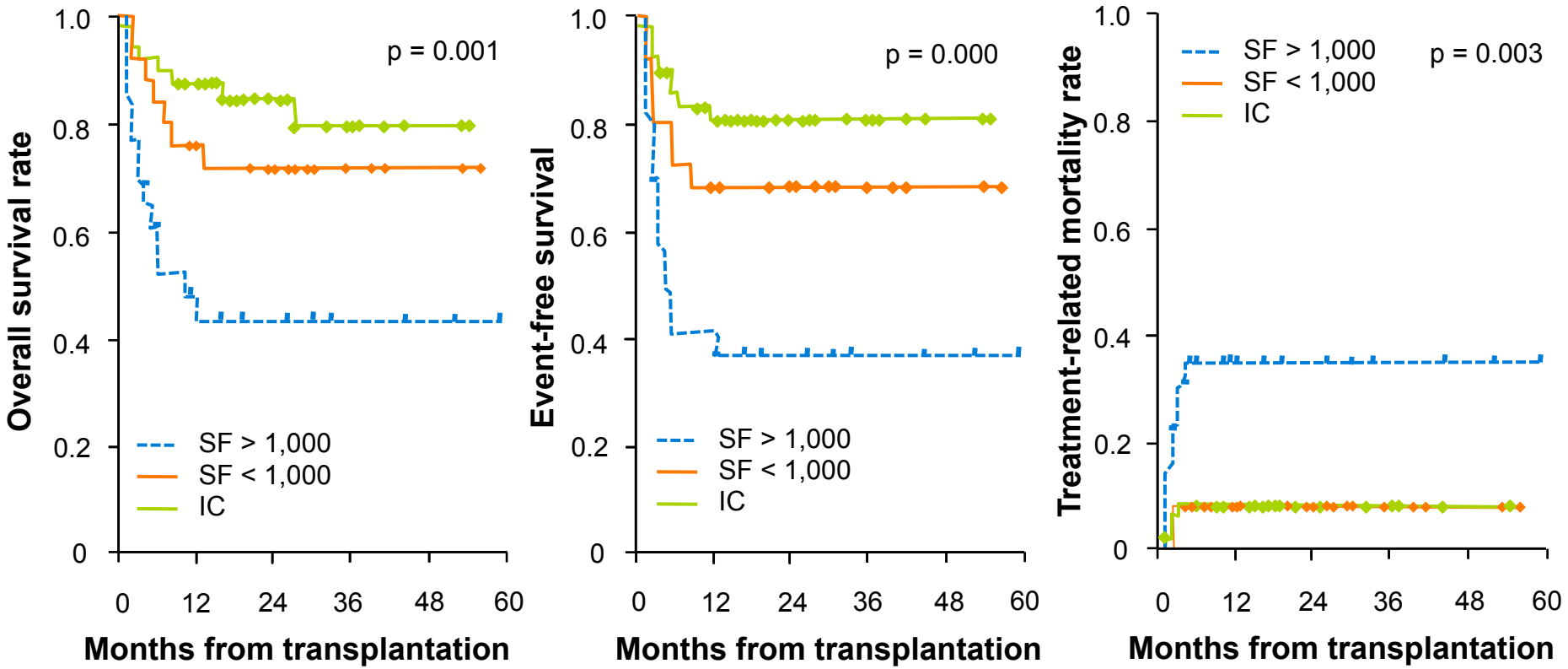
Non-relapse mortality by serum ferritin level prior to SCT

The impact of serum ferritin remained unchanged when the model was adjusted for albumin level

Alessandrino EP, et al. Haematologica. 2010;95:476-84.

Iron chelation prior to HSCT improves survival

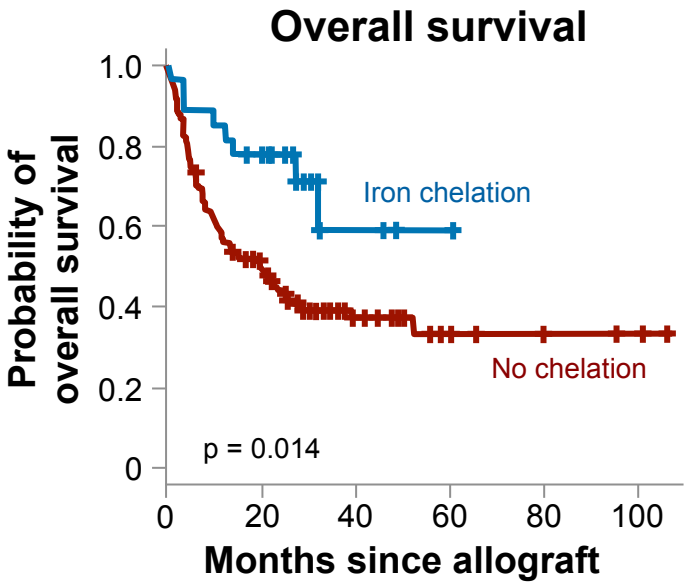
(retrospective study, 101 pediatric pts)



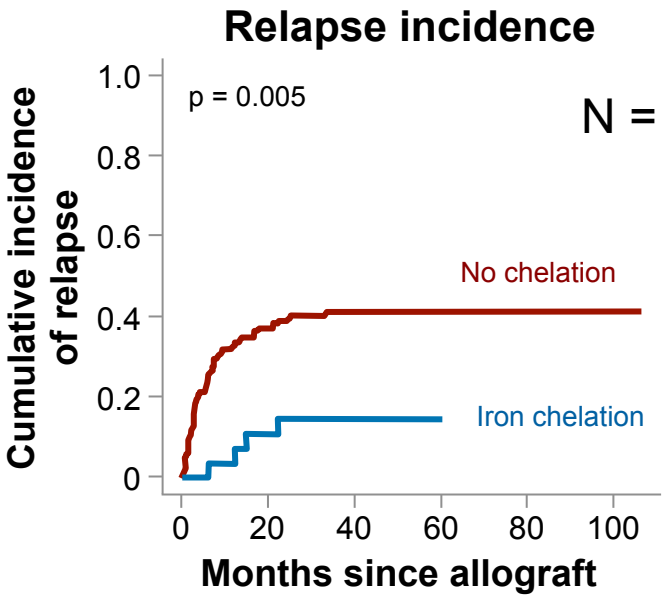
IC = patients with serum ferritin decreased to < 1,000 µg/L with ICT before HSCT;
ICT = iron chelation therapy;
SF > 1,000 = patients with serum ferritin ≥ 1,000 µg/L at the time of HSCT;
SF < 1,000 = patients with serum ferritin < 1,000 µg/L at the time of HSCT, without ICT.

Lee JW, et al. Bone Marrow Transplant. 2009;44:793-7.

ICT following allogeneic HSCT



HR 0.34 (0.15–0.76), p = 0.008



HR 0.22 (0.07–0.73), p = 0.012

- Conclusions: IOL at HSCT has a negative impact on TRM and overall survival; the use of iron chelation following HSCT was associated with a reduced risk of relapse, possibly by depriving leukaemic cells of iron

Michallet M, et al. Blood. 2013;122:abstract 180.

Which MDS patients undergoing allo-SCT could benefit from treatment of iron overload ?

GITMO working conference on iron chelation in MDS

- "...all MDS patients who are transfusion-dependent and are potential candidates for allo-SCT should receive ICT to prevent iron accumulation"
- "If iron overload has occurred in patients for whom a myeloablative allo-SCT has been planned, ...an attempt should be performed to reduce body iron stores. However, ...the accomplishment of the reduction of iron overload should not cause a delay in transplantation"
- "The Expert Panel recommendation for peri-transplantation ICT in MDS patients with iron overload is to offer IV deferoxamine infusion (40 mg/kg/day as a 24-hour i.v. infusion)"
- "In patients with MDS and iron overload after SCT, iron removal through phlebotomy is the first-choice therapy (6 mL/kg blood withdrawal at 14-day intervals). For those patients who cannot be phlebotomized due to low Hb level or cardiac impairment, deferoxamine or deferasirox should be considered. The optimal strategy, however, remains to be defined"

Alessandrino EP, et al. Am J Hematol. 2011;86:897-902.

Deferasirox can Improve Hematopoiesis in MDS: Recent data

Study	n	Risk IPSS	RBC response	Neutrophil response	PLT response
Cilloni D et al. 2011[1]	57	Low/Int-1	45.6%	NR	NR
List A et al. 2012[2]	173 52 77	Low/Int-1	15%	15%	22%
Gattermann N et al. 2012[3]	247 50 100	Low/Int-1	21.5%	22%	13%
Nolte F et al. 2012[4]	50	Low/Int-1	11%	NR	NR
Angelucci E et al. 2012[5]	152	Low/Int-1	Transfusion independence in 14.5%	NR	NR

RBC, PLT and neutrophil responses are assessed according to IWG 2006 criteria (1-3); NR, not reported

[1]CIlloni D *et al*. *Blood* 2011;118:abst 611. [2]List A *et al. J Clin Oncol*. 2012;30:2134-9. [3]Gattermann N *et al. Haematologica* 2012;97:1364-71; [4]Nolte *F et al. Ann Hematol*. 2012 Oct 17. [Epub ahead of print]; [5]Angelucci E *et al*. *Blood* 2012;118:abst 425.

Table 1 Major features indicated in the clinical studies reporting hematologic improvement (HI) during deferasirox treatment

Reference	No. pts	HI-E	HI-plts	HI-PMN	Biological parameters
EPIC [22]	247	53 (21.7 %) 11.8 % TI 8.9 % ↑ Hb	13 (13 %)	50 (22 %)	No significant changes in SF and LIP between responders and non-responders
US03 [23]	173	26 (15 %)	17/77 (22 %)	8/52 (15 %)	No significant changes in SF and LIP between responders and non-responders
German [24]	50	2/33 (6 %)	3/10 (30 %)	–	–
GIMEMA [25]	152	16/152 (11 %)	18/125 (15 %)	1/41 (3 %)	No significant changes in SF between responders and non-responders
Italian cooperative group [26]	105	41/105 (44.5 %)	nr	nr	HI not related to SF changes
REL [27]	53	19 (35.1 %)	8/13 (61 %)	13/17 (76.4 %)	No correlations

TI transfusion independence, *SF* serum ferritin, *Hi-E* erythroid improvement, *HI-Plts* platelet improvement, *HI-PMN* neutrophil improvement, *LIP* labile iron pool

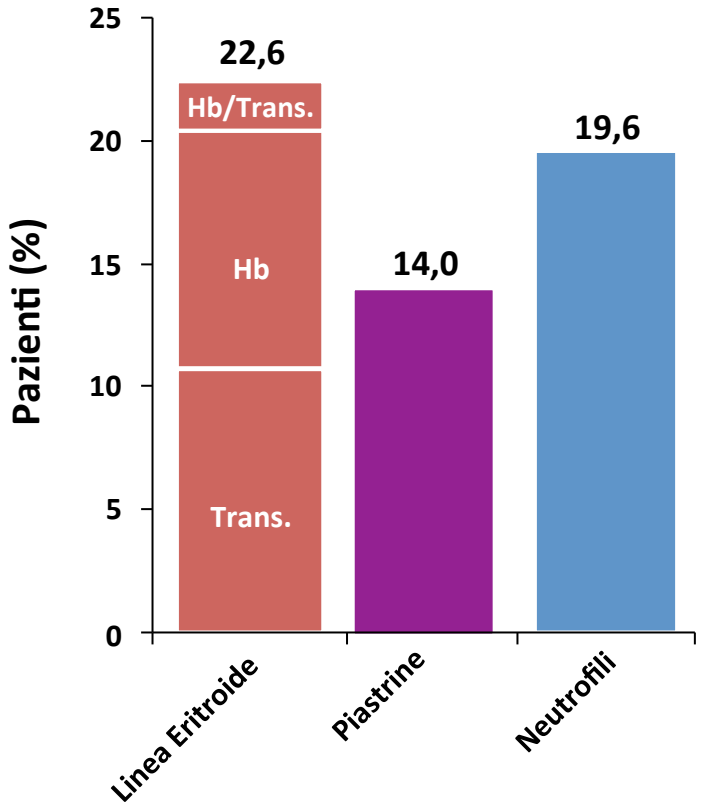
Hematologic responses to deferasirox therapy in transfusion-dependent patients with myelodysplastic syndromes

Norbert Gattermann,[1] Carlo Finelli,[2] Matteo Della Porta,[3] Pierre Fenaux,[4] Michael Stadler,[5] Agnes Guerci-Bresler,[6] Mathias Schmid,[7] Kerry Taylor,[8] Dominique Vassilieff,[9] Dany Habr,[10] Andrea Marcellari,[10] Bernard Roubert,[11] and Christian Rose[12]

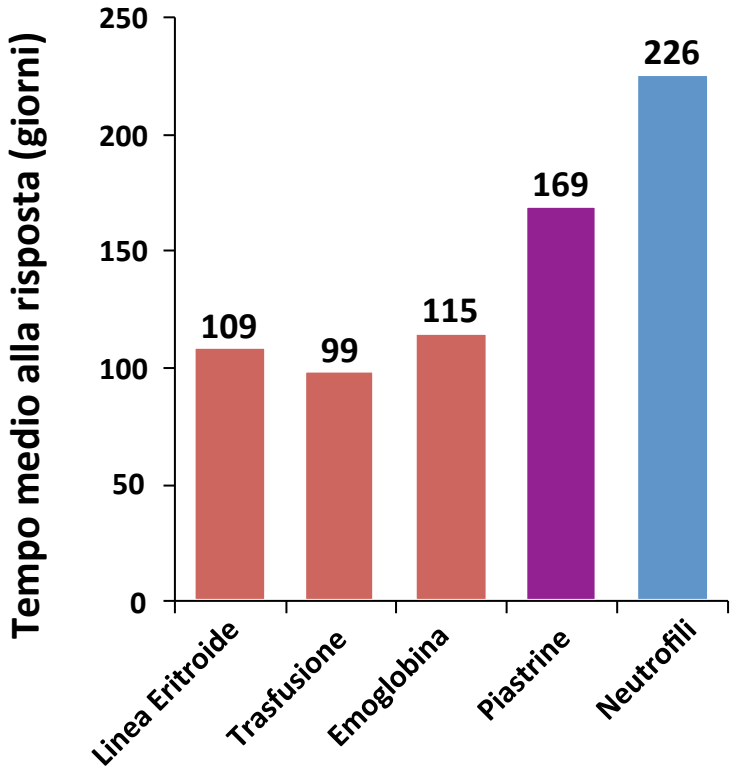
[1]Heinrich-Heine-Universität, Düsseldorf, Germany; [2]Policlinico S. Orsola-Malpighi, Bologna, Italy; [3]IRCCS Policlinico S. Matteo, Pavia, Italy; [4]Service d'hématologie Clinique, Hôpital Avicenne/Université Paris, Bobigny, France; [5]Medizinische Hochschule Hannover, Hannover, Germany; [6]CHU Brabois, Vandoeuvre Cédex, France; [7]Stadtspital Triemli, Zurich, Switzerland; [8]Mater Hospital, Brisbane, Australia; [9]Assistance Publique-Hôpitaux de Paris, Hôpital Cochin, Paris, France; [10]Novartis Pharmaceuticals, East Hanover, NJ, USA; [11]Novartis Pharma AG, Basel, Switzerland, and [12]Hôpital Saint-Vincent de Paul, Lille, France

Citation: Gattermann N, Finelli C, Della Porta M, Fenaux P, Stadler M, Guerci-Bresler A, Schmid M, Taylor K, Vassilieff D, Habr D, Marcellari A, Roubert B, and Rose C. Hematologic responses to deferasirox therapy in transfusion-dependent patients with myelodysplastic syndromes. Haematologica 2012;97(9):1364-1371. doi:10.3324/haematol.2011.048546

Risposta ematologica



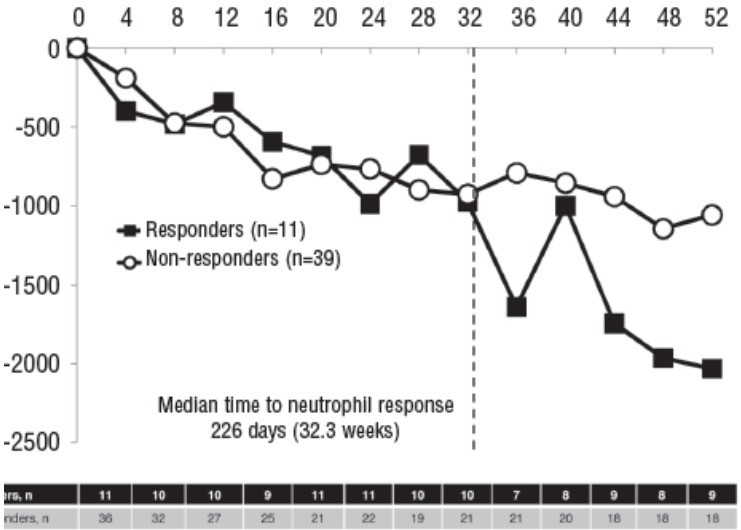
Tempo alla risposta ematologica



Gattermann N, et al. Haematologica 2012

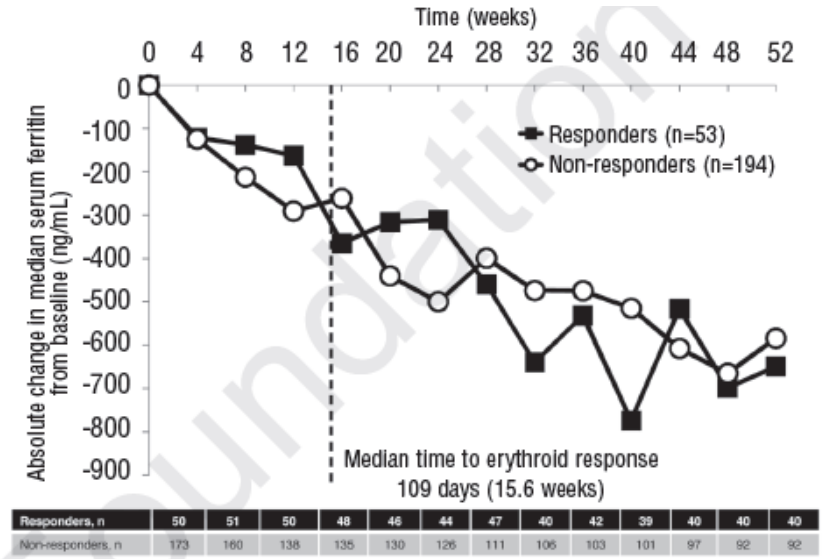
Ferritina Serica

Risposta Neutrofila



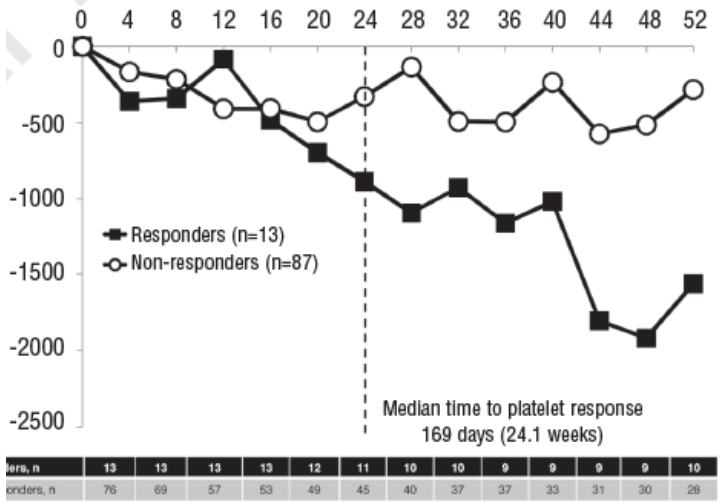
ers, n	11	10	10	9	11	11	10	10	7	8	9	8	9
nders, n	36	32	27	25	21	22	19	21	21	20	18	18	18

Risposta Eritroide



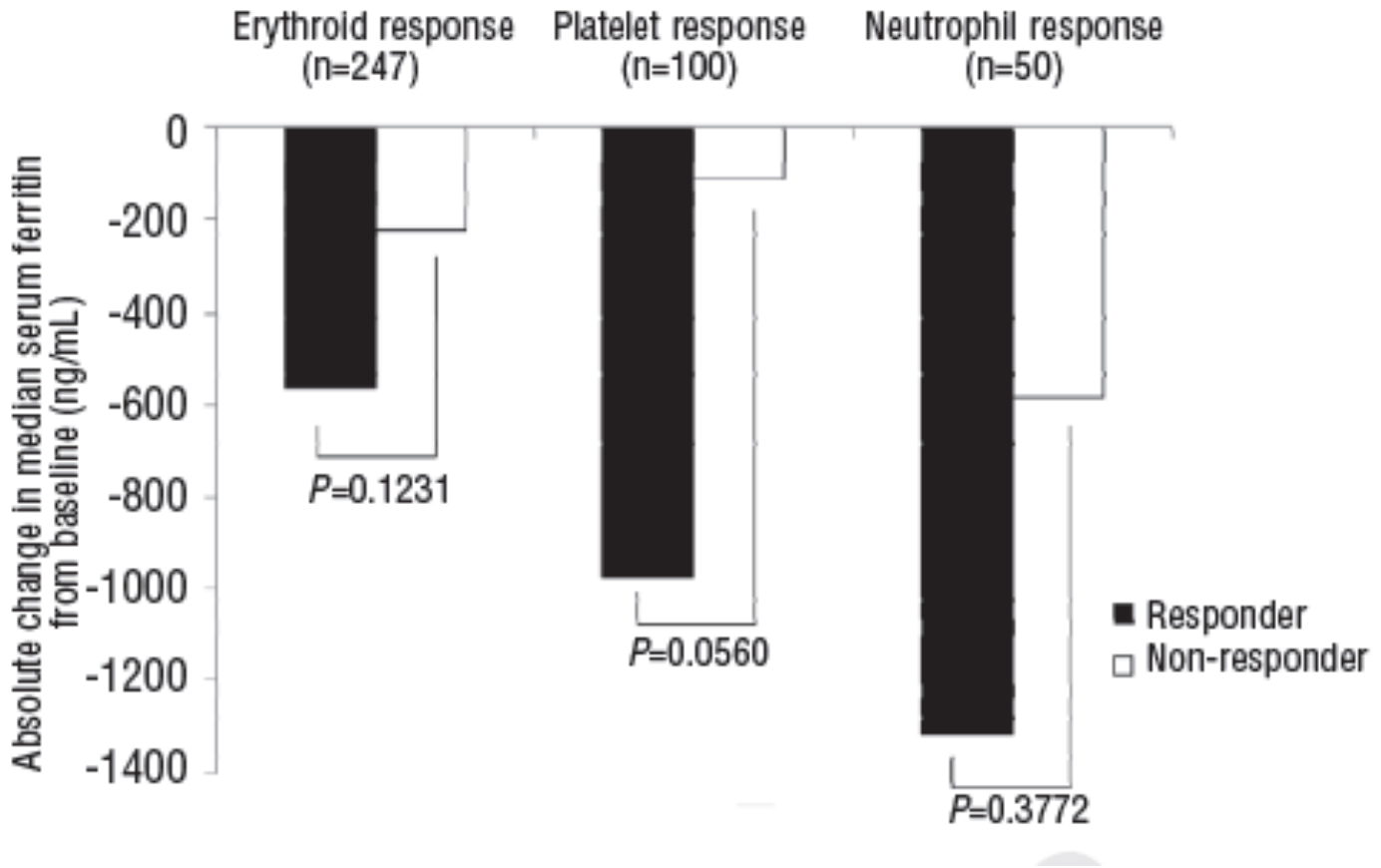
Responders, n	50	51	50	48	46	44	47	40	42	39	40	40	40
Non-responders, n	173	160	138	135	130	126	111	106	103	101	97	92	92

Risposta Piastrinica



ders, n	13	13	13	13	12	11	10	10	9	9	9	9	10
onders, n	76	69	57	53	49	45	40	37	37	33	31	30	28

Gattermann et al, Hematologica 2012



La risposta ematologica non correla direttamente con la riduzione della ferritina sierica

Gattermann et al, Hematologica 2012

VOLUME 30 · NUMBER 17 · JUNE 10 2012

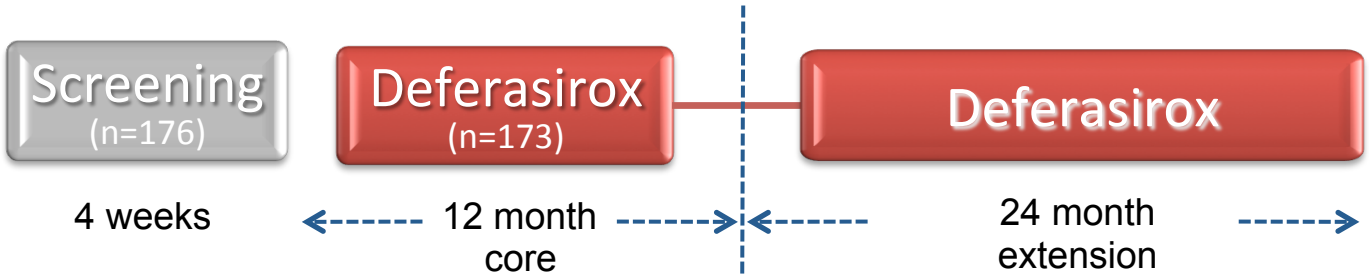
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

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

Alan F. List, Maria R. Baer, David P. Steensma, Azra Raza, Jason Esposito, Noelia Martinez-Lopez, Carole Paley, John Feigert, and Emmanuel Besa

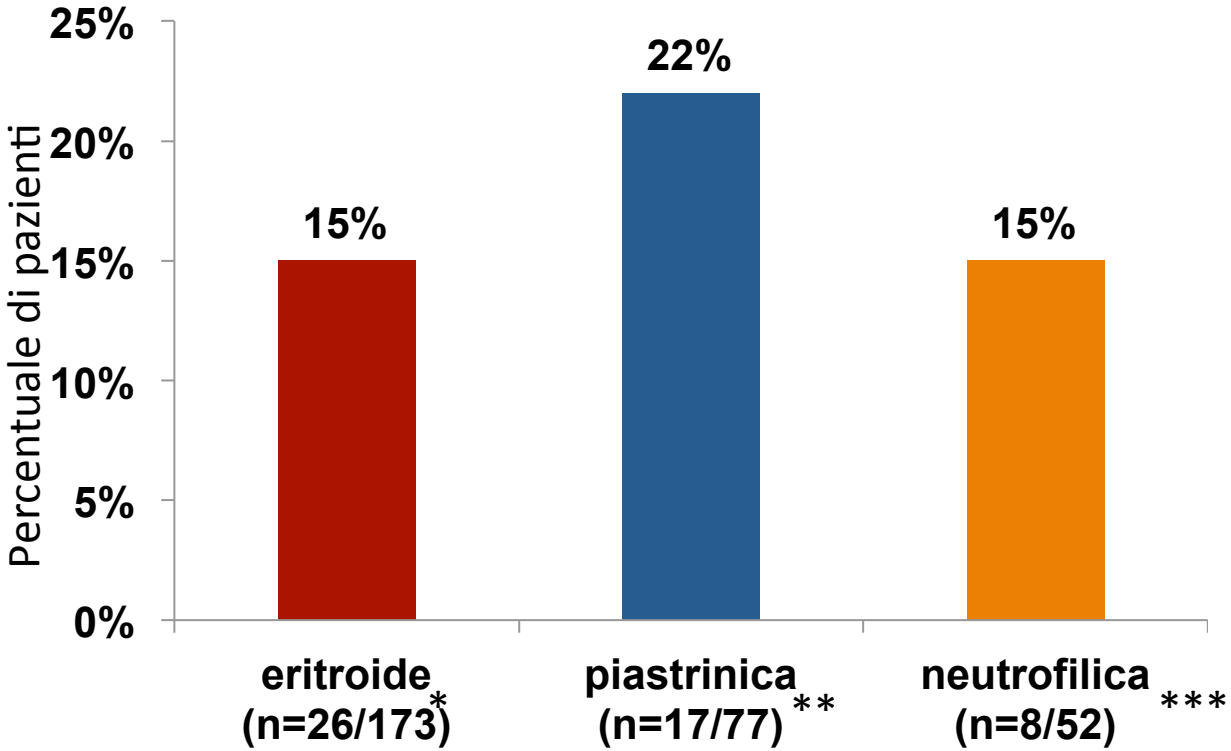
- Studio prospettico, multicentrico, di 3-aa, per stabilire sicurezza ed efficacia del deferasirox in 173 pazienti, con MDS a rischio basso o intermedio-1 (72%)
- Criteri di inclusione: almeno 20 unita' RBC, ferritina serica > 1,000 ng/mL.
- Accettabile creatinina aumentata fino a 2 volte il valore normale



Pazienti analizzati per risposta ematologica secondo criteri IWG 2006

N= 173

Durata risposta ≥8 settimane



Risposta ematologica

Tempo mediano alla risposta 169 gg (range 84-382)

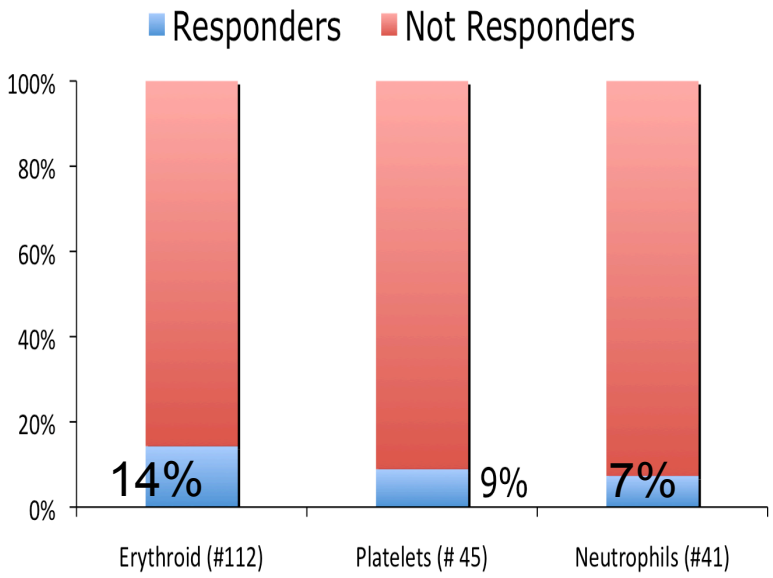
*1pz assumeva anche lenalidomide, 2 EPO

** 1 pz assumeva EPO+ AZA

*** 1 pz assumeva EPO, 1 EPO+decitabina, 1 lenalidomide

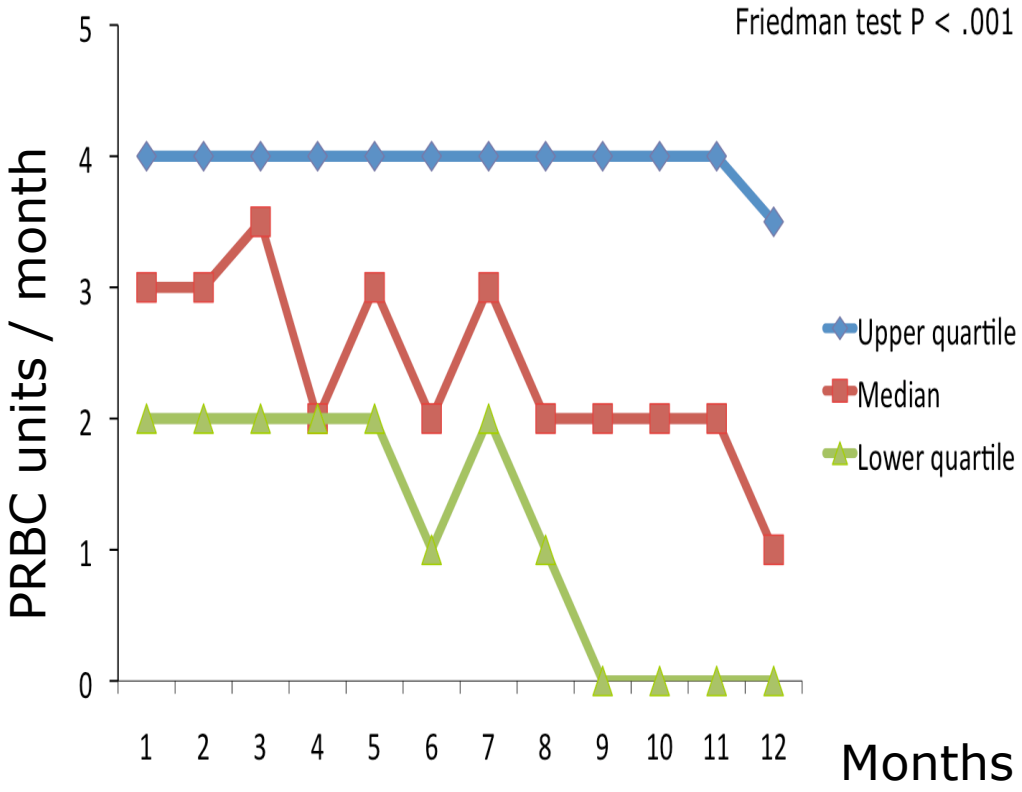
List AF, et al. J Clin Oncol 2012;30(17):2134-9

Risposta Ematologica



PRBC Units

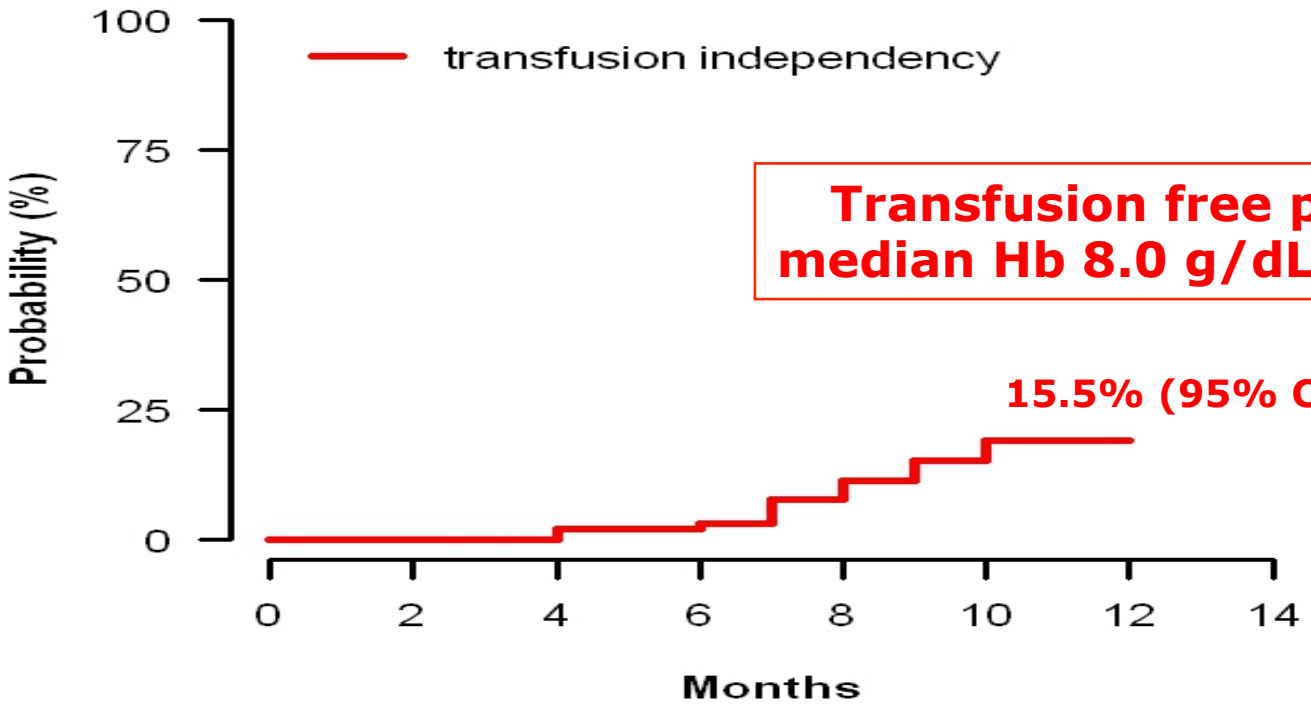
In 68 pts dopo 1 anno di trattamento



- Partendo da livelli paragonabili di Emoglobina pre-trasfusione, il fabbisogno trasfusionale si riduceva durante il trattamento [mediana PRBC/mese 3 (2-5) vs 1 (0-4) dopo 1 anno (P= 0.0001)]

Angelucci E et al. Eur J Haematol, 2014.

Probabilita' di Trasfusione-indipendenza



Transfusion free patients: median Hb 8.0 g/dL (7.3-8.6)

15.5% (95% CI 15.3–15.8)

- 22 pz TI, con una probabilita' del 5.5% (95%CI 5.4-5.6), 15.7% (95%CI 15.4-15.9) e 19.7% (95% CI 19.4-20) dopo 6, 9 e 12 mesi di trattamento.

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

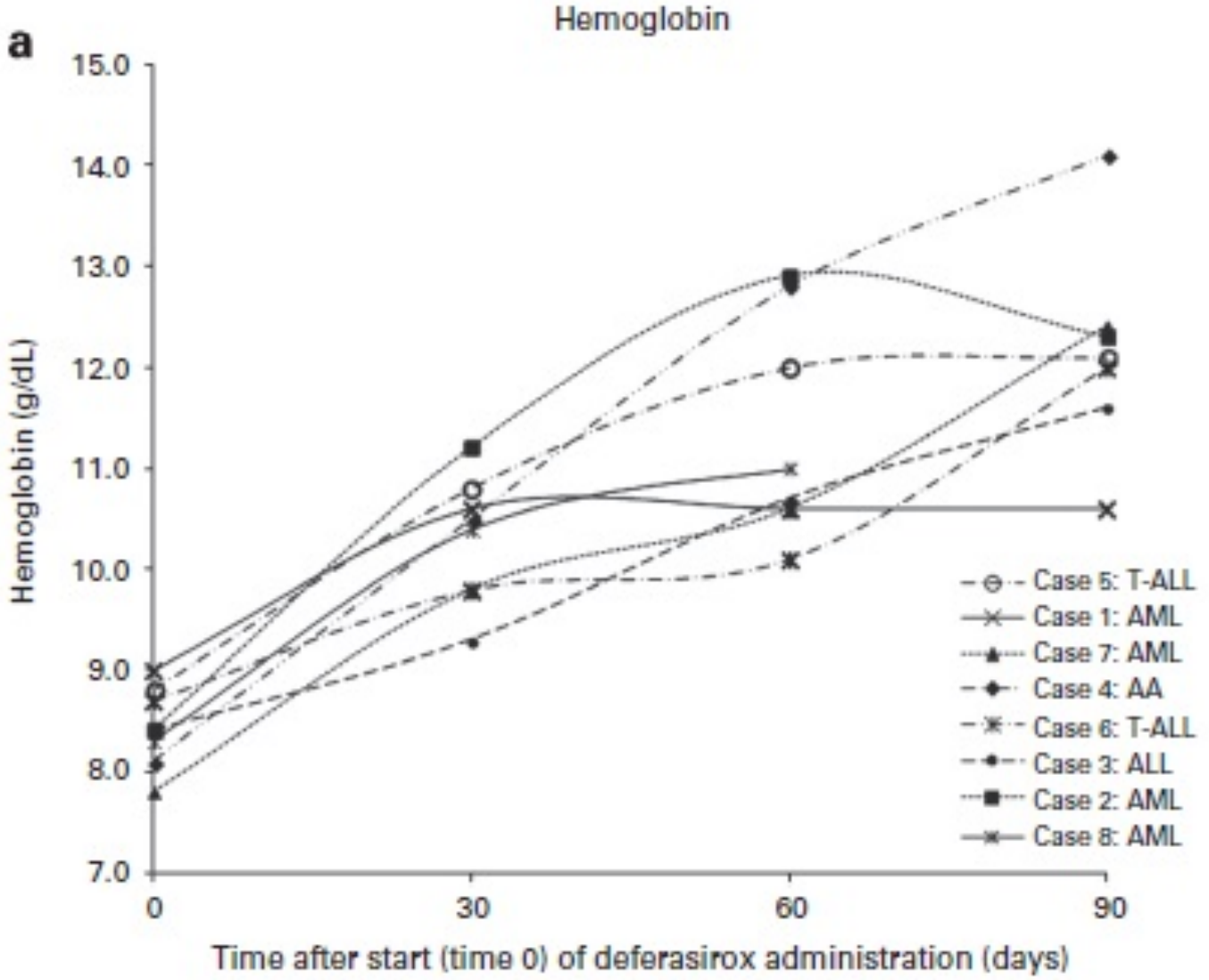
Angelucci E et al. Eur J Haematol, 2014.

Table 1. Characteristics of patients

Patient	*Disease*	*Conditioning regimen*	*Donor*	*DFX dosage (mg/day)*	*Time of first DFX dose after HSCT (months)*	*Median time (days) from first DFX dose to RBC independence*
Case 1	AML	BU 16 mg/kg Cy 120 mg/kg ATG[1] 7.5 mg/kg	MUD	500 for 10 days 500 every other day	10	20
Case 2	AML	BU 12.8 mg/kg Cy 120 mg/kg ATG[1] 7.5 mg/kg	MUD	500 reduced to 250	6	20
Case 3	ALL	TBI 12 Gy Cy 120 mg/kg ATG[1] 7.5 mg/Kg	MUD	500	5	30
Case 4	AA	Cy 200 mg/kg ATG[1] 7.5 mg/kg	MUD	750	3	30
Case 5	ALL	TBI 12 Gy Cy 120 mg/Kg	Sibling	500 for 2 weeks than 750	5	21
Case 6	ALL	TBI 12 Gy Cy 120 mg/kg ATG[1] 7.5 mg/Kg	MUD	500	6	28
Case 7	AML	BUn 12.8 mg/kg Cy 120 mg/kg	Sibling	250	4	21
Case 8	AML	BU 9.6 mg/kg Fludarabine 150 mg/kg	Sibling	250	5	25

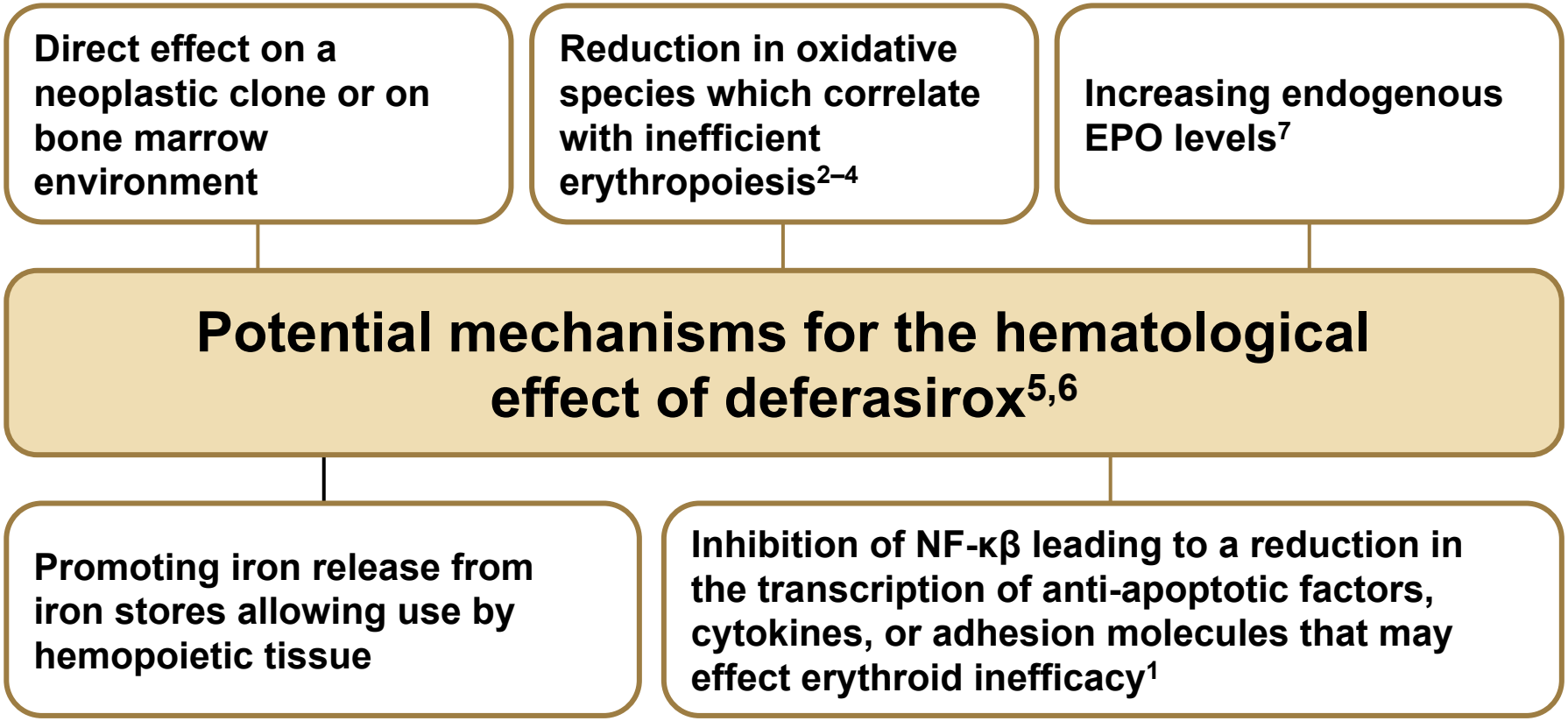
Abbreviations: AA = aplastic anemia; AML = acute myeloid leukemia; ALL = acute lymphoblastic leukemia; ATG = anti human thymocyte immunoglobulin (rabbit); BU = Busulphan; Cy = Cyclophosphamide; DFX = deferasirox; HSCT = hematopoietic stem cell transplantation; MUD = matched unrelated donor; TBI = total body irradiation.

Visani et al, Deferasirox improves hematopoiesis after allogeneic hematopoietic SCT. Bone Marrow Transplantation (2014)



Visani et al, Deferasirox improves hematopoiesis after allogeneic hematopoietic SCT. Bone Marrow Transplantation (2014)

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.

Increased Oxidative Stress in MDS

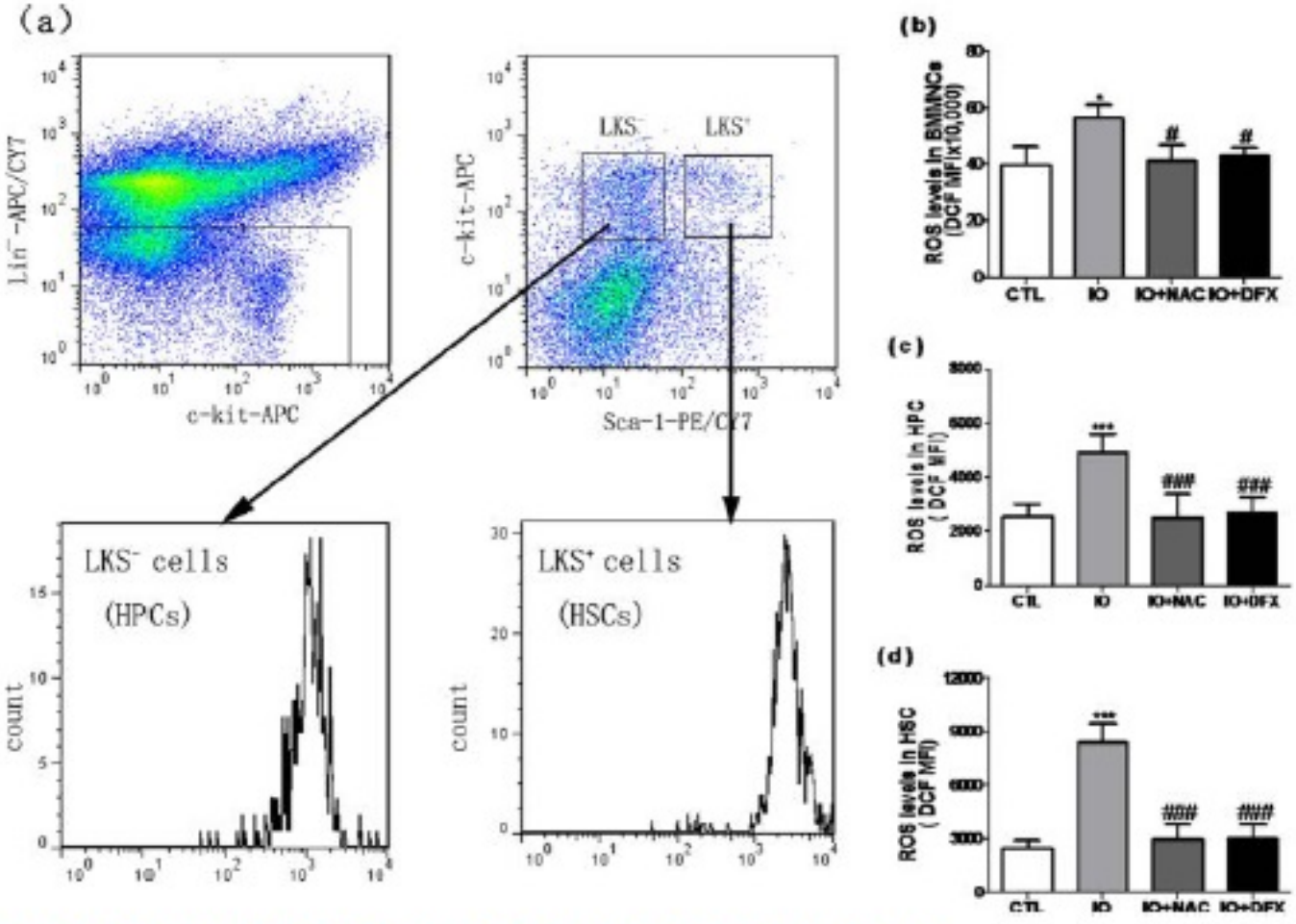
Bowen D, Wang L, Frew M, Kerr R, Groves M (2003)
Antioxidant enzyme expression in myelodysplastic and acute myeloid leukemia bone marrow: Further evidence of a pathogenetic role for oxidative stress?
Haematologica 88:1070-1072

Ghoti H, Amer J, Winder A, Rachmilewitz EA, Fibach E (2007)
Oxidative stress in red blood cells, platelets and polymorphonuclear leukocytes from patients with myelodysplastic syndrome.
Eur J Haematol 79:463-467

Novotna B, Bagryantseva Y, Siskova M, Neuwirtova R (2009)
Oxidative DNA damage in bone marrow cells of patients with low-risk myelodysplastic syndrome.
Leukemia Research 33:340-343

Ghoti H, Fibach E, Merkel LD, Perez-Avraham G, Grisariu S, Rachmilewitz E (2010)
Changes in parameters of oxidative stress and free iron biomarkers during treatment with deferasirox is iron-overloaded patients with myelodysplastic syndromes.
Haematologica 95:1433-1434

Iron overload enhanced intracellular ROS production.



Xiao Chai et al. ROS-mediated iron overload injures the hematopoiesis of bone marrow by damaging hematopoietic stem/progenitor cells in mice. Sci Rep. 2015; 5: 10181.

Research Article

Uptake of Non-Transferrin Iron by Erythroid Cells

Eugenia Prus and Eitan Fibach

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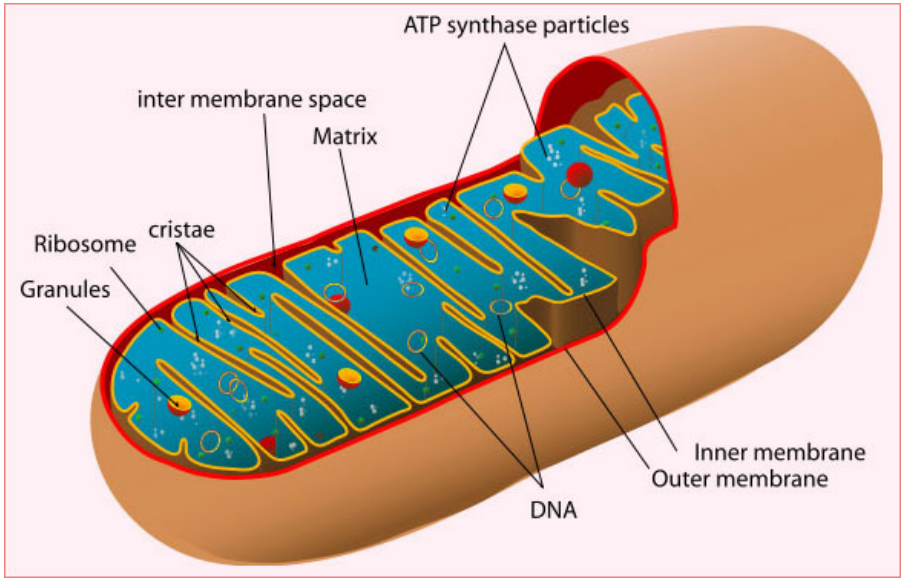
Received 20 September 2010; Accepted 7 November 2010

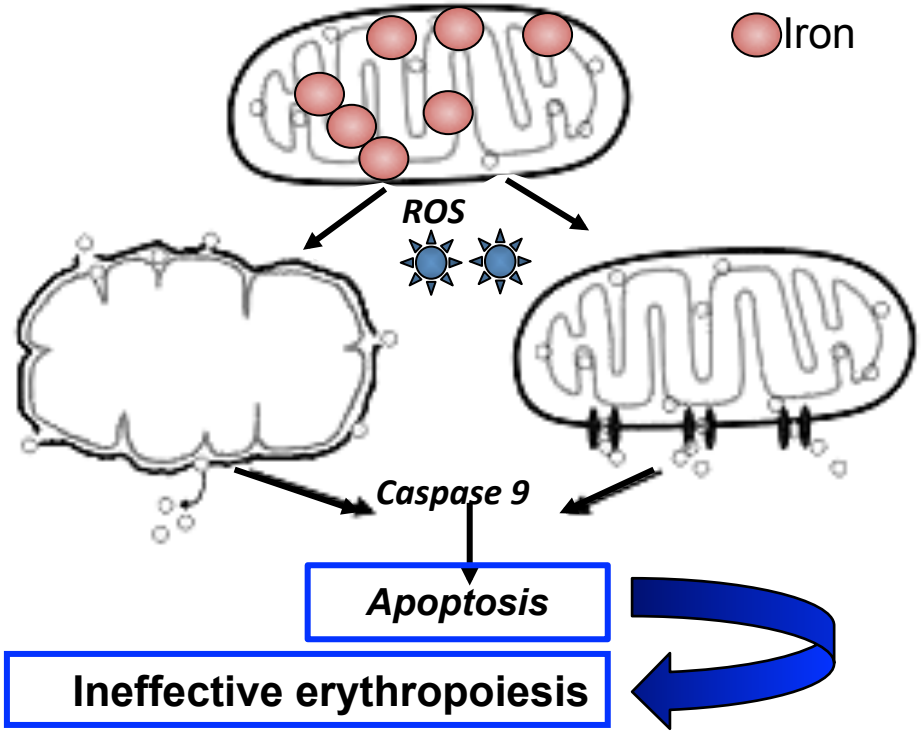
- RBCs, retics, and developing erythroid precursors take up iron through a Tf-independent pathway.
- This pathway is operative under pathological iron-overload situation in the presence of non-Tf iron in the serum.
- The incoming non-Tf iron does not participate in haeme synthesis and Hb production, but induces ROS generation, which results in cytotoxicity and a decrease in the erythroid cell yield.

ROS Promote Apoptosis through Activation of the Caspase Cascade

Iron is also a potentially toxic metal
Labile iron can catalyze the production of toxic radicals:

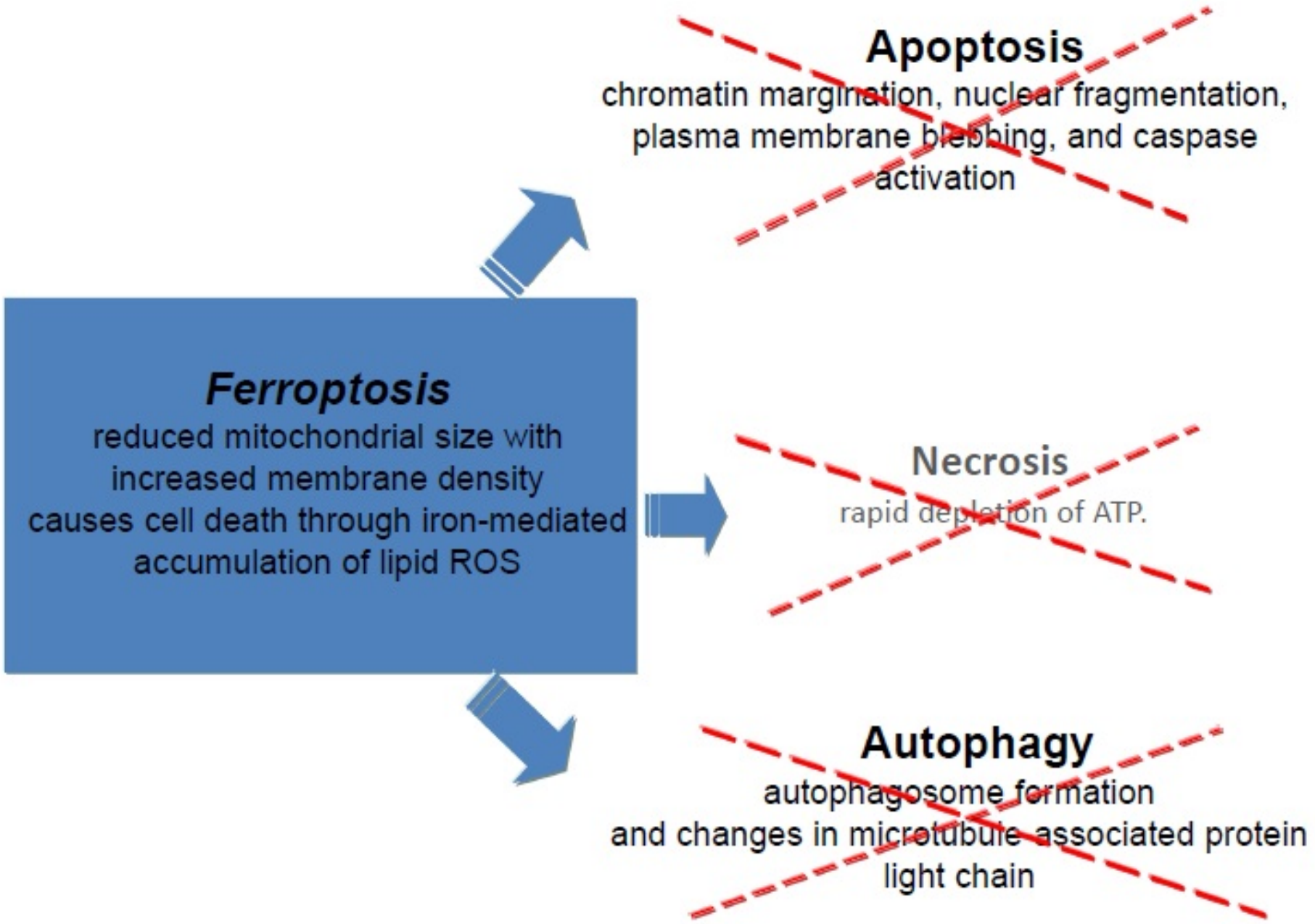
$$O_2^{\bullet -} + H_2O_2 \xrightarrow{Fe(II)} O_2 + OH^- + OH^{\bullet}$$ that can damage the cells



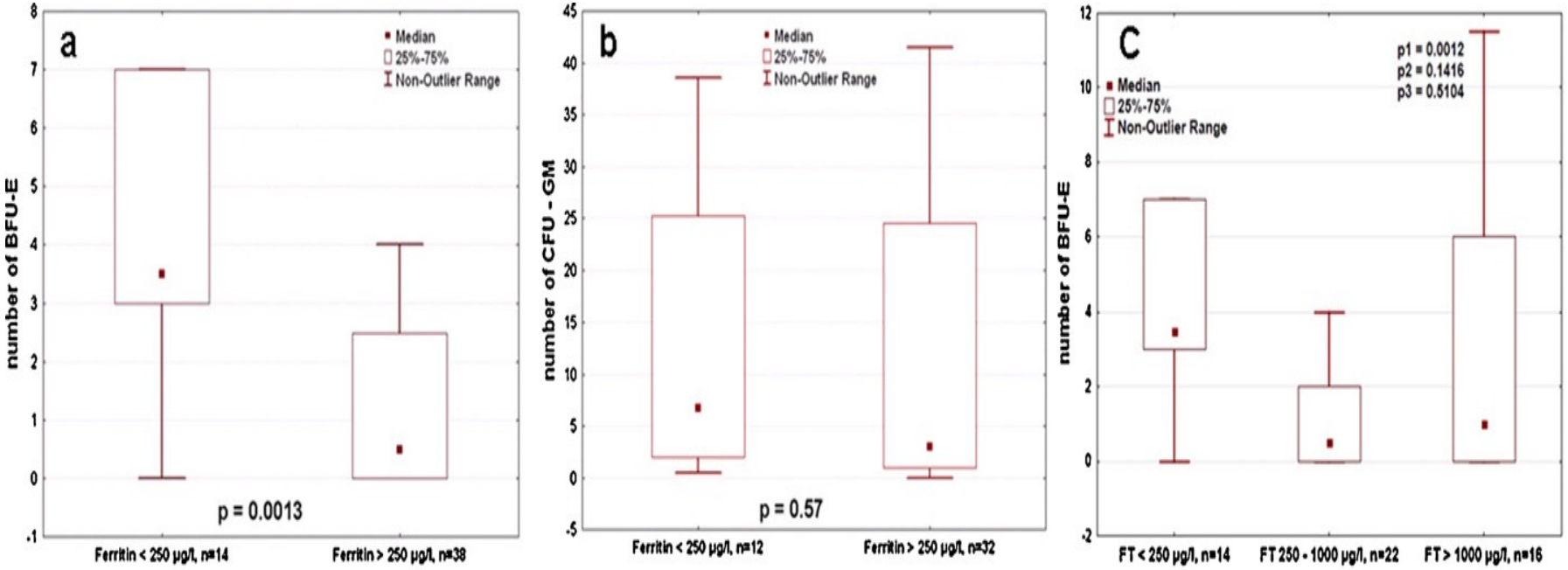


Zuo Y, *et al. Cell Res*. 2009;19:449-57.

Manz DH et al; Ann.N.Y.Acad.Sci Feb 2016



Iron overload suppresses the proliferation of erythroid progenitors cells (BFU-E)



"We demonstrate that iron overload suppresses the proliferation of erythroid progenitors cells (BFU-E), while the myeloid compartment (CFU-GM) was not found to be affected. Even patients with slightly elevated ferritin values show an impaired proliferation capacity in comparison to patients with normal ferritin levels. Furthermore, we show that this negative impact is reversible by sufficient iron chelation therapy."

J. Hartmann et al. / Leukemia Research *37 (2013) 327– 332*

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SCIENTIFIC REPORTS

OPEN

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Published: 13 May 2015

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

Xiao Chai[1,2], 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[1] & 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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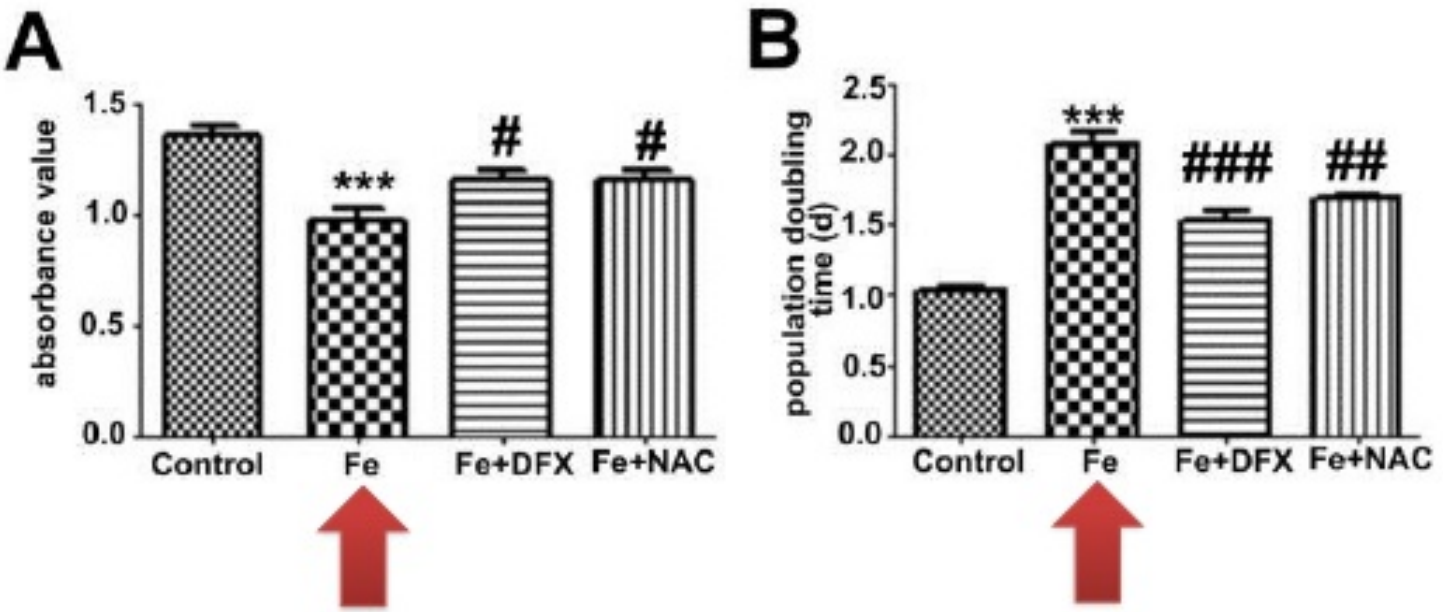
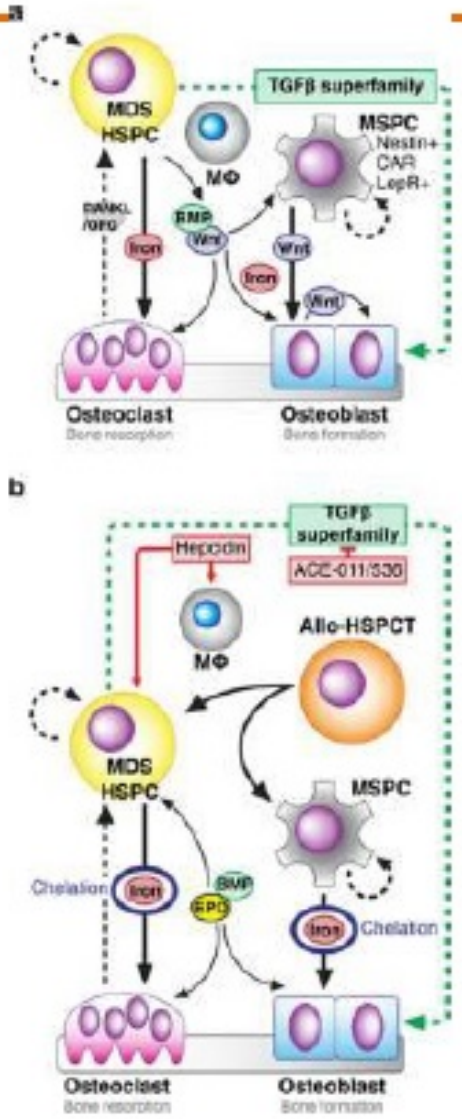
Yuchen Zhang et al.PLoS One. 2015; 10(3): e0120219
Effects of Iron Overload on the Bone Marrow Microenvironment in Mice

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.

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

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*

Ashish Banerjee,[1,2] Nicole A. Mifsud,[3] Robert Bird,[4,5] Cecily Forsyth,[6] Jeff Szer,[7] Constantine Tam,[8] Sybil Kellner,[9] Andrew Grigg,[10] Penelope Motum,[11] Mark Bentley,[12] Stephen Opat[13] and George Grigoriadis[1,2,13,14]

[1]*Centre for Cancer Research, MIMR PHI Institute of Medical Research,* [2]*Centre for Inflammatory Diseases, Monash University,* [3]*Departments of Medicine and Allergy, Immunology and Respiratory Medicine, Monash University, Clayton, Vic.,* [4]*Haematology, Princess Alexandra Hospital,* [5]*School of Medicine, Griffith University, Brisbane, Qld,* [6]*Haematology, Jarrett Street Specialist Centre, North Gosford, NSW,* [7]*Clinical Haematology, Royal Melbourne Hospital, Melbourne,* [8]*Haematology, Peter MacCallum Cancer Centre, East Melbourne, Vic.,* [9]*Haematology, Cotton Tree Specialist Centre, Cotton Tree, Qld,* [10]*Department of Clinical Haematology, Austin Hospital, Heidelberg, Vic.,* [11]*Haematology Department, Liverpool Hospital, Liverpool, NSW,* [12]*Haematology, Queensland Haematology and Oncology Group, Brisbane, Qld,* [13]*Clinical Haematology, Monash Health, Clayton, Vic., and* [14]*Department of Haematology, Alfred Health, Melbourne, Australia*

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.

Banerjee, Br J Haematol 2015

The starting dose of deferasirox is set based on transfusion requirement

Recommended deferasirox dose	→	20 mg/kg/day

Starting doses may also be modified as follows

Transfusion requirement	Therapeutic goal	Deferasirox dose
pRBC > 14 mL/kg/month (~4 adult units)	Reduction of body iron	30 mg/kg/day
pRBC > 7 mL/kg/month (~2 adult units)	Maintenance of body iron	10 mg/kg/day

For patients well managed on deferoxamine, suggested starting dose may be numerically half the deferoxamine dose, e.g.

DFO 40 mg/kg/day for 5 days per week	→	Deferasirox 20 mg/kg/day

Deferasirox Summary of Product Characteristics.

During iron chelation therapy

- Dose adjustments[1]
  - every 3 to 6 months during deferasirox therapy, based on the trends in serum ferritin
  - tailored to the individual patient's response (including presence of adverse events) and therapeutic goals
  - in steps of 5 to 10 mg/kg

- Monitor patient adherence regularly

1. Deferasirox Summary of Product Characteristics.

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]

[a] Department of Hematology and Oncology, University Hospital Mannheim, Medical Faculty Mannheim of the University of Heidelberg, Germany
[b] Hematology and Bone Marrow Transplant Unit, and Medical Oncology Department, Ospedale Oncologico "Armando Businco", Cagliari, Italy
[c] Department of Cellular Biotechnologies and Hematology, "La Sapienza" University, Rome, Italy
[d] Comprehensive Cancer Center and Department of Hematology, Oncology, and Clinical Immunology, Heinrich Heine University, Düsseldorf, Germany
[e] Division of Hematology, University of Florence, Florence, Italy
[f] Department of Hematology, Institute Paoli Calmettes, Marseille, France

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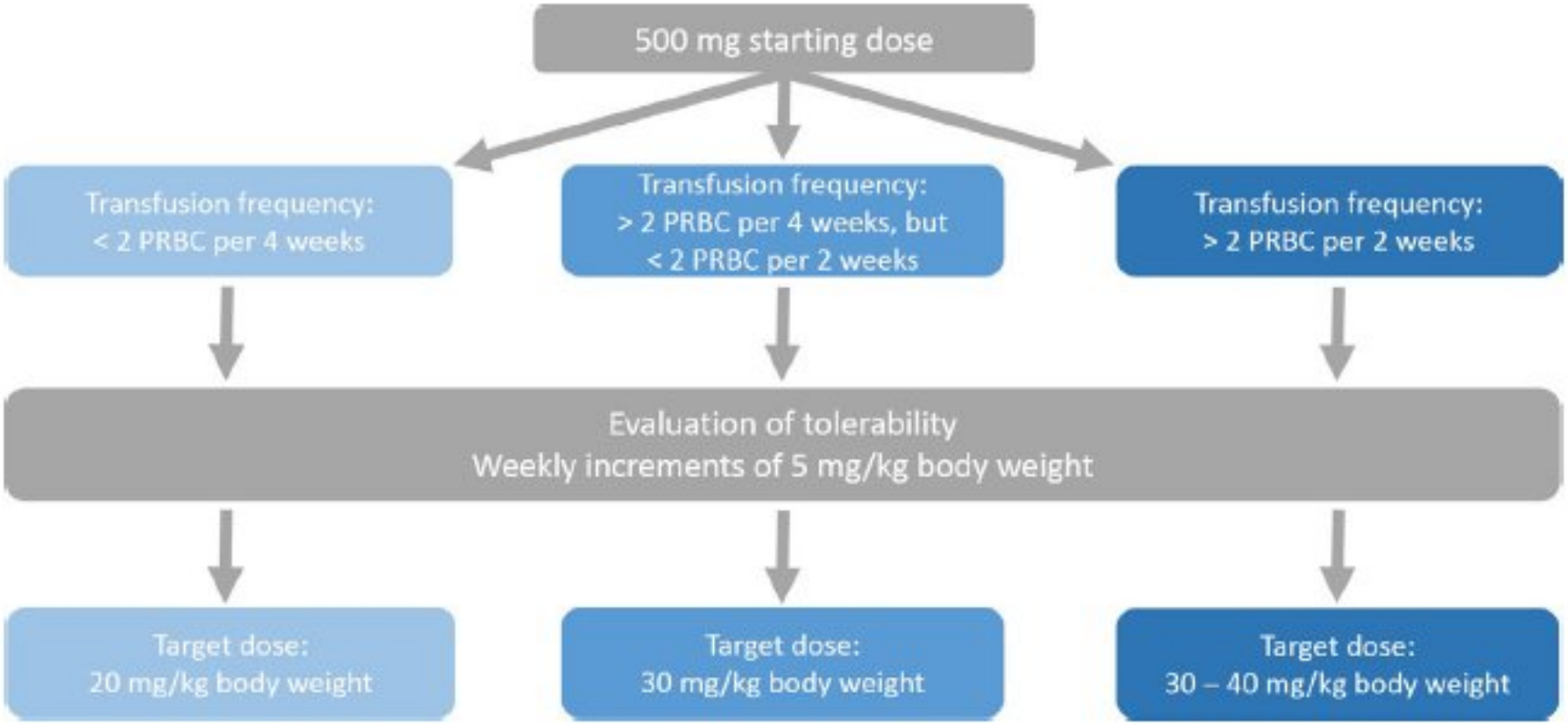
Nolte, Leuk Res 2015



Nolte, Leuk Res 2015

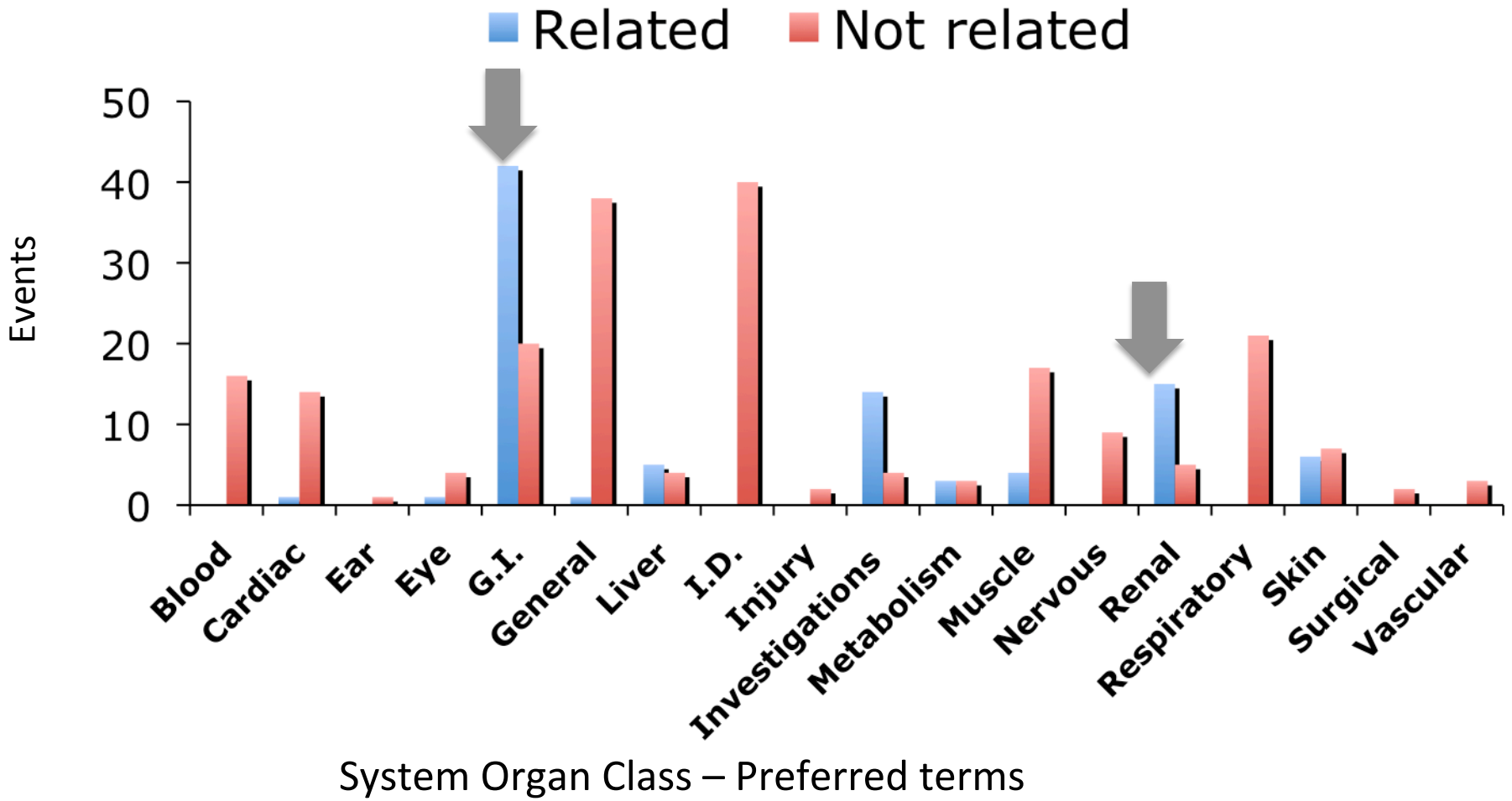
Frequency of adverse events (AEs) during deferasirox treatment

AE	Frequency (% patients)	Observations
Non-progressive increase in serum creatinine	36	Mild, mostly within normal range; dose dependent, often resolve spontaneously; may be alleviated by dose reduction
Gastrointestinal disturbance (nausea, vomiting, diarrhea, abdominal pain)	26	Dose-dependent, mostly mild to moderate, generally transient and self-limiting even with continued therapy
Skin rash	7	Dose-dependent, mostly mild to moderate, generally transient and self-limiting with continued therapy
Elevation in liver transaminases	2	Most patients had elevated levels prior to deferasirox treatment Elevations >10 x ULN were uncommon (0.3%)
High-frequency hearing loss and lenticular opacities	≤1	Uncommonly observed with patients taking deferasirox

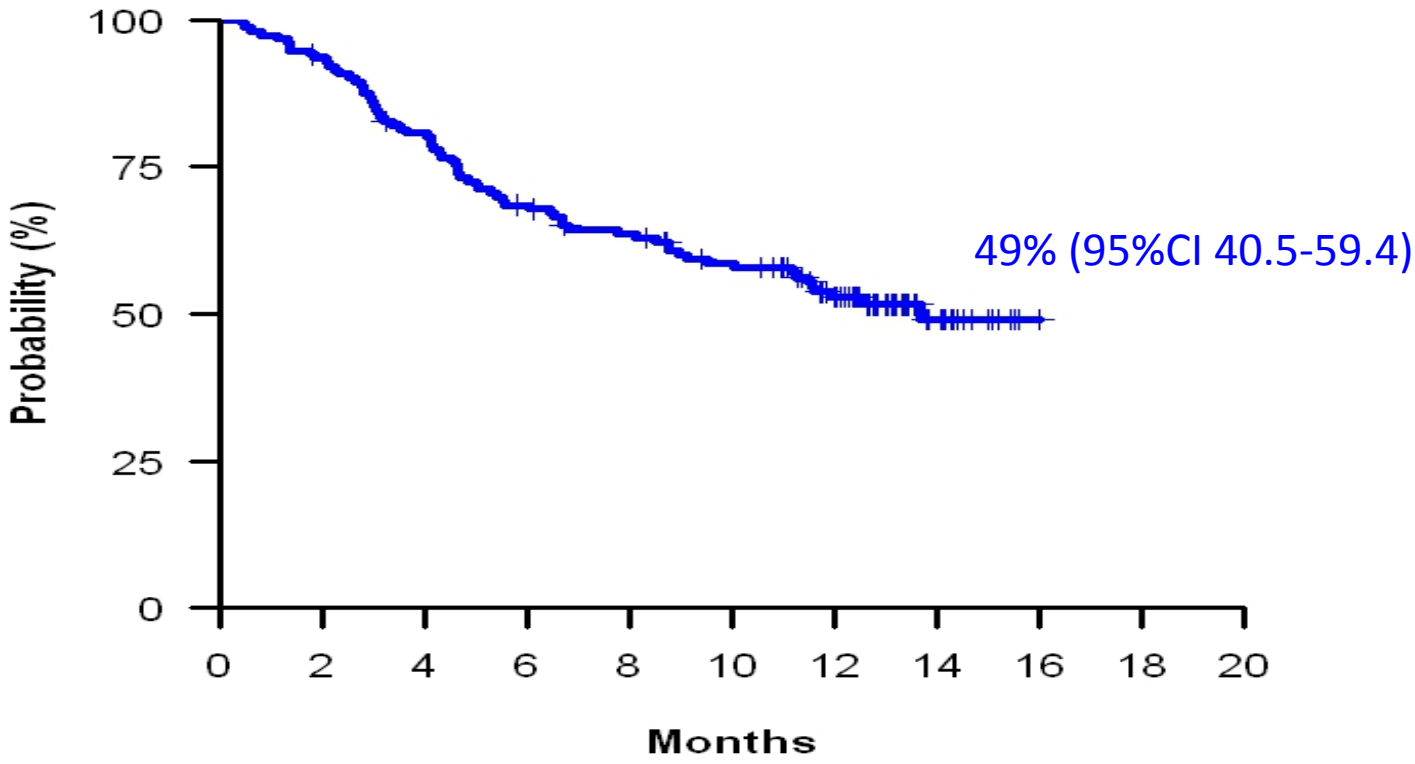
EXJADE® (deferasirox) Core Data Sheet 2011. Novartis Pharma AG. National Prescribing Information should be followed

Adverse events

System Organ Class classification of related and not related AEs



K-M probability of continuing therapy



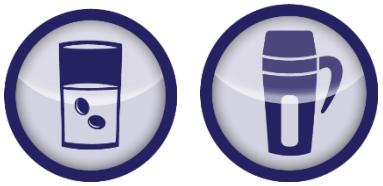
Causes of therapy discontinuation

Cause	Patients	%	
Adverse Event	28	33.3	33%
Death	22	26.2	36%
Disease progression	8	9.5	
Consent withdrawal	9	10.7	31%
Lost at follow up	8	9.5	
No response	2	2.4	
Serum ferritin < 500 ng/ml (no PRBC)	2	2.4	
Medical decision	5	6.0	
Total	84	100	

Deferasirox

Film-Coated Tablets-FTC

Rationale of deferasirox FCT



- Deferasirox DT for oral suspension:[1]
  - a lengthy mixing process
  - consumption on an empty stomach
  - patient education on how to mix and properly take deferasirox DT
  - risk of patient failing to consume full dose

- The palatability of deferasirox DT:
  - was more favorable during the assessment phase
  - with 47% of patients ratings for palatability being favorable while[2]
  - only 38% were favorable during the run-in phase[2]

Different administration options may improve palatability and GI tolerability, which could have a positive impact on treatment adherence[2].

1. Exjade. Riassunto delle Caratteristiche del Prodotto. Aprile 2016.
2. Goldberg SL, et al. *Pediatr Blood Cancer.* 2013;60(9):1507-1512.

Indications

Deferasirox Film-Coated Tablets (FCT): Strength-Adjusted Formulation of deferasirox Tablets (DT) for Oral Suspension

Deferasirox FCT

- contains the **same active ingredient** as deferasirox DT[1,2]
- deferasirox FCT should be **swallowed** once daily with water or other liquids[2]
- film-coated tablets may be taken with or without a **light** meal*[2]
- does not contain sodium lauryl sulfate or lactose as does deferasirox DT[3+]
- lactose possibly implicated in GI side effects[3]

*<7% fat content and approximately 250 kilo calories (1046 kilo joules). Excludes foods with a high-fat content

Lactase deficit [4]:

- found in 40% of Italian population
- remarkably high level in Naples area
- increasing trend from North to South Italy, where hemoglobin disorders such as thalassemia are most common[5]

1. Exjade. Riassunto delle Caratteristiche del Prodotto. Aprile 2016
2. Deferasirox FCT. Summary of Product Characteristics. www.ema.europa.eu/docs/it_IT/document_library/EPAR_-_Product_Information/human/000670/WC500033925.pdf
3. Chalmers AW et al.Ther Clin Risk Manag 2016; 12: 201-2018
4. Franzè A et al. *Rivista della Società di Medicina Generale* 2010; 3: 36-40.
5. Cataldo F. *Ital J Pediatr* 2012; 38: 32.

Differences Across Deferasirox Formulations

Appearance, Excipient Composition, and Administration

Deferasirox FCT

(EMA Approval in 2016)

Tablets are ovaloid in shape

Tablet color ranges from light to dark blue, depending on strength

Tablets do not contain lactose or sodium lauryl sulfate (SLS)

Tablets are swallowed whole with liquid

Can be taken with or without a light meal

Deferasirox Tablets for Oral Suspension

(EMA Approval in 2006)

Tablets are circular in shape and white in color

Tablets contain lactose and SLS

Administration procedure:

- Disperse in orange juice, apple juice, or water
- Stir until tablets are dissolved completely
- Drink the entire solution immediately
- Any remaining DFX DT should be re-suspended in a small volume of liquid and taken immediately

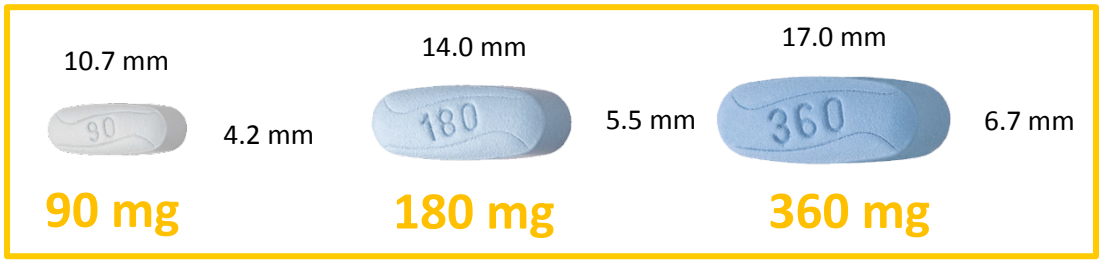
Must be taken on an empty stomach (at least 30 min before food)

Exjade. Riassunto delle Caratteristiche del Prodotto. Aprile 2016

Pharmaceutical technique

Innovation of deferasirox FCT formulation

- The choice of excipients used was based on compatibility test[1].
- Excipients were chosen to optimize the dissolution profile and stability whilst minimizing adverse effects[1,2].
- The film-coated tablets do not contain lactose which will ensure better acceptance in lactose-intolerant patients[1,2].
- The film-coated tablets require less disintegrant as they are intended to be swallowed rather than dispersed[1,2].
- As a result, the percentage of active substance in the deferasirox FCT formulation increased, resulting in smaller tablets that are easier to swallow[1].



Images do not reflect actual sizes of deferasirox FCT

The deferasirox FCT and DT formulations have similar pharmacological parameters[3].

1. Exjade. EMA Assessment Report. 28 January 2016
2. Deferasirox FCT. Summary of product Characteristics. www.ema.europa.eu/docs/it_IT/document_library/EPAR_-_Product_Information/human/000670/WC500033925.pdf
3. Chalmers AW et al.Ther Clin Risk Manag 2016; 12: 201-2018.

Deferasirox dosing and administration

Deferasirox DT

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

- **Multistep preparation may conflict with daily activities**
- **Restrictions on taking with food**
- **Palatability issues can make administration a challenge**

Deferasirox FCT

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

- **No preparation or mixing required**
  For pts who are unable to swallow a whole tablet, it may be crushed and sprinkled on soft food
- **May be taken with a light meal**
- **Does not contain lactose and sodium lauryl sulfate**

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

Main clinical pharmacological acquisitions

- DFX Film Coated tablet showed comparable PK to the DFX dispersible tablet but the peak serum concentration (C_{max}) were approximately 30% higher.[1]
- DFX Film Coated tablet is also 36% more bioavailable than the DFX dispersible tablet.[1]
- Therefore, when converting a patient from DFX dispersible tablets for oral suspension to DFX Film Coated tablets, the dosage should be decreased by 30%.[1]
  - For instance, a patient who is receiving DFX dispersible tablet at a dose of 30 mg/kg/day should be given DFX Film Coated tablets at 21 mg/kg/day

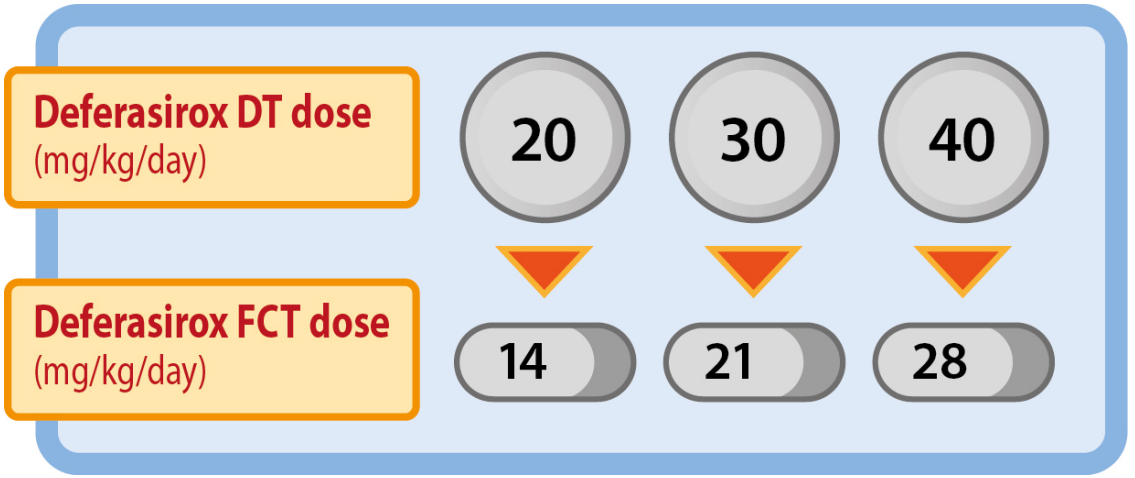
Deferasirox tablets for oral suspension	Nuova formulazione compresse rivestite con film
10 mg/kg/day 20 mg/kg/day* 30 mg/kg/day 40 mg/kg/day	7 mg/kg/day 14 mg/kg/day* 21 mg/kg/day 28 mg/kg/day

Note: * Recommended starting dose.

1. Chalmers AW et al.Ther Clin Risk Manag 2016; 12: 201-2018.

Deferasirox DT dose conversion to deferasirox FCT

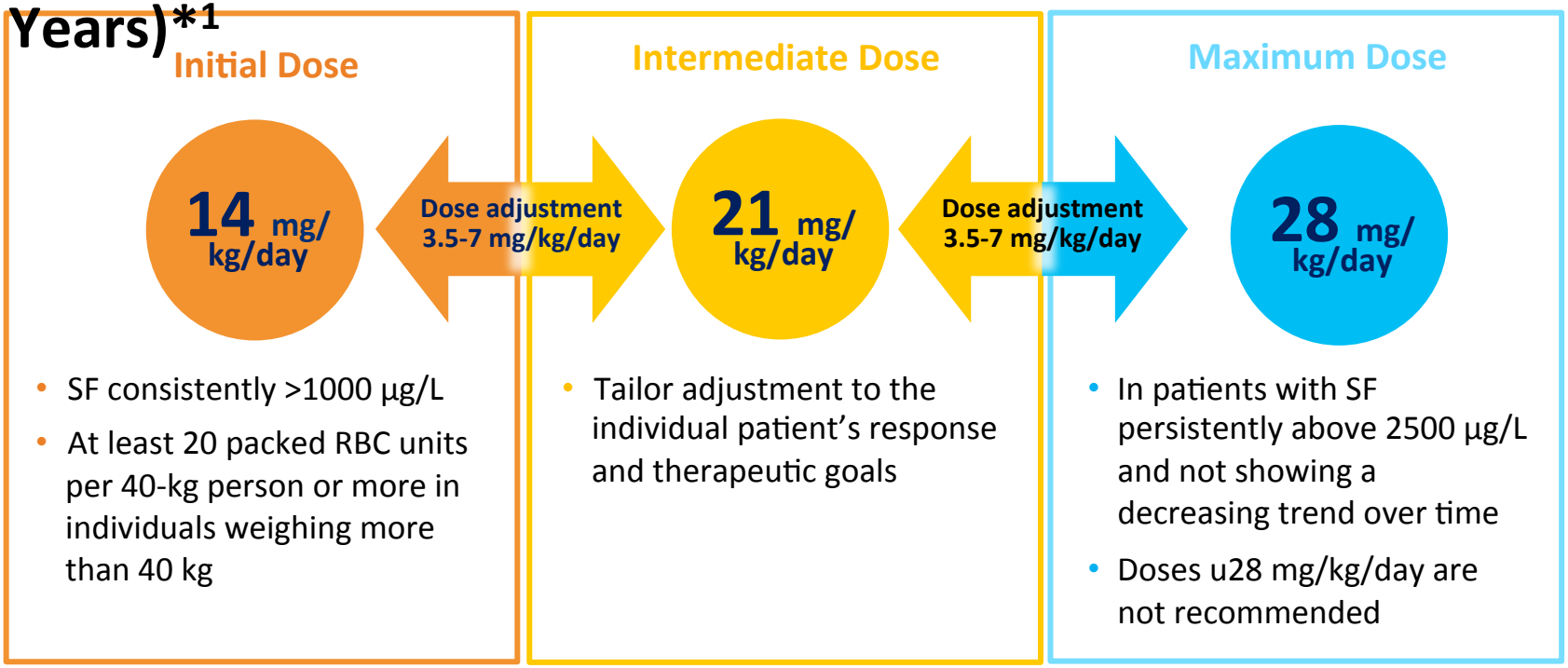
- For patients who are currently receiving chelation therapy with deferasirox DT and converting to deferasirox FCT, the dose of deferasirox FCT should be about 30% lower, rounded to the nearest whole tablet, because of higher bioavailability[1]
- For example, if a patient is currently taking deferasirox DT at 20 mg/kg/day, their dosage with deferasirox FCT should be 14 mg/kg/day[2]



1. 1. Deferasirox FCT. Summary of Product Characteristics. www.ema.europa.eu/docs/it_IT/document_library/EPAR_-_Product_Information/human/000670/WC500033925.pdf
2. Chalmers AW et al.Ther Clin Risk Manag 2016; 12: 201-2018.

Dosage

Deferasirox FCT dosage and administration: patients with transfusional hemosiderosis (aged ≥2 Years)*[1]



Titrate to the appropriate dose based on patient iron burden, tolerability, treatment goals, and treatment response

*Dosing recommendations for deferasirox FCT differ for patients with NTDT syndromes. In these patients, starting dosage is 7 mg/kg/day and the maximum dosage is 14 mg/kg/day.

RBC, Red Blood cells

1. Deferasirox FCT. Summary of Product Characteristics. www.ema.europa.eu/docs/it_IT/document_library/EPAR_-_Product_Information/human/000670/WC500033925.pdf

Reminder (2/2)

Method of administration

For oral use.

- The film-coated tablets should be swallowed whole with some water.

- For patients who are unable to swallow whole tablets, the film-coated tablets may be crushed and administered by sprinkling the full dose onto soft food, e.g. yogurt or apple sauce (pureed apple). The dose should be immediately and completely consumed, and not stored for future use.

- The film-coated tablets should be taken once a day, preferably at the same time each day, and may be taken on an empty stomach or with a light mea.

1. Exjade. Riassunto delle Caratteristiche del Prodotto. Aprile 2016
2. Deferasirox FCT. Summary of Product Characteristics. www.ema.europa.eu/docs/it_IT/document_library/EPAR_-_Product_Information/human/000670/WC500033925.pdf

Received: 19 August 2016 | Revised: 23 January 2017 | Accepted: 26 January 2017

DOI: 10.1002/ajh.24668

RESEARCH ARTICLE

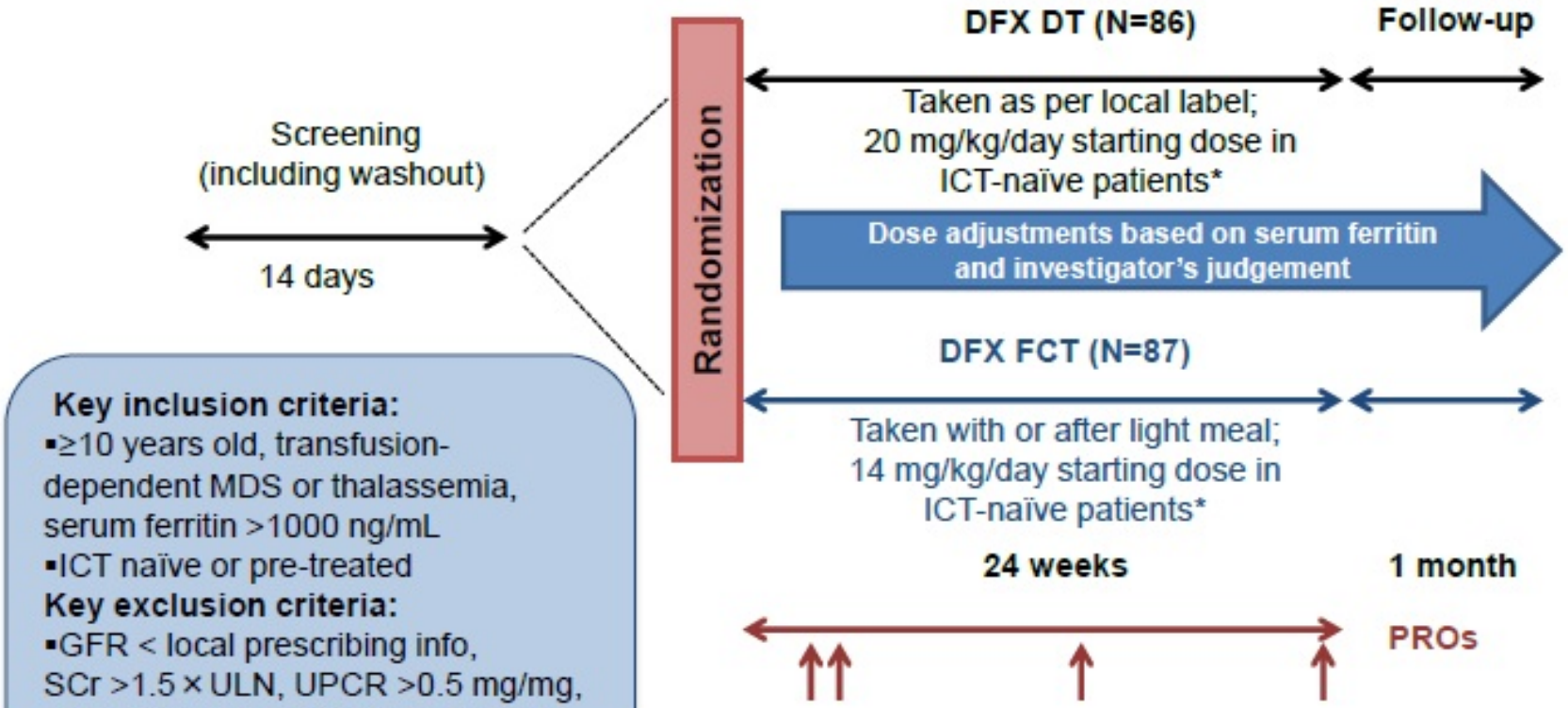
WILEY

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

Ali T. Taher[1] | Raffaella Origa[2] | Silverio Perrotta[3] | Alexandra Kourakli[4] | Giovan Battista Ruffo[5] | Antonis Kattamis[6] | Ai-Sim Goh[7] | Annelore Cortoos[8] | Vicky Huang[8] | Marine Weill[9] | Raquel Merino Herranz[9] | John B. Porter[10]

Am J Hematol. 2017;92:420–428.

ECLIPSE was an open-label, randomized, multicenter, two-arm, Phase II study



Key inclusion criteria:
- ≥10 years old, transfusion-dependent MDS or thalassemia, serum ferritin >1000 ng/mL
- ICT naïve or pre-treated

Key exclusion criteria:
- GFR < local prescribing info, SCr >1.5 × ULN, UPCR >0.5 mg/mg, ALT >5 × ULN, impaired GI function

- PRO questionnaires were completed at weeks 2, 3, 13, and ≤7 days of last dose
- GI symptom diary was completed daily

*Pre-treated patients received DT or FCT dose equivalent to their pre-washout dose. ALT, alanine aminotransferase; GFR, glomerular filtration rate; GI, gastrointestinal ; ICT, iron chelation therapy; PRO, patient-reported outcome; SCr, serum creatinine; ULN, upper limit of normal; UPCR, urine protein to creatinine ratio

Most patients had transfusion-dependent thalassemia

Disease history	DFX DT N=86	DFX FCT N=87	Total N=173
Types of anemia, n (%)			
Myelodysplastic syndromes (MDS)	16 (18.6)	16 (18.4)	32 (18.5)
MDS with very low risk as per the IPSS-R	1 (1.2)	5 (5.7)	6 (3.5)
MDS with low risk as per the IPSS-R	8 (9.3)	10 (11.5)	18 (10.4)
MDS with INT risk as per the IPSS-R	7 (8.1)	1 (1.1)	8 (4.6)
Transfusion-dependent thalassemia	70 (81.4)	70 (80.5)	140 (80.9)
Missing	0	1 (1.1)	1 (0.6)

- Mean ± SD time since diagnosis was 21.1 ± 11.66 years

Time since the diagnosis (years) = (Screening visit 1 date – date of diagnosis +1) / 365.25
IPSS-R, International Prognostic Scoring System, Revised

Assessment of overall safety

Summary of adverse events by severity and treatment

	DFX DT N=86		DFX FCT N=87	
Category	n (%)	95% CI	n (%)	95% CI
Any AEs	77 (89.5)	81.1, 95.1	78 (89.7)	81.3, 95.2
Mild	69 (80.2)	70.2, 88.0	71 (81.6)	71.9, 89.1
Moderate	48 (55.8)	44.7, 66.5	45 (51.7)	40.8, 62.6
Severe	22 (25.6)	16.8, 36.1	17 (19.5)	11.8, 29.4

Overall, 89.5% of patients in the DFX DT and 89.7% of patients in the DFX FCT arm had at least one AE during the treatment period
Fewer moderate and severe AEs were experienced with DFX FCT

PRO instruments specifically measured health outcomes for deferasirox chelation therapy

- **Modified Satisfaction with Iron Chelation Therapy** (modified SICT) assessed domain scores for:
  - Adherence (six questions)
  - Satisfaction/preference (two questions)
  - Concern (three questions)
- **Palatability questionnaire** (taste, aftertaste, ability to consume medicine, perception of medicine)
- **GI tolerability diary** (pain in your belly, nausea, vomiting, constipation, diarrhea)

The PRO instruments are fully validated – qualitative, linguistic and psychometric evaluation[1]

1. Huang VW *et al. International Society for Pharmacoeconomics and Outcomes Research (ISPOR-EU) 19th Annual European Congress, Vienna, Austria October* 2016;PCN210

Overall PRO conclusions

- Patients were satisfied with both FCT and DT during the study period
- There was a clear preference in favor of FCT in all domains for the modified SICT (a clinically meaningful difference in these PRO instruments is >1 point)
- FCT patients showed good satisfaction on palatability score
- GI issues were generally not a major concern for the overall patient population in this study
  - The FCT arm showed numerically lower GI summary scores

Why assess iron loading in MDS?

- To verify effective iron overload
- To predict organ damage from iron overload
  - what is the evidence linking each measure to outcome?
  - Time lapse to eventually develop damage ??
- To monitor cellular damage from iron overload

Diagnostic tools for the evaluation of body iron status in MDS patients

Diagnostic tool	Characteristics	Advantages	Disadvantages
Calculation of transfusion iron burden	▪ Provide a direct quantitative estimate of the iron body burden	▪ Easy to calculate; inexpensive	▪ Unreliable in patients with bleeding or chelation therapy
Serum ferritin	▪ Indirect serological estimation of iron body burden	▪ Widely available; easy to perform; low-cost; repeatable	▪ Unreliable in patients with inflammation, liver function deficiency, and ascorbate deficiency
Serum transferrin saturation	▪ High sensitivity and specificity in non-transfused patients	▪ Widely available; easy to perform; low-cost; repeatable	▪ No quantitative correlation to iron burden
SQUID	▪ Direct instrumental estimation of hepatic iron concentration	▪ Non-invasive; repeatable	▪ Expensive; not widely available; not validated; significant underestimation; not applicable for cardiac assessment
MRI R2	▪ Indirect instrumental estimation of iron tissue concentration	▪ Non-invasive; repeatable; validated on the liver	▪ Expensive, not widely available; reliable up to LIC of 15 mg/g dry wt; not applicable for cardiac assessment
MRI T2*	▪ Indirect instrumental estimation of iron tissue concentration	▪ Non-invasive; repeatable; validated on the heart; providing information on cardiac function	▪ Expensive; not widely available; complex, requiring a skilled radiologist; not validated on the liver
Liver biopsy	▪ Provides a direct estimation of iron overload	▪ Validated and quantitative method to estimate hepatic iron concentration (gold standard)	▪ Invasive (cannot be employed in many patients with MDS)
NTBI	▪ Research tool at present	▪ Non-invasive method; estimates generation of toxic iron fraction	▪ Not validated; not widely available
Serum hepcidin	▪ Research tool at present	▪ Non-invasive method; identifies patients at high-risk of iron loading	▪ Not widely available; not useful in clinical practice

LIC, liver iron concentration; MRI, magnetic resonance imaging

Alessandrino EP, et al. Am J Hematol. 2011;86:897-902.

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Alessandrino EP, et al. Am J Hematol. 2011;86:897-902.

Transfusion therapy results in iron overload

- 1 blood unit contains 200–250 mg iron
- 20 units = 4 g of iron
- **Iron transfused (mg) = volume transfused x hematocrit (Hct) x 1.08**

Whole blood: 0.47 mg iron/mL “Pure” red cells: 1.08 mg iron/mL

Porter JB. Br J Haematol. 2001;115:239-52.

Apporto di ferro trasfusionale (*iron intake*)

Calcolo del ferro contenuto in una sacca di sangue (mg)

- Apporto di ferro trasfusionale (mg) = Volume globuli rossi trasfusi (mL) x 1,08
- Volume globuli rossi trasfusi (mL) = Volume della sacca (mL) x ematocrito (%)

- Esempio:
- 285 mL di sangue trasfuso x 65% ematocrito = 185 mL → volume di globuli rossi trasfusi
- 185 mL di globuli rossi trasfusi x 1,08 = 200 mg Fe → apporto di ferro trasfusionale per sacca

Calcolo del ferro trasfusionale giornaliero medio a paziente (mg/kg/die)

Sacche trasfuse	Quantità totale di ferro in un mese	Apporto di ferro trasfusionale giornaliero (per es.: adulto 50 kg)
2- 4 sacche/mese	**400 mg - 800 mg**	**0,3 - 0,5 mg/kg/die**
< 2 sacche/mese	**< 400 mg**	**< 0,3 mg/kg/die**
> 4 sacche/mese	**> 800 mg**	**> 0,5 mg/kg/die**

Cohen AR et al. Blood. 2008;111:583-587

SIE, SIES, GITMO Guidelines
Chelation in MDS

- Iron chelation therapy is recommended in all patients with low-INT1 IPSS risk disease who receive regular red-cell transfusion therapy; the therapy should be started after the patients has received **20 packed red blood cell units (i.e. 4 grams of iron)** (grade B).

Santini et al, Leuk Res 2010

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Alessandrino EP, et al. Am J Hematol. 2011;86:897-902.

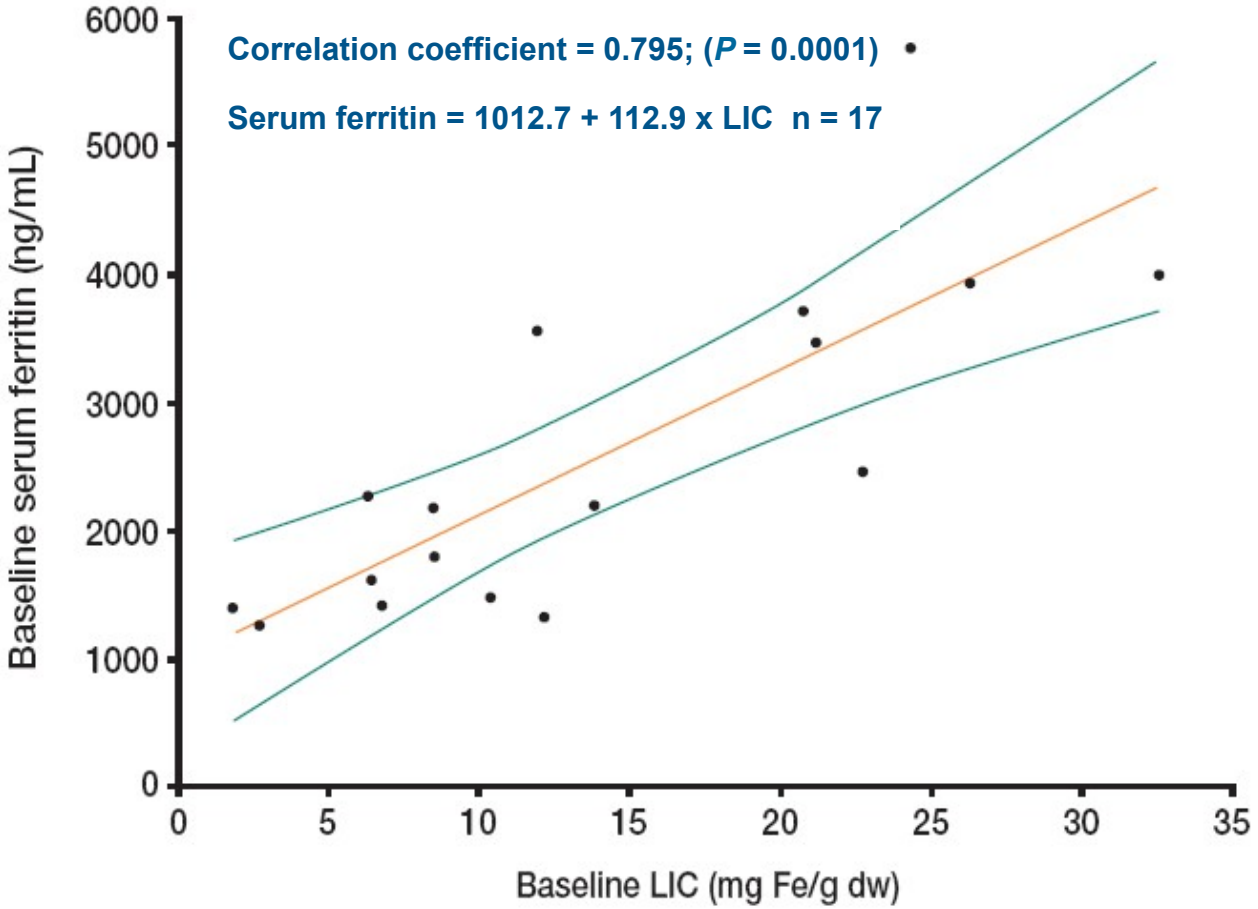
Measuring and interpreting serum ferritin

Advantages	Disadvantages
■ Easy to assess ■ Inexpensive ■ Repeat measures are useful for monitoring chelation therapy ■ Positive correlation with shortened overall survival in MDS	■ Indirect measurement of iron burden ■ Fluctuates in response to inflammation, abnormal liver function, and metabolic deficiencies ■ Serial measurement required

Why measure serum ferritin?

- Clear evidence linking long-term serum ferritin control to outcome
- Convenience and low cost
  - permit frequent repeated measurements
  - **allow early trend recognition**
- Serum ferritin trend increasing
  - focus on adherence
  - consider dose increase
  - chelator regime change
- Serum ferritin trend decreasing
  - if rapid, dose adjust to minimize risks of over chelation for "soft landing"
  - if levels are already low – dose reduction to allow maintenance of current level

Severe iron overload in patients with MDS: correlation between baseline LIC and serum ferritin

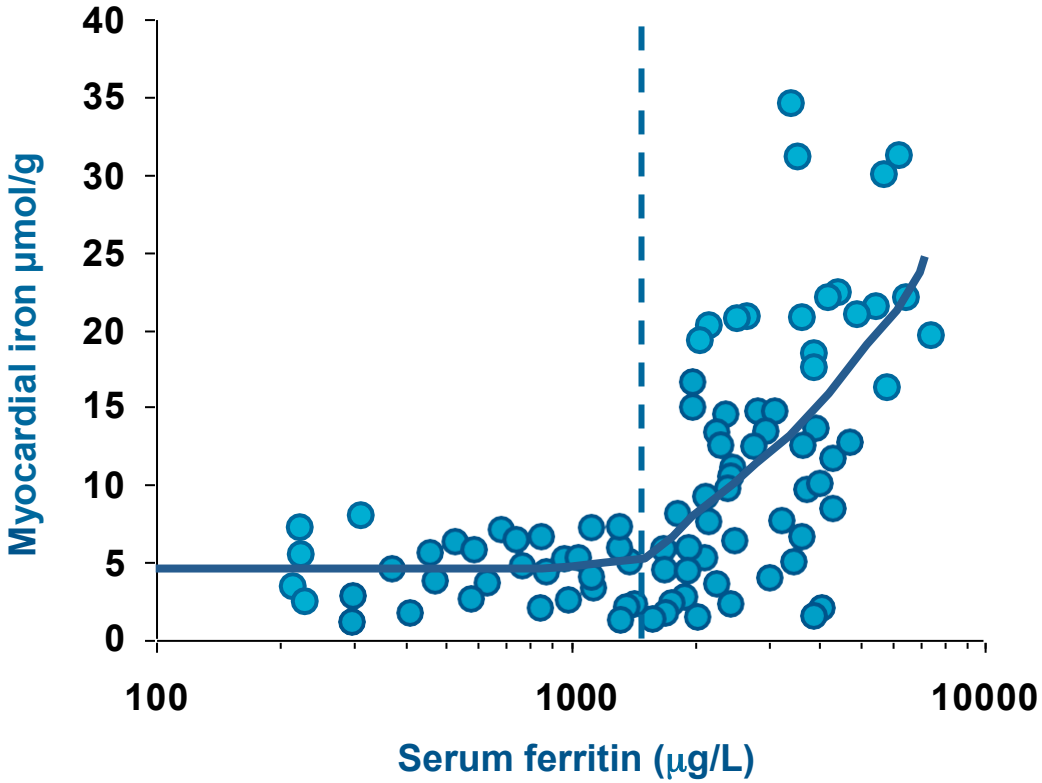


Note: Central line represents the estimated regression line, while the outer lines represent upper and lower 95% confidence intervals for mean baseline serum ferritin at a given baseline LIC

Gattermann N *et al.* Presented at MDS symposium 2007 [*Leuk Res* 2007;31(1):abst P129]

Study 2409

Relationship between serum ferritin and myocardial iron



Patient group (n=14)

- 11 MDS
- 1 DBA
- 1 chronic hemolysis of unknown origin
- 1 acute myeloid leukemia in complete remission

Cardiac iron loading associated with serum ferritin levels >1800 µg/L

Jensen PD et al. *Blood* 2003;101:4632–4639

DBA=Diamond-Blackfan anemia

So – why not *just* use serum ferritin?

- Variability in LIC accounts for only 57% of variability in serum ferritin[1]
  - raised by inflammation or tissue damage
  - lowered by vitamin C deficiency[2]
- Above 4,000 µg/L SF derived from hepatocytes rather than RES[3]
- Relationship of serum ferritin to body iron (LIC) varies in *different diseases*
  - low relative to LIC in β-thalassaemia intermedia[4] (hepatocellular > macrophages)
  - higher and variable in SCD[5]
- Relationship of serum ferritin to LIC differs with *different chelators*[6,7]

SCD = sickle cell disease.

1. Brittenham GM, et al. Am J Hematol. 1993;42:81-5.
2. Chapman RW, et al. J Clin Pathol. 1982;35:487-91.
3. Worwood M. Br J Haematol. 1980;46:409-16.
4. Origa R. Haematologica. 2007;92:583-8.
5. Porter JB, Huehns ER. Acta Haematologica. 1987;78:198-205.
6. Fischer R, et al. Br J Haematol. 2003;121:938-48.
7. Ai Leen Ang, et al. Blood. 2010;116:[abstract 4246].

Why assess and control liver iron?

- Serum ferritin alone may not reflect true body iron and chelation trends
- LIC predicts total body storage iron in TM[1]
- Absence of pathology
  - heterozygotes of HH where liver levels < 7 mg/g dry wt
- Liver pathology
  - abnormal ALT if LIC > 17 mg/g dry wt[2]
  - liver fibrosis progression if LIC > 16 mg/g dry wt[3]
- Cardiac pathology at high levels
  - increased LIC linked to risk of cardiac iron in unchelated patients[2,6]
  - LIC > 15 mg/g dry wt association with cardiac death
    - all of 15/53 TM patients who died[4]
    - improvement of subclinical cardiac dysfunction with venesection alone post-BMT[5]

ALT = alanine aminotransferase;
BMT = bone marrow transplantation;
HH = hereditary haemochromatosis.

1. Angelucci E, et al. N Engl J Med. 2000;343:327-31. 2. Jensen PD, et al. Blood. 2003;101:91-6.
3. Angelucci E, et al. Blood. 2002;100:17-21. 4. Brittenham GM, et al. N Engl J Med.

Why assess and control liver iron?

- Iron-associated toxic effects, such as liver fibrosis and cardiac and pancreatic insufficiency, are expected when liver iron content exceeds a threshold of 90–125 μmol/g (5–7 mg/g) dry wt

How to assess LIC?
What measures are available?

- Biopsy
  - fresh/fixed
  - wet/dry
  - size and iron distribution
- SQUID
  - availability
  - standardization
- MRI
  - gradient echo (T2*)[1] (R2*)[5]
  - spin echo (T2) (R2) ferriscan[4]
  - SIR with gradient[3] or spin echo[2]

But ……
do all these measures give equivalent values?

MRI = magnetic resonance imaging; SIR = signal intensity ratio;
SQUID = superconducting quantum interference device.

1. Anderson LJ, et al. Eur Heart J. 2001;22:2171-9.
2. Jensen PD, et al. Blood. 2003;101:91-6. 3. Gandon Y, et al. Lancet. 2004;363:357-62.
4. St Pierre TG, et al. NMR Biomed. 2004;17:446-58. 5. Wood JC, et al. Blood. 2005;106:1460-65.

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Alessandrino EP, et al. Am J Hematol. 2011;86:897-902.

Techniques for Measurement of LIC Using MRI

- Signal intensity ratio (SIR) methods
  - Spin echo with SIR (1.5 tesla)[1]
  - Gradient echo with SIR[2]
- Relaxometry methods *(standard method)*
  - Gradient echo T2*[3]
    - Less accurate at levels >15 mg/g
    - Single or multiple breath holds
    - Images acquired in 10-12 seconds
  - Gradient echo R2*=1/T2*[4]
  - Spin echo T2, R2 (FerriScan)[5]
    - Linear over larger range, longer acquisition time
    - Permits free breathing

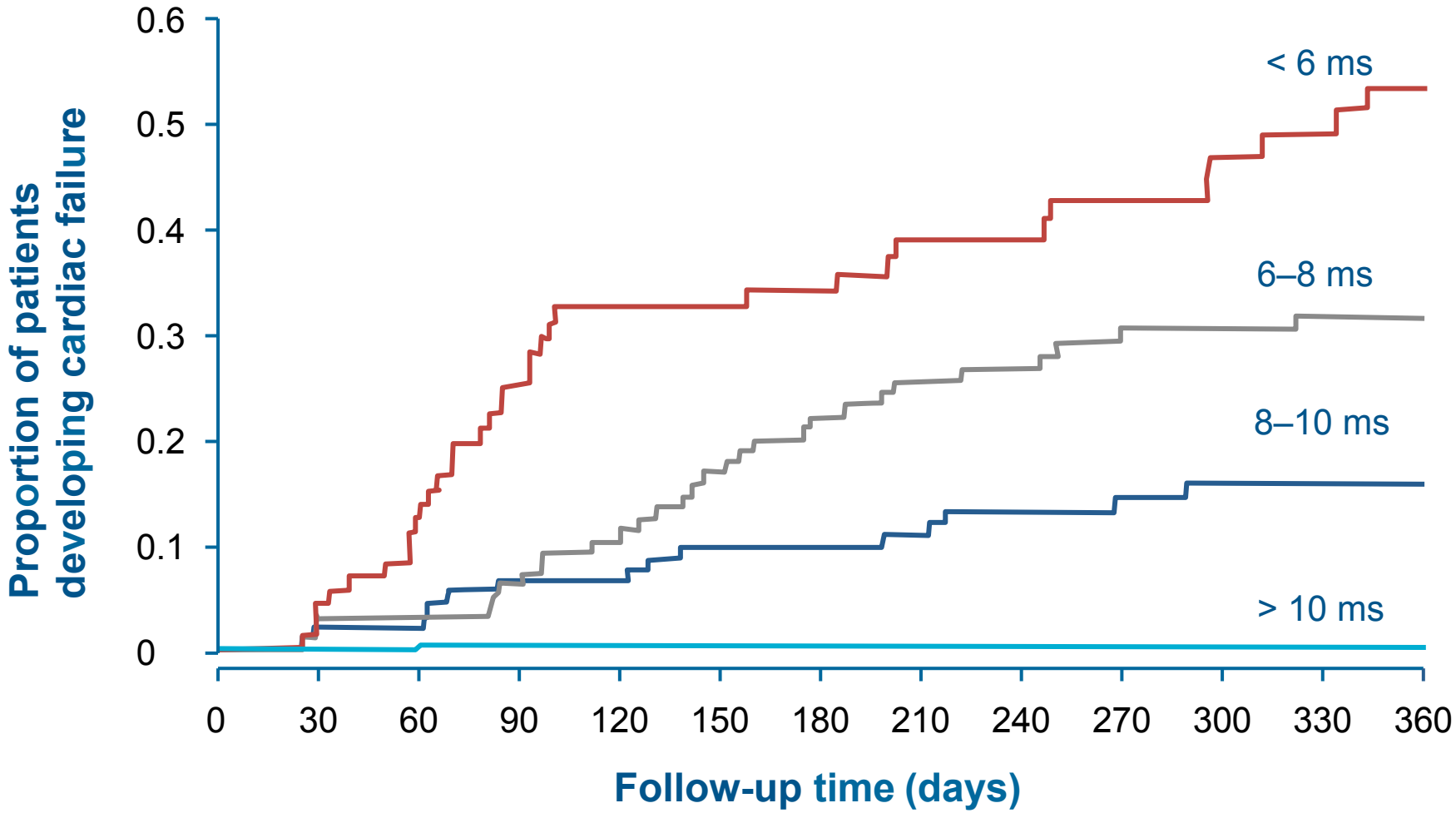
1. Jensen PD, et al. Blood. 2003;101:91-6; 2. Gandon Y, et al. Lancet. 2004;363:357-62; 3. Anderson LJ, et al. Eur Heart J. 2001;22:2171-9; 4. Wood JC, et al. Blood. 2005;106:1460-5; 5. St Pierre TG, et al. Blood. 2005;105:855-61.

So why not *just* measure serum ferritin and LIC?

- While sustained high levels of serum ferritin and or LIC increase risk of cardiac iron
  - some patients do not have cardiac iron despite sustained high LIC and serum ferritin levels
  - some patients have high cardiac iron despite low current levels of serum ferritin and LIC[1]
- Good evidence of relationship of cardiac iron measures (cardiac T2*) and risk of cardiac failure in next year[2]

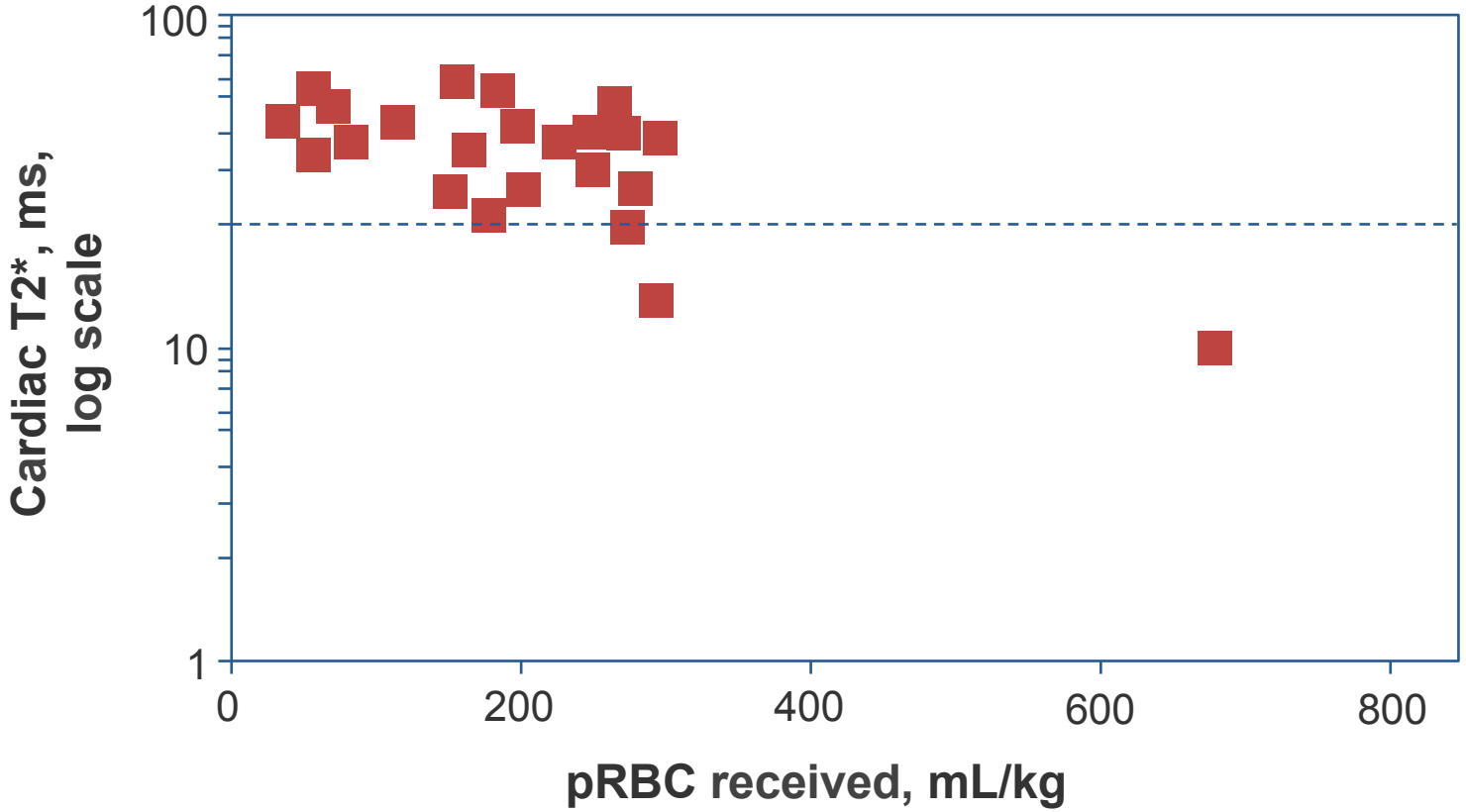
1. Anderson LJ, et al. Eur Heart J. 2001;22:2171-9.
2. Kirk P, et al. Circulation. 2009;120:1961-8.

Relationship between cardiac T2* and cardiac failure



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

Role of T2* MRI in MDS patients



Di Tucci AA, et al. Haematologica. 2008;93:1385-8.

How to estimate cardiac iron?

What are the key elements for reliable cardiac iron assessment ?

MRI setup	1.5 or 3 tesla MRI with ECG to trigger the MRI cardiac
	package software that performs gated sequences
	A T2* sequence post-processing software
Data acquisition	Single slice is adequate
	Black-blood superior to bright-blood MRI (reduces noise)[1]
Region of interest	Inter-ventricular septum
	Multi-slice multi-region[2] probably unnecessary because septum representative of heart at post-mortem[3]
Analysis software	Approved software is preferable
External validation	Staff training and validation key to reliable results
Data presentation	R2* proportional to tissue iron, but T2* more familiar

1. He T, et al. Magn Reson Med. 2008;60:1082-9. 2. Pepe A, et al. Haematologica. 2010;96:41-7.
3. Carpenter .JP, et al. J Cardiovasc Magn Reson. 2009;11 Suppl. 1:P224.

ECG = electrocardiogram.

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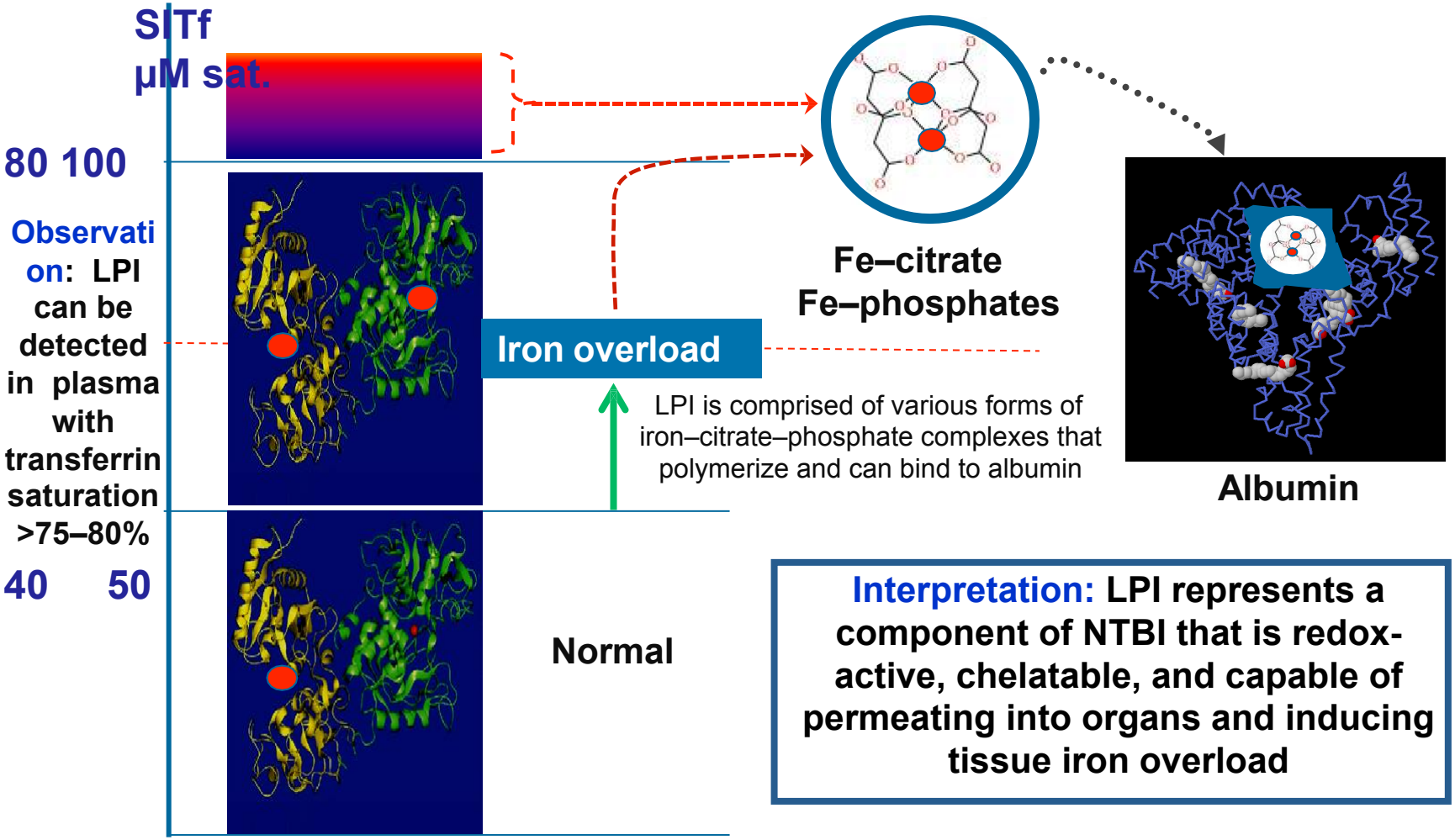
NTBI and LPI for assessment of iron loading?

- NTBI found when transferrin approaches saturation[1]
- LPI is a chelatable redox-active component of NTBI[2]
- In TM, NTBI and LPI values correlate approximately with
  - serum ferritin[3–5] and LIC[6]
- Values also reflect erythropoietic rate
  - increased by suspension of erythropoiesis[7]
  - increased by ineffective erythropoiesis[8]
- Values may be increased by transfusional iron loading rate[9]
- LPI removed in presence of chelator[2]
- NTBI partially removed with DFO[4,10]
- Low levels in SCD relative to other forms of iron overload[11]
- Value as research tool rather than for routine assessment

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. Al Refaie FN, et al. Br J Haematol. 1992;82:431-6. 4. Porter JB, et al. Blood. 1996;88:705-14. 5. Pootrakul P, et al. Blood. 2004;104;1504-10. 6. Daar S, et al. Eur J Haematol. 2009;82:454-7. 7. Bradley SJ, et al. Br J Haematol. 1997;99:337-43. 8. Wickramsinghe SN, et al. Br J Haematol. 1999;107:522-5.
9. Porter JB. Eur J Haematol. Submitted 2011. 10. Evans P, et al. Transl Res. 2010;156:55-67.11. Porter JB, et al. Blood. 2008;112:[abstract 3881]..

Labile pool of iron (LPI)

LPI appears in plasma when transferrin iron-binding capacity is exceeded

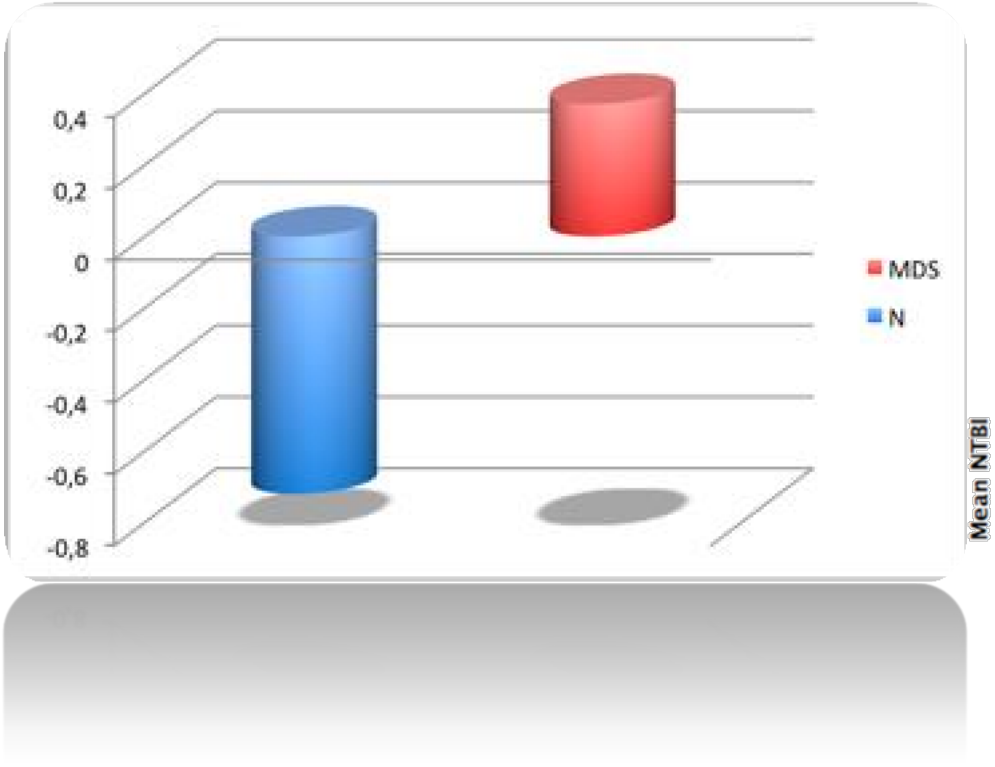


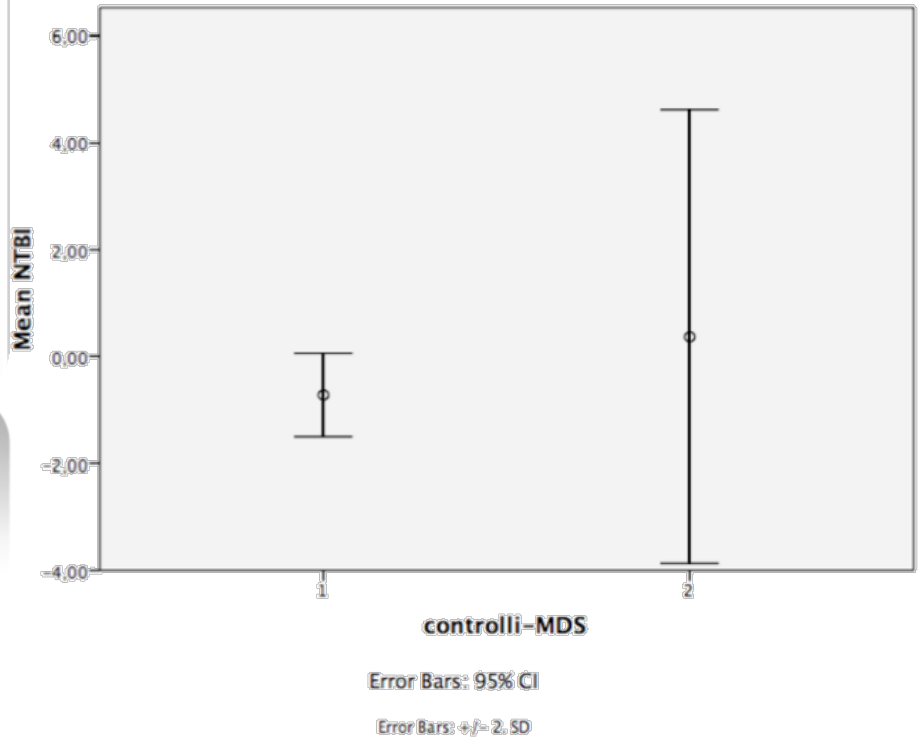
Interpretation: LPI represents a component of NTBI that is redox-active, chelatable, and capable of permeating into organs and inducing tissue iron overload

SI = saturation index; Tf sat. = transferrin saturation.

Cabantchik et al. Best Pract Res Clin Haematol. 2005;18:277

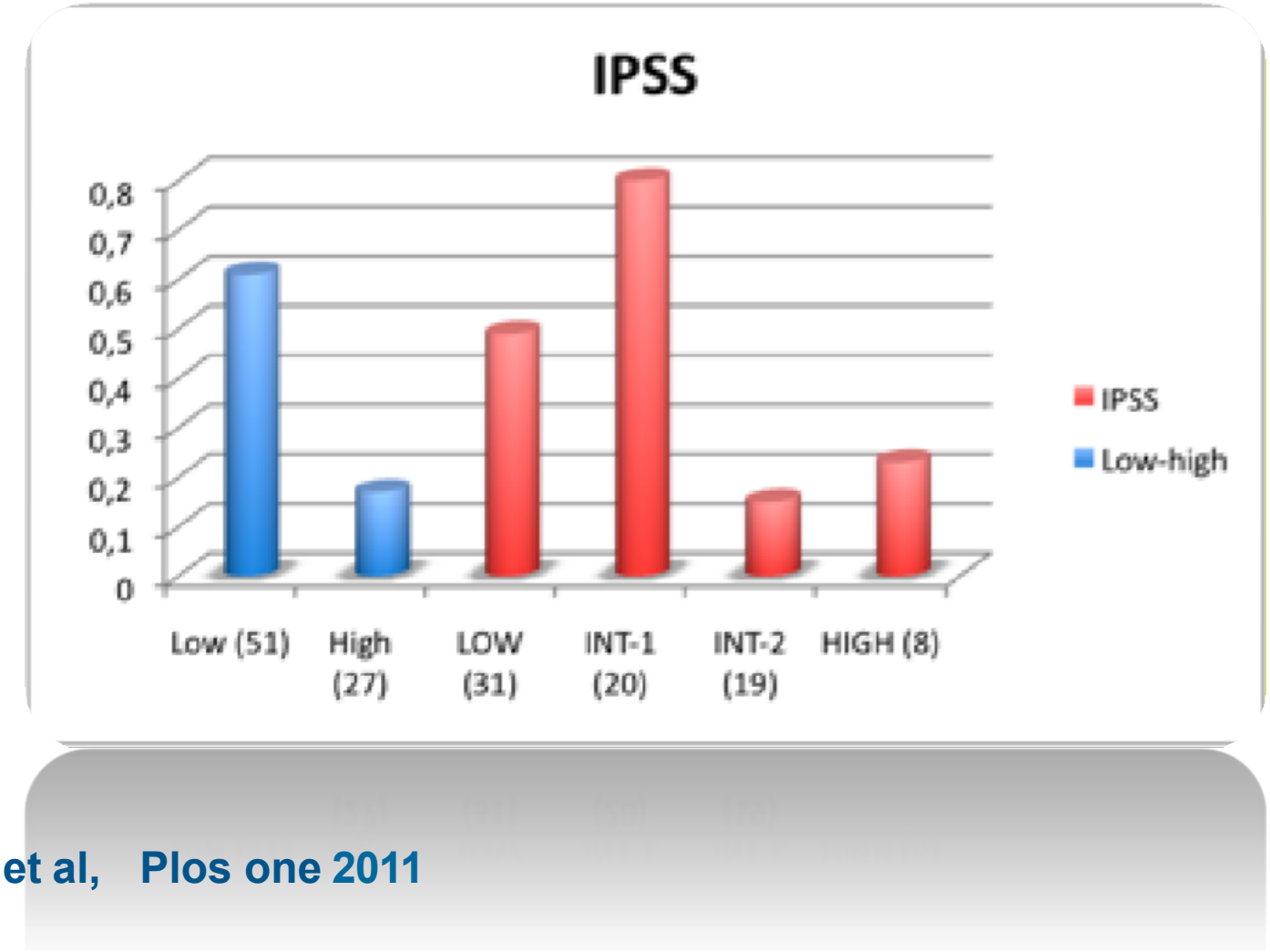
NTBI in MDS cases vs healthy controls





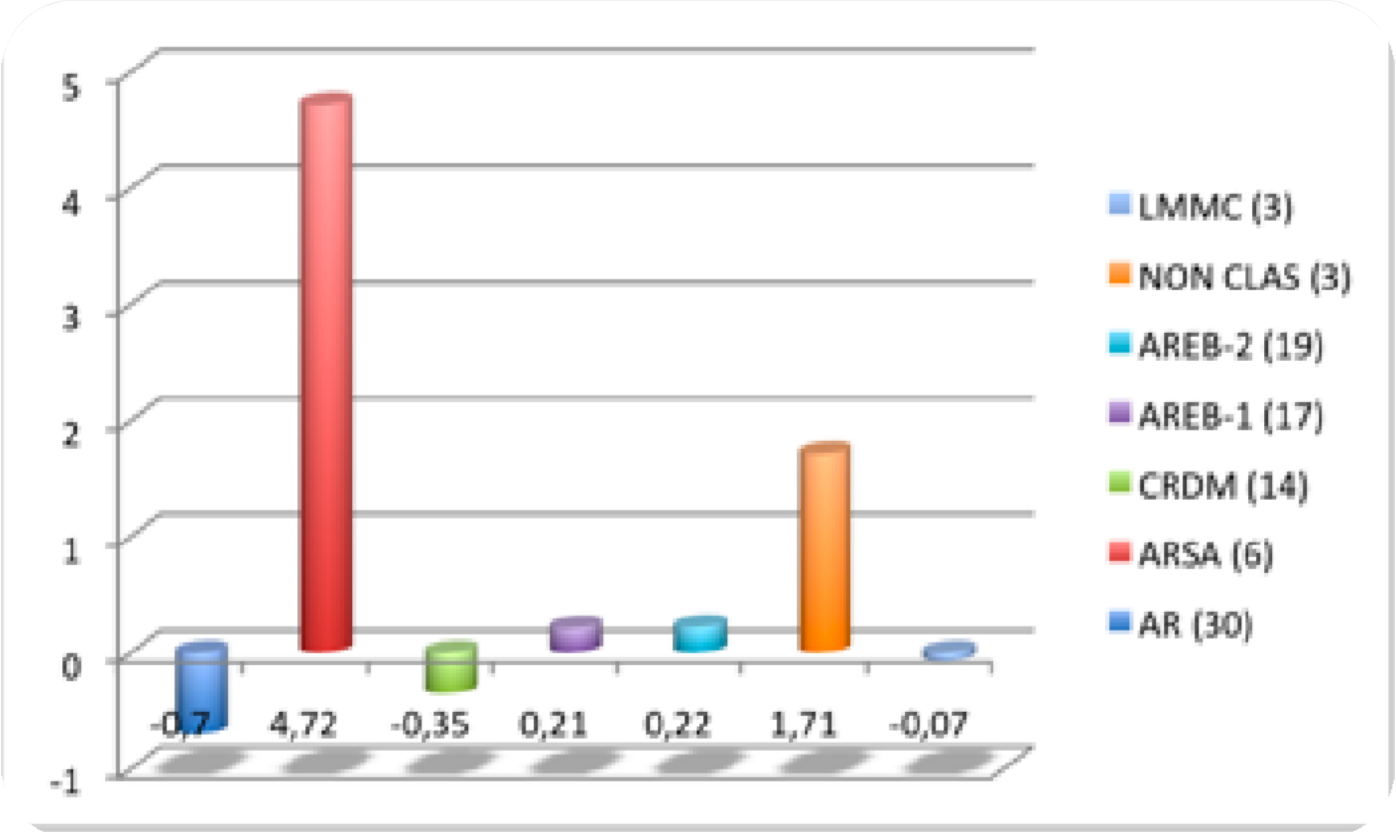
Santini et al, Plosone 2012

NTBI levels in different IPSS risk groups of MDS



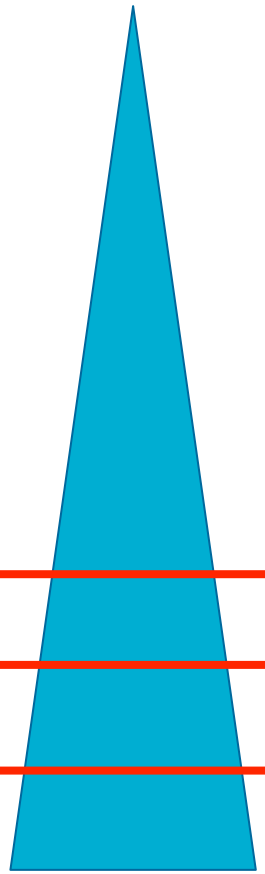
Santini et al, Plos one 2011

Livelli di NTBI in relazione alla classificazione WHO delle MDS



P=0,000, ma solo il valore di ARSA si discosta particolarmente dalle medie degli altri gruppi

Assessment – when?

Observation	Frequency	Expense
Iron intake rate	Each transfusion registered	
Chelation dose and frequency	3 monthly	
Liver function	3 monthly	
Sequential serum ferritin	3 monthly	
Glucose tolerance test, thyroid, calcium metabolism	Yearly	
Liver iron	Yearly	
Cardiac function	3-6 monthly	
Cardiac iron (T2*)	When T not clear, FE low	

bjh guideline

Guidelines for the diagnosis and management of adult aplastic anaemia

Sally B. Killick, Writing Group Chair[1] Nick Bown,[2] Jamie Cavenagh,[3] Inderjeet Dokal,[4] Theodora Foukaneli,[5] Anita Hill,[6] Peter Hillmen,[6] Robin Ireland,[7] Austin Kulasekararaj,[7] Ghulam Mufti,[7] John A. Snowden,[8] Sujith Samarasinghe,[9] Anna Wood, BCSH Task Force Member[10] and Judith C. W. Marsh[7] on behalf of the British Society for Standards in Haematology

There are few published data regarding iron chelation therapy in AA. A large study was the 1-year Evaluation of Patients' Iron Chelation with Exjade study **(Lee et al, 2010)**. This confirmed that **chelation with deferasirox can be administered safely in patients with AA (no drug-induced cytopenias were noted), and can reduce the serum ferritin**. However, dose adjustments are required to adequately chelate those who are heavily transfusion dependent**. Impaired renal function is observed with deferasirox,** and **the drug should be used with caution in AA patients who are taking CSA.** Deferasirox is licensed for use in transfusion-dependent anaemia, but only as second line therapy when desferrioxamine is inadequate or contra-indicated. Deferiprone is efficacious but not recommended in neutropenic patients (Cermak et al, 2011). For those responding to immunosuppression, or after a successful HSCT, venesection is recommended for iron overload.

British Journal of Haematology, 2016, 172, 187–207

Tailoring iron chelation by iron intake and serum ferritin: the prospective EPIC study of deferasirox in 1744 patients with transfusion-dependent anemias

Maria Domenica Cappellini,[1] John Porter,[2] Amal El-Beshlawy,[3] Chi-Kong Li,[4] John F. Seymour,[5] Mohsen Elalfy,[6] Norbert Gattermann,[7] Stéphane Giraudier,[8] Jong-Wook Lee,[9] Lee Lee Chan,[10] Kai-Hsin Lin,[11] Christian Rose,[12] Ali Taher,[13] Swee Lay Thein,[14] Vip Viprakasit,[15] Dany Habr,[16] Gabor Domokos,[17] Bernard Roubert,[17] and Antonis Kattamis[18] on behalf of the EPIC study investigators*

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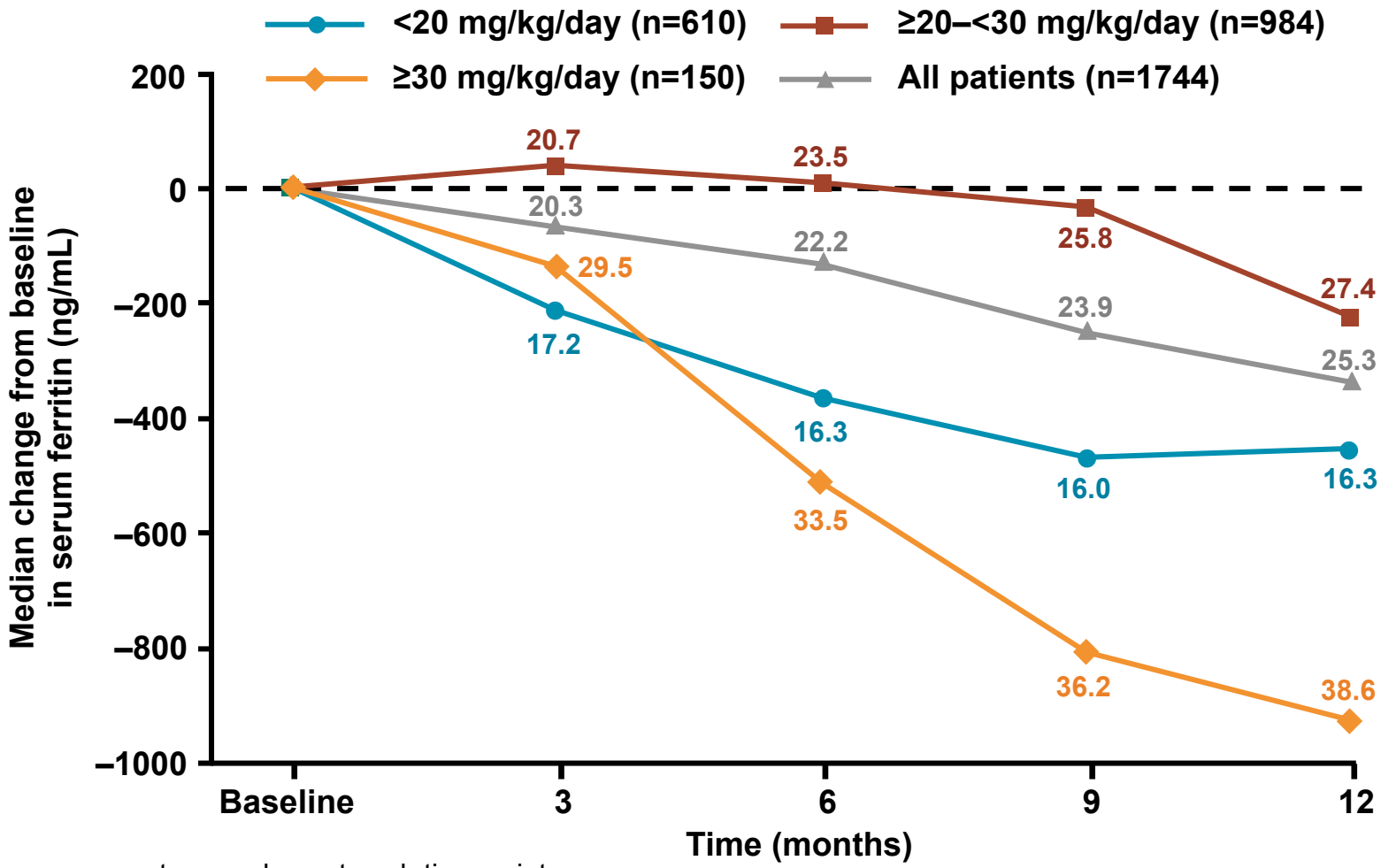
Haematologica 2010; 95(4)

Deferasirox reduces serum ferritin levels over 1 year of treatment in patients with various transfusion-dependent anemias



Values represent mean dose at each time point

Cappellini MD et al. *Haematologica* 2010;95:557–566

Study 2409

Change in serum ferritin levels after 1 year of deferasirox treatment in patients with various transfusion-dependent anemias

	<20 mg/kg/ day (n=610)	≥20–<30 mg/ kg/day (n=984)	≥30 mg/kg/ day (n=150)	All patients (n=1744)
Mean actual dose ± SD (mg/kg/day)	–	–	–	22.2±5.9
Median serum ferritin at baseline (ng/mL)	2608	3165	5048	3135
Median serum ferritin at end of study (ng/mL)	2240	2991	4215	2830
Absolute change in serum ferritin (ng/mL)	–279	–198	–882	–264
P-value*	<0.0001	0.013	<0.0001	<0.0001
Mean iron intake (mg/kg/ day)	0.36	0.44	0.37	0.41

*Change from baseline; analyzed by LOCF method

Cappellini MD *et al*. *Haematologica* 2010;95:557–566

Study 2409

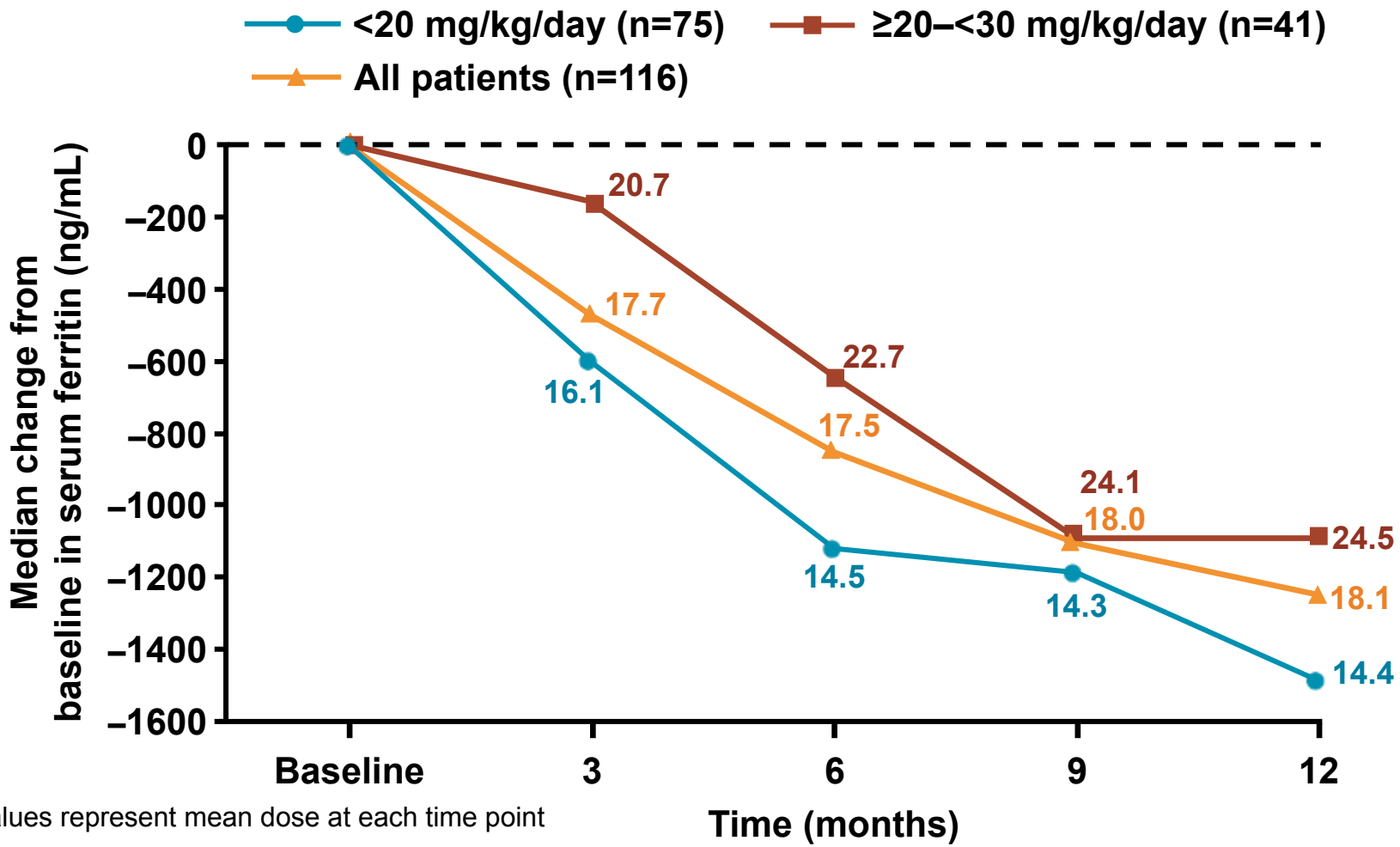
Iron chelation therapy with deferasirox in patients with aplastic anemia: a subgroup analysis of 116 patients from the EPIC trial

Jong Wook Lee,[1] Sung-Soo Yoon,[2] Zhi Xiang Shen,[3] Arnold Ganser,[4] Hui-Chi Hsu,[5] Dany Habr,[6] Gabor Domokos,[7] Bernard Roubert,[7] and John B. Porter,[8] on behalf of the EPIC study investigators

[1]The Catholic University of Korea, Seoul, South Korea; [2]Seoul National University College of Medicine, Seoul, South Korea; [3]Ruijin Hospital, Shanghai Second Medical University, Shanghai, China; [4]Medizinische Hochschule Hannover, Hannover, Germany; [5]Taipei City Hospital, Taipei, Taiwan; [6]Novartis Pharmaceuticals, East Hanover, NJ; [7]Novartis Pharma AG, Basel, Switzerland; and [8]University College London, London, United Kingdom

The prospective 1-year Evaluation of Patients' Iron Chelation with Exjade (EPIC) study enrolled a large cohort of 116 patients with aplastic anemia; the present analyses evaluated the efficacy and safety of deferasirox in this patient population. After 1 year, median serum ferritin decreased significantly from 3254 ng/mL at baseline to 1854 ng/mL ($P < .001$). Decreases occurred in chelation-naive (3229-1520 ng/mL; $P < .001$, last-observation-carried-forward analysis), and previously chelated (3263-2585 ng/mL; $P = .21$, last-observation-carried-forward analysis) patients and were reflective of dose adjustments and ongoing iron intake. Baseline labile plasma iron levels were within normal range despite high serum ferritin levels. The most common drug-related adverse events were nausea (22%) and diarrhea (16%). Serum creatinine increases more than 33% above baseline and the upper limit of normal occurred in 29 patients (25%), but there were no progressive increases; concomitant use of cyclosporine had a significant impact on serum creatinine levels. The decrease in mean alanine aminotransferase levels at 1 year correlated significantly with reduction in serum ferritin ($r = 0.40$, $P < .001$). Mean absolute neutrophil and platelet counts remained stable during treatment, and there were no drug-related cytopenias. This prospective dataset confirms the efficacy and well characterizes the tolerability profile of deferasirox in a large population of patients with aplastic anemia. This study was registered at www.clinicaltrials. gov as #NCT00171821.
(*Blood*. 2010;116(14):2448-2454)

Deferasirox reduces serum ferritin over 1 year of treatment in patients with AA



Values represent mean dose at each time point

Lee JW *et al.* Presented at ASH 2008 [*Blood* 112(11);abst 439]; Lee JW *et al*. *Blood* 2010;116:2448–2454

Study 2409

Change in serum ferritin levels after 1 year of deferasirox treatment in patients with AA

	<20 mg/kg/day (n=75)	≥20–<30 mg/kg/day (n=41)	All patients (n=116)
Mean actual dose ± SD (mg/kg/day)	–	–	17.6 ± 4.8
Median serum ferritin at baseline (ng/mL)	3263	3238	3254
Median serum ferritin at end of study (ng/mL)	1819	2191	1854
Absolute change in serum ferritin (ng/mL)	–970	–884	–964
P-value*	<0.0001	0.28	<0.001
Mean iron intake (mg/kg/day)	0.21	0.31	0.25

*Change from baseline; analyzed by LOCF method

Lee JW *et al*. *Blood* 2010;116:2448–2454

Study 2409

Table 4. Patients with increase in serum creatinine more than 33% above baseline on 2 consecutive visits and/or serum creatinine above ULN, with and without concomitant cyclosporine use

Cyclosporine use	n (%)	Two values > ULN,* no. (%)	Two consecutive values > 33%,* no. (%)	Two consecutive values > 33% and > ULN,* no. (%)
No cyclosporine	95 (82)	8 (8.4)	34 (35.8)	19 (20.0)
Concomitant cyclosporine	21 (18)	3 (14.3)	3 (14.3)	10 (47.6)†
Total	116 (100)	11 (9.5)	37 (31.9)	29 (25.0)

*Categories are mutually exclusive.

†$P < .001$ versus patients with no concomitant use of cyclosporine.

Hematologic responses in patients with aplastic anemia treated with deferasirox: a post hoc analysis from the EPIC study

Jong Wook Lee,[1] Sung-Soo Yoon,[2] Zhi Xiang Shen,[3] Arnold Ganser,[4] Hui-Chi Hsu,[5] Ali El-Ali,[6] Dany Habr,[7] Nicolas Martin,[6] and John B. Porter[8]

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ABSTRACT

Reports are emerging of hematologic responses associated with iron chelation therapy; however, studies are limited in aplastic anemia patients. Deferasirox reduced iron overload in aplastic anemia patients enrolled in the EPIC (Evaluation of Patients' Iron Chelation with Exjade®) study (n=116). A *post hoc* analysis of hematologic responses was conducted on 72 patients with evaluable hematologic parameters (according to UK guideline criteria), 24 of whom received deferasirox without concomitant immunosuppressive treatment. Partial hematologic responses were observed in 11 of 24 (45.8%) patients; all became transfusion-independent. One patient had an additional platelet response and one patient had an additional platelet and hemoglobin response. Mean serum ferritin levels at end of study were significantly reduced in partial hematologic responders (n=11; –3948±4998 ng/mL; baseline 6693±7014 ng/mL; percentage change from baseline –45.7%; P=0.0029). In non-responders, the reduction in serum ferritin was less pronounced (n=13; –2021±3242 ng/mL; baseline 4365±3063 ng/mL; % change from baseline –27.6%; P=0.0171). Alongside reduction in iron overload, deferasirox may, therefore, improve hematologic parameters in a subset of aplastic anemia patients. Further investigation is required to elucidate the mechanisms involved. (*Clinicaltrials.gov identifier: NCT00171821*)

Haematologica. 2013 Jul;98(7):1045-8

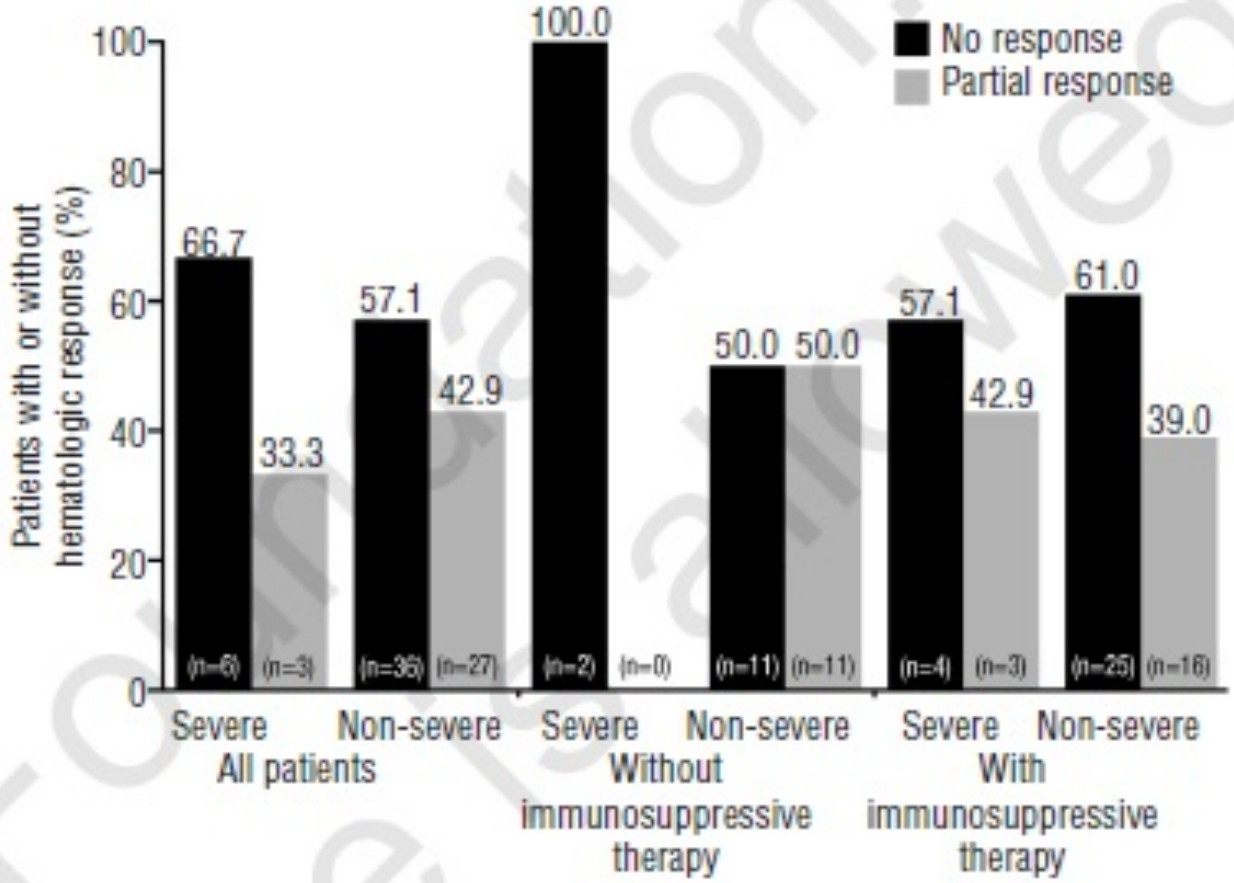
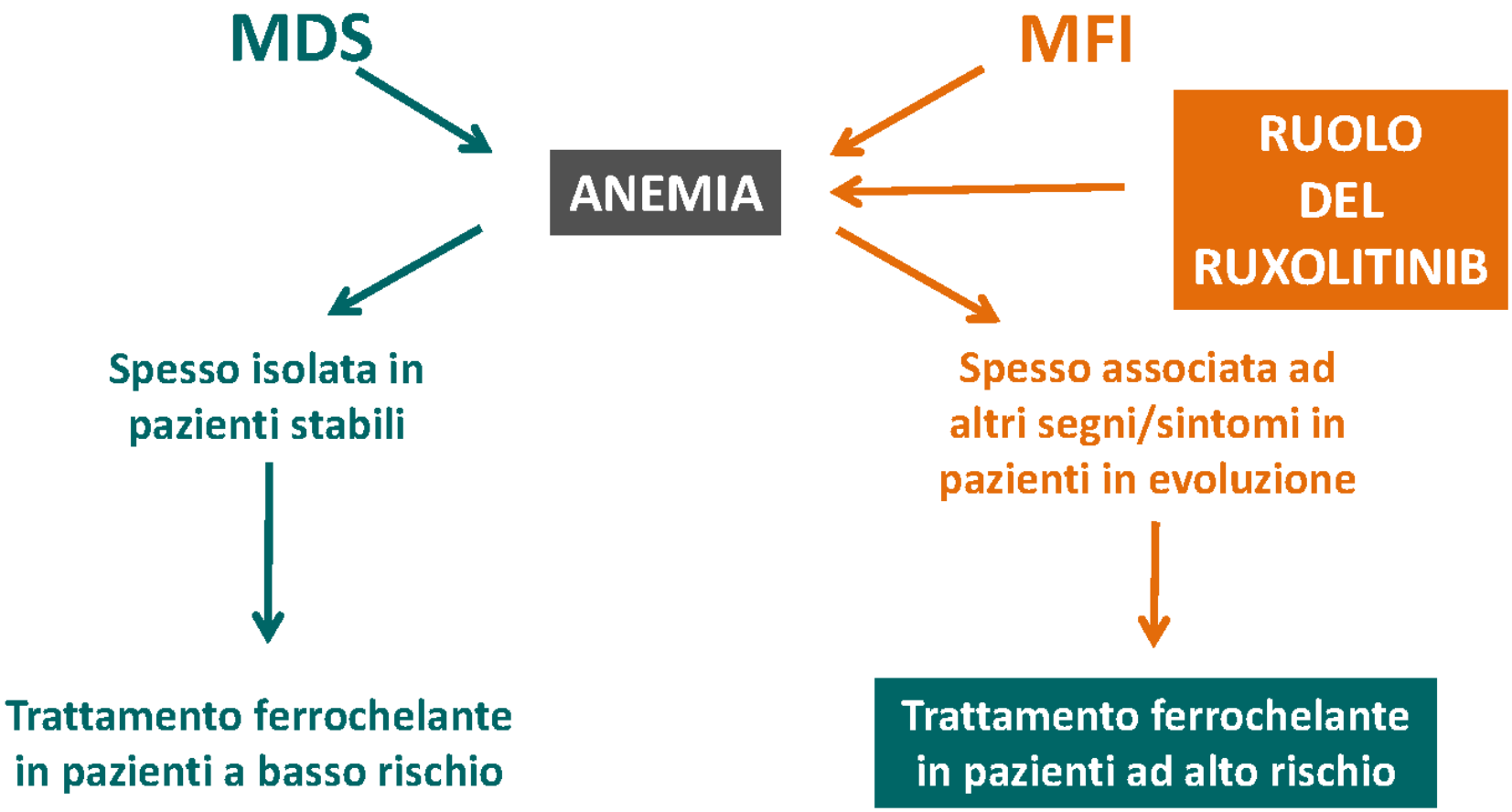


Figure 2. Hematologic responses with or without immunosuppressive treatment in patients with severe AA and non-severe AA.

…ma le mielofibrosi sono diverse!



Sindromi mieloproliferative e deferasirox: alcuni case report presenti in letteratura

AUTORE	ANNO	N° PAZ	ETA'	TIPO RISPOSTA EMATOLOGICA	DOSE DFX	TEMPO ALLA RISPOSTA	RIDUZIONE FERRITINA
DI TUCCI	2007	1	61	Hb > 12 g/dl No trasfusioni	20 mg/Kg	5 mesi	SI
MESSA	2008	1	76	Hb 10 g/dl GR ridotti	10 mg/Kg	1 mese	NO
MATSUKI	2012	1	81	Hb > 12 g/dl No trasfusioni	10 mg/Kg	4 mesi	SI
TESCH	2013	1	67	Hb > 12 g/dl No trasfusioni	20 mg/Kg	2 mesi	SI
LISETTE	2013	1	75	Hb > 13 g/dl No trasfusioni	10 mg/Kg	2 mesi	SI

Di Tucci AA, et al. Eur J Hematol 2007;78, 540-42
Messa E, et al. Acta Haematol 2008;120, 70-74
Matsuki E, et al. Rinsho Ketsueki 2012;53, 78-82
Tesch H, et al. Onkologie 2013;36, 205-208
Lisette del C, et al. Case Rep Hematol 2013;520712

Mielofibrosi e deferasirox:
casistiche omogenee per valutare la terapia ferrochelante

MONOCENTRICHE

↓

EMATOLOGIA
OSPEDALE SAN GERARDO
MONZA

↓

10 pazienti
9/2010→12/2013

POLICENTRICHE

↓

GRUPPO LAZIALE
SMC Ph-negative

↓

37 pazienti
11/2008→10/2016

Elli EM, et al. Mediterr J Hematol Inf ect Dis 2014 Jun 1;6(1):e2014042

Gruppo Laziale. Eur J Hematol 2015

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Original Article

Iron Chelation Therapy with Deferasirox in the Management of Iron Overload in Primary Myelofibrosis

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This article is available from: http://www.mjhid.org/article/view/13167

Abstract. Deferasirox (DSX) is the principal option currently available for iron-chelation-therapy (ICT), principally in the management of myelodysplastic syndromes (MDS), while in primary myelofibrosis (PMF) the expertise is limited. We analyzed our experience in 10 PMF with transfusion-dependent anemia, treated with DSX from September 2010 to December 2013. The median dose tolerated of DSX was 750 mg/day (10 mg/kg/day), with 3 transient interruption of treatment for drug-related adverse events (AEs) and 3 definitive discontinuation for grade 3/4 AEs. According to IWG 2006 criteria, erythroid responses with DSX were observed in 4/10 patients (40%), 2 of them (20%) obtaining transfusion independence. Absolute changes in median serum ferritin levels (Delta ferritin) were greater in hematologic responder (HR) compared with non-responder (NR) patients, already at 6 months of ICT respect to baseline. Our preliminary data open new insights regarding the benefit of ICT not only in MDS, but also in PMF with the possibility to obtain an erythroid response, overall in 40 % of patients. HR patients receiving DSX seem to have a better survival and a lower incidence of leukemic transformation (PMF-BP). Delta ferritin evaluation at 6 months could represent a significant predictor for a different survival and PMF-BP. However, the tolerability of the drug seems to be lower compared to MDS, both in terms of lower median tolerated dose and for higher frequency of discontinuation for AEs. The biological mechanism of action of DSX in chronic myeloproliferative setting through an independent NF-κB inhibition could be involved, but further investigations are required.

European Journal of Haematology

European Journal of Haematology 96 (643–649)

ORIGINAL ARTICLE

Chelation efficacy and erythroid response during deferasirox treatment in patients with myeloproliferative neoplasms in fibrotic phase

Roberto Latagliata[1], Chiara Montagna[1], Raffaele Porrini[2], Ambra Di Veroli[3], Sabrina Crescenzi Leonetti[4], Pasquale Niscola[5], Fabrizio Ciccone[6], Antonio Spadea[7], Massimo Breccia[1], Luca Maurillo[3], Angela Rago[8], Francesca Spirito[9], Michele Cedrone[10], Marianna De Muro[11], Marco Montanaro[12], Alessandro Andriani[13], Antonino Bagnato[4], Enrico Montefusco[2], Giuliana Alimena[1]

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Abstract

At present, very few data are available on deferasirox (DFX) in the treatment of patients with Philadelphia-negative myeloproliferative neoplasms in fibrotic phase (FP-MPN) and transfusion dependence. To address this issue, a retrospective analysis of 28 patients (22 male and 6 female) with FP-MPN and iron overload secondary to transfusion dependence was performed, based on patients enrolled in the database of our regional cooperative group who received treatment with DFX. DFX was started after a median interval from diagnosis of 12.8 months (IR 7.1–43.1) with median ferritin values of 1415 ng/mL (IR 1168–1768). Extra-hematological toxicity was reported in 16 of 28 patients (57.1%), but only two patients discontinued treatment due to toxicity. Among 26 patients evaluable for response (≥6 months of treatment), after a median treatment period of 15.4 months (IR 8.1–22.3), 11 patients (42.3%) achieved a stable and consistent reduction in ferritin levels <1000 ng/mL. As for hematological improvement, 6 of 26 patients (23%) showed a persistent (>3 months) rise of Hb levels >1.5 g/dL, with disappearance of transfusion dependence in four cases. Treatment with DFX is feasible and effective in FP-MPN with iron overload. Moreover, in this setting, an erythroid response can occur in a significant proportion of patients.

Key words myeloproliferative neoplasms; deferasirox; chelation treatment; hematological improvement

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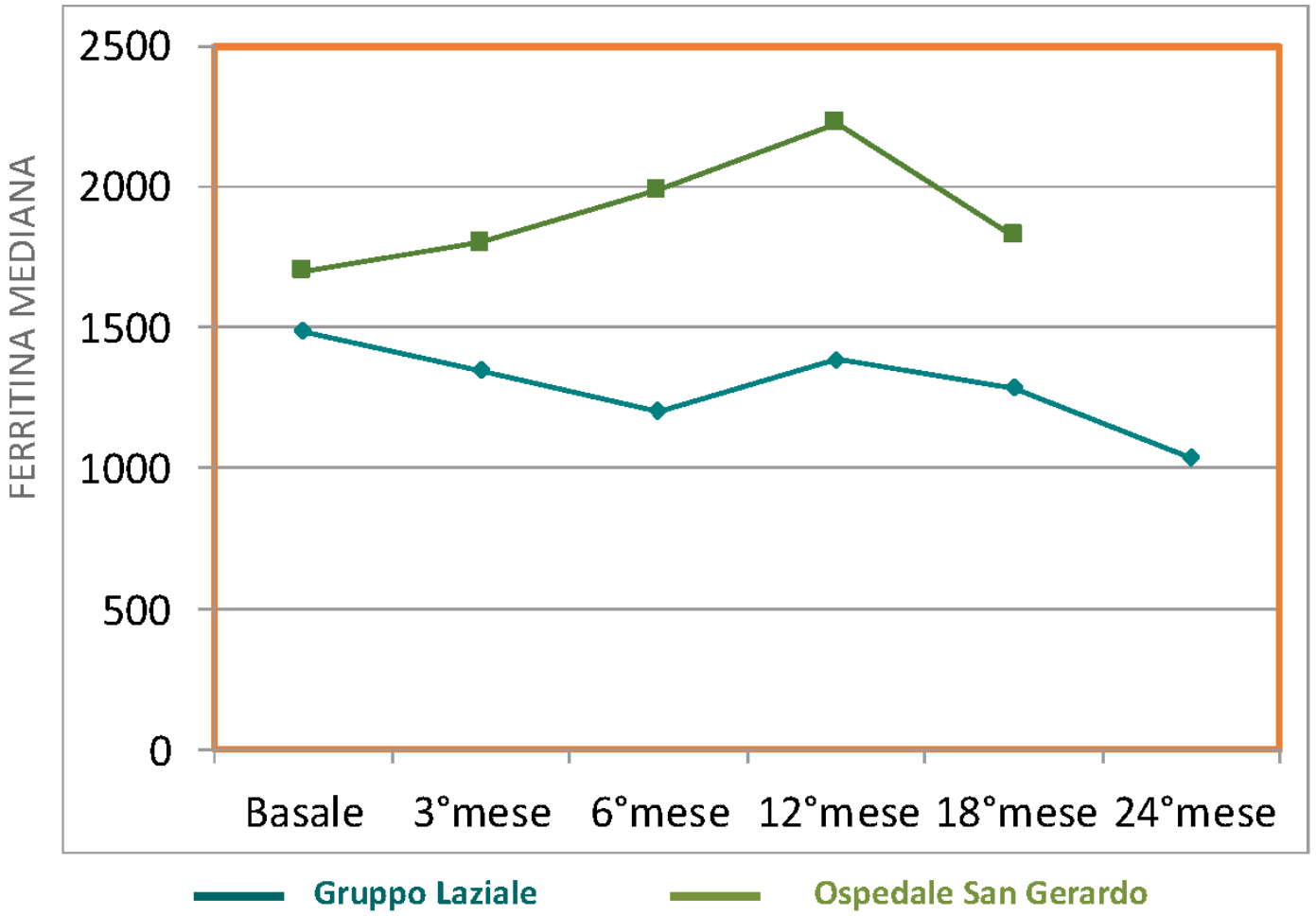
Caratteristiche dei pazienti (1)

	OSPEDALE SAN GERARDO	GRUPPO LAZIALE
N° totale	10	37
M/F	7/3	29/8
Tipo di malattia:		
Mielofibrosi idiopatica	10	33
Mielofibrosi post-TE	/	3
Mielofibrosi post-PV	/	1
Età mediana alla diagnosi (anni)	65,5	68,8
Range	49 – 81	53 - 84
Intervallo diagnosi-deferasirox (mesi)	43,5	12,3
Range	7,5 – 207	5,0 - 102

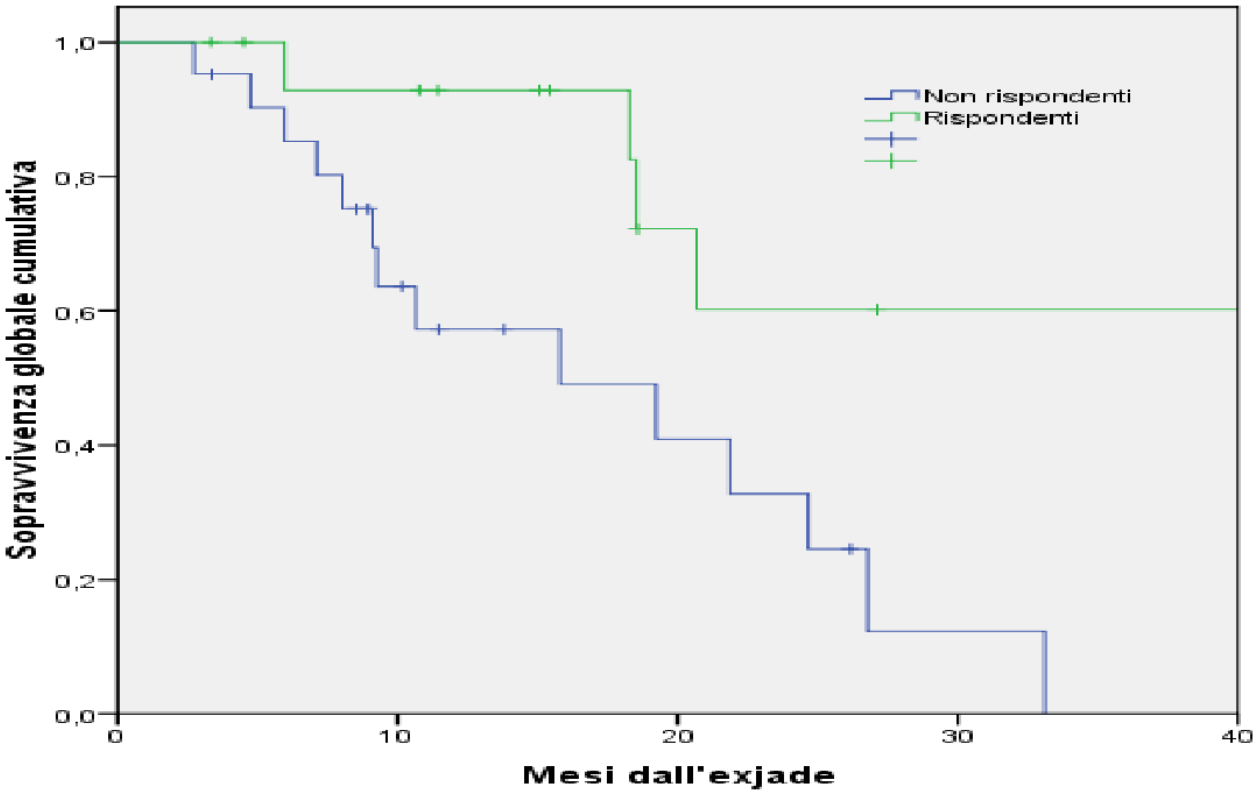
Sindromi mieloproliferative e deferasirox: quale tossicità?

	OSPEDALE SAN GERARDO	GRUPPO LAZIALE
TOSSICITA' GASTRO-INTESTINALE	NR	7/37 (18,9%)
TOSSICITA' RENALE	NR	10/37 (27,0%)
TOSSICITA' CUTANEA	NR	3/37 (8,1%)
SOSPENSIONE TEMPORANEA	3/10 (30%)	18/37 (48,6%)
SOSPENSIONI DEFINITIVE	5/10 (50%) 1 tox G-I 2 tox renale 1 tox cutanea 1 tox epatica	3/37 (8,1%) 1 tox G-I 1 tox renale 1 tox cutanea

Mielofibrosi e deferasirox: quale risposta ferrochelante complessiva?



La risposta individuale al trattamento ha un significato clinico?



p= 0.007

SV mediana pazienti rispondenti alla ferrochelazione 46.9 mesi (IC50% 23.6 – 70.1)

SV mediana pazienti resistenti alla ferrochelazione 15.8 mesi (IC50% 2.9 – 28.7)

Mielofibrosi e deferasirox: quale recupero ematologico?

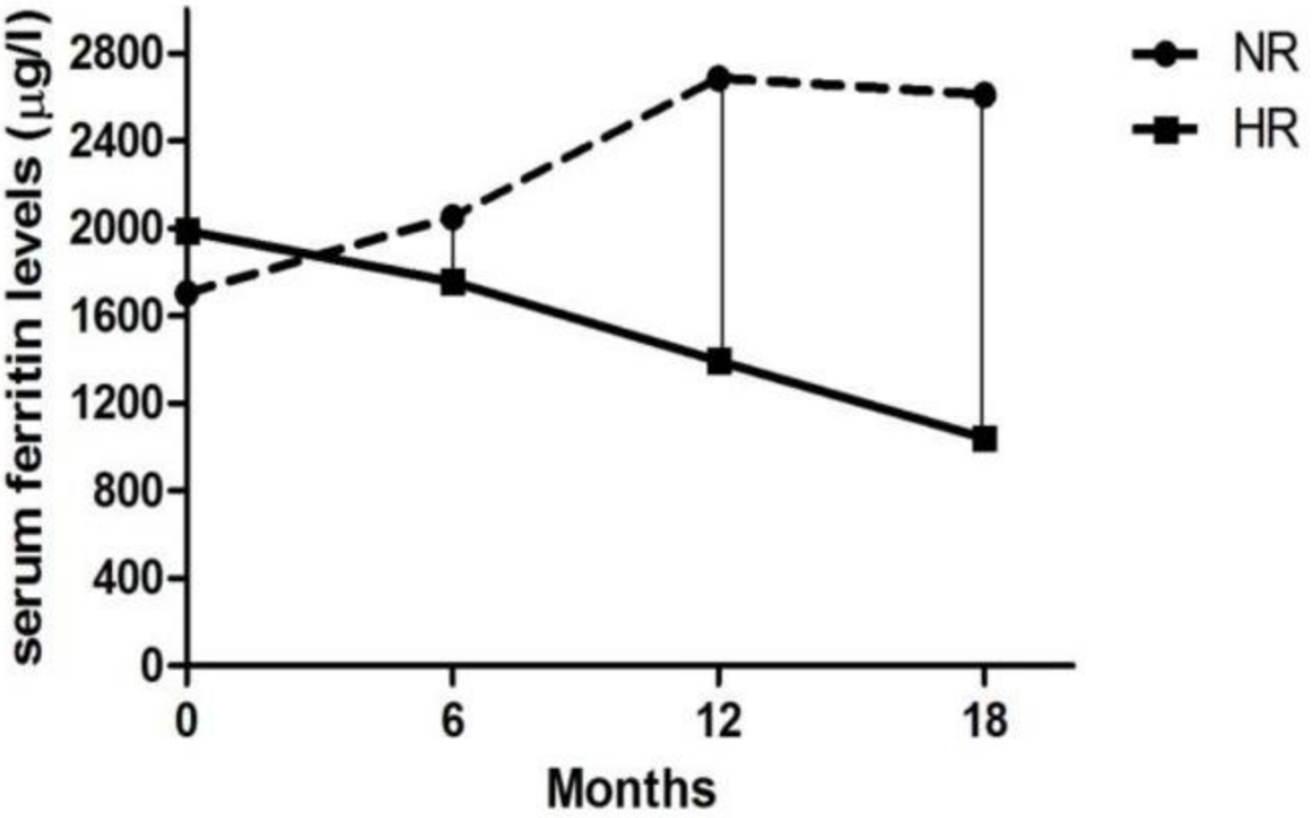
	OSPEDALE SAN GERARDO	GRUPPO LAZIALE
PAZIENTI CON RECUPERO EMATOLOGICO	**4/10 (40,0%)**	**7/37 (18,9%)**
AUMENTO DELL'Hb > 1.5 g/dl	**2/4**	**2/7**
SCOMPARSA DEL FABBISOGNO TRASFUSIONALE	**2/4**	**5/7**
AUMENTO PLTS/GB	**0/10**	**0/37**

CONSIDERANDO ASSIEME LE CASISTICHE 11/47 (23,4%)

Mielofibrosi e deferasirox: che rapporto fra recupero ematologico e risposta ferrochelante?

	Riduzione ferritina consensuale	Non risposta ferrochelante
Paz con recupero ematologico (San Gerardo)	4	/
Paz con recupero ematologico (Gruppo Laziale)	4	3

Andamento nel tempo della ferritina: pazienti con o senza recupero ematologico



Elli EM, et al. Mediterr J Hematol Inf ect Dis 2014 Jun 1;6(1):e2014042

Deferasirox nelle mielofibrosi: qualche considerazione riassuntiva

	OSPEDALE SAN GERARDO	GRUPPO LAZIALE
Il DFX è efficace nel ridurre la ferritina?	+/-	+
Il DFX è in grado di dare recupero ematologico?	SI (40%)	SI (19%)
Il recupero ematologico interessa anche PLTS e GB?	NO	NO
Il recupero ematologico è sempre consensuale alla riduzione della ferritina?	SI	NO
Esistono fattori predittivi del recupero ematologico?	SI	NO
Come è la tossicità del DFX nelle SMP?	> SMD	≤SMD

MOLTI ASPETTI DA CHIARIRE SU CASISTICHE PIU' AMPIE

Oncology Research and Treatment

Novel Insights from Clinical Practice

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Transfusion Independency and Histological Remission in a Patient with Advanced Primary Myelofibrosis Receiving Iron-Chelation Therapy with Deferasirox

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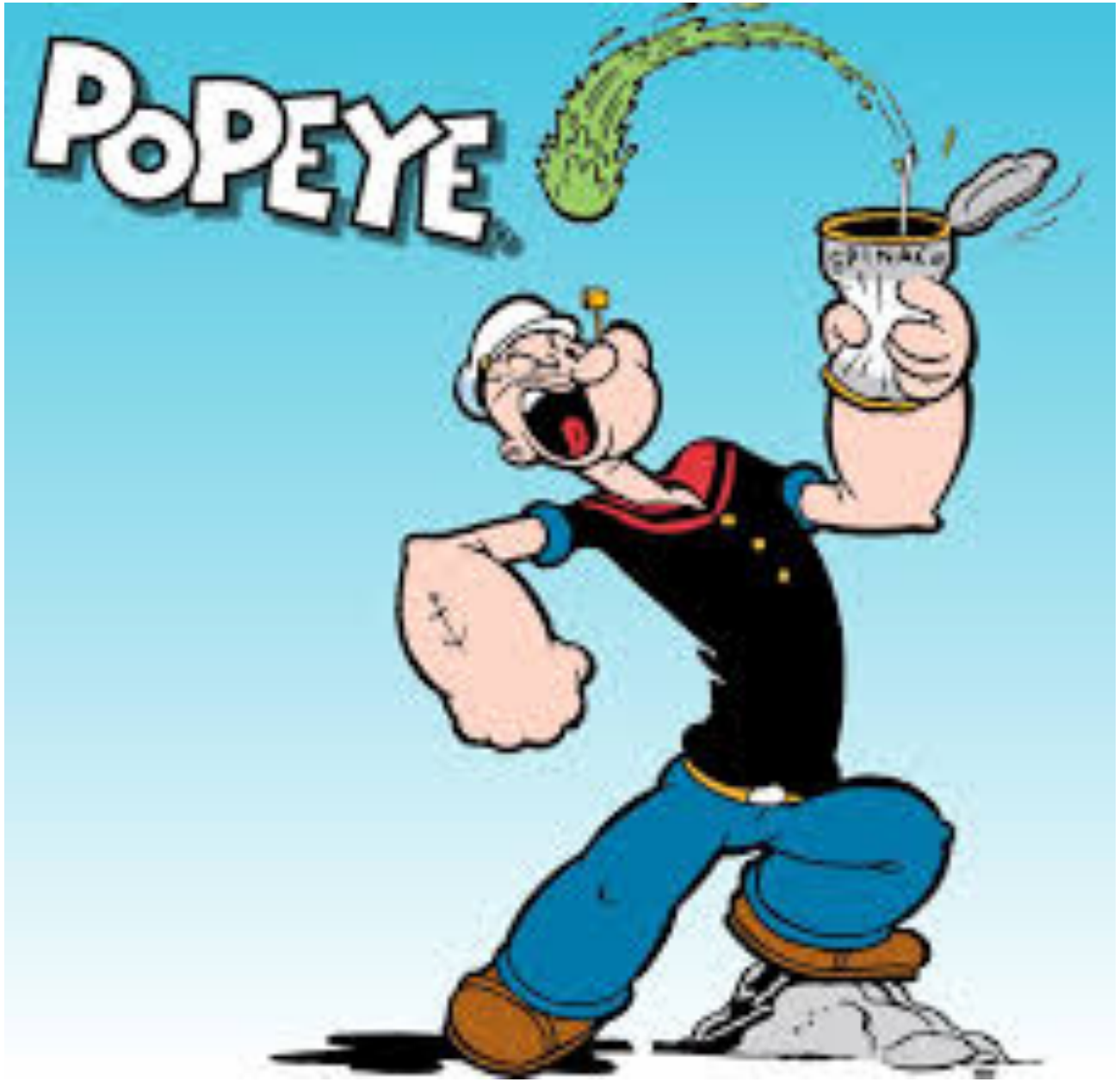
Background: Iron overload is a common problem in patients with primary myelofibrosis and anemia due to transfusion dependency. This results in organ damage and toxic effects on hematopoietic cells in the bone marrow. At present, iron chelation therapy is not recommended in patients with myeloproliferative syndromes.

Case Report: We describe a very interesting development in a patient with primary myelofibrosis receiving iron chelation. **Transfusion independency and a nearly complete histological remission of the underlying disease occurred within a few weeks of therapy**. In addition, a change in molecular genetic findings was observed. Initially a *JAK2* and a *U2AF1* mutation were detected in the core biopsy. **During and after therapy the *U2AF1* mutation progressed, whereas the *JAK2* mutation could no longer be verified.**

Conclusion: The improvement in hematopoiesis might results from reduction of oxidative stress on hematopoietic progenitor cells or other unclear deferasirox-mediated effects, whereas the reason for the change in molecular genetic findings is unclear. It appears that deferasirox might have a modulating effect on JAK2-kinase mutations. However, further investigation of selective molecular suppression properties of deferasirox are warranted.


POPEYE
SPINACH