FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

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

La ferrochelazione nel paziente mielodisplastico

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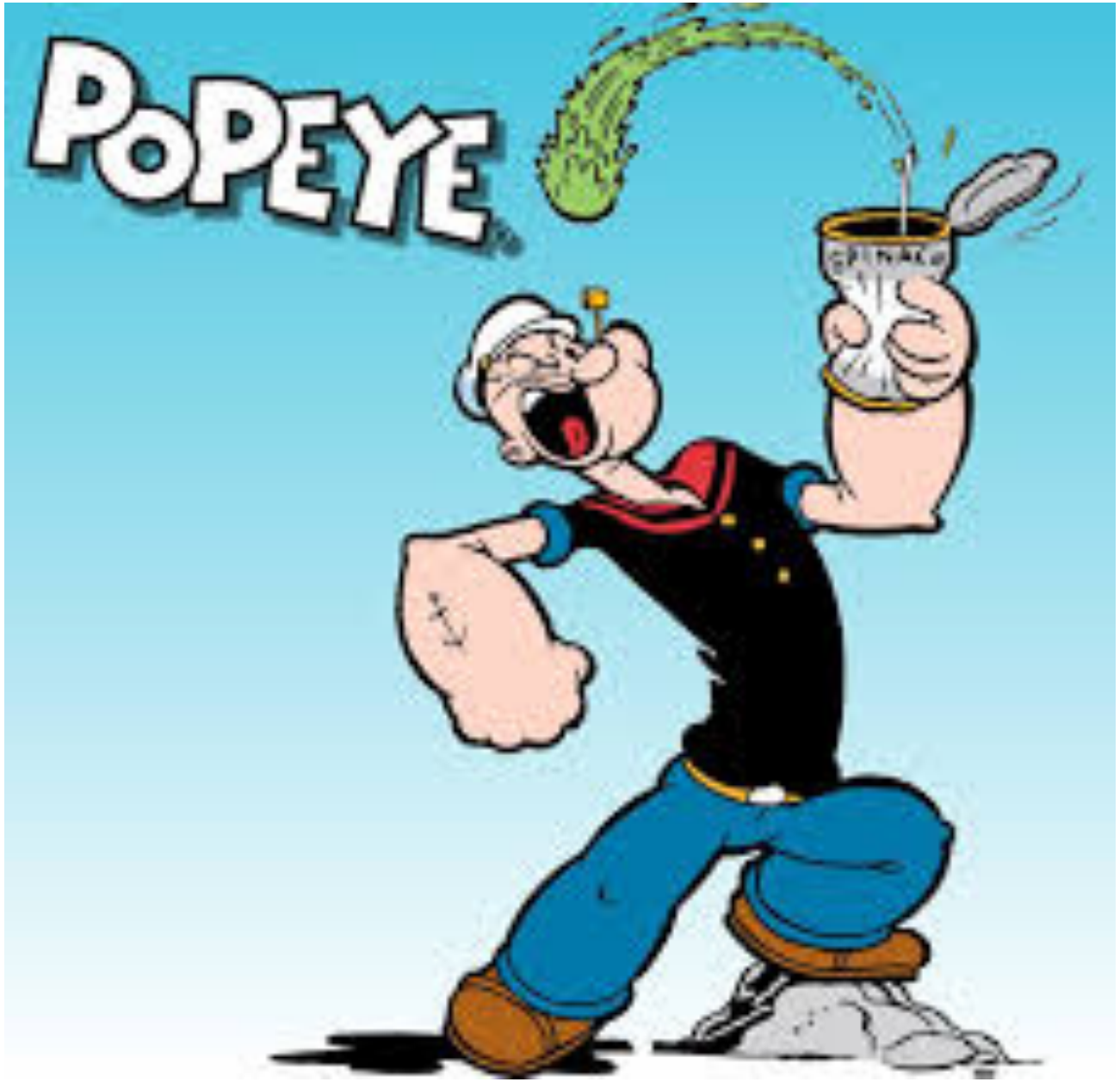
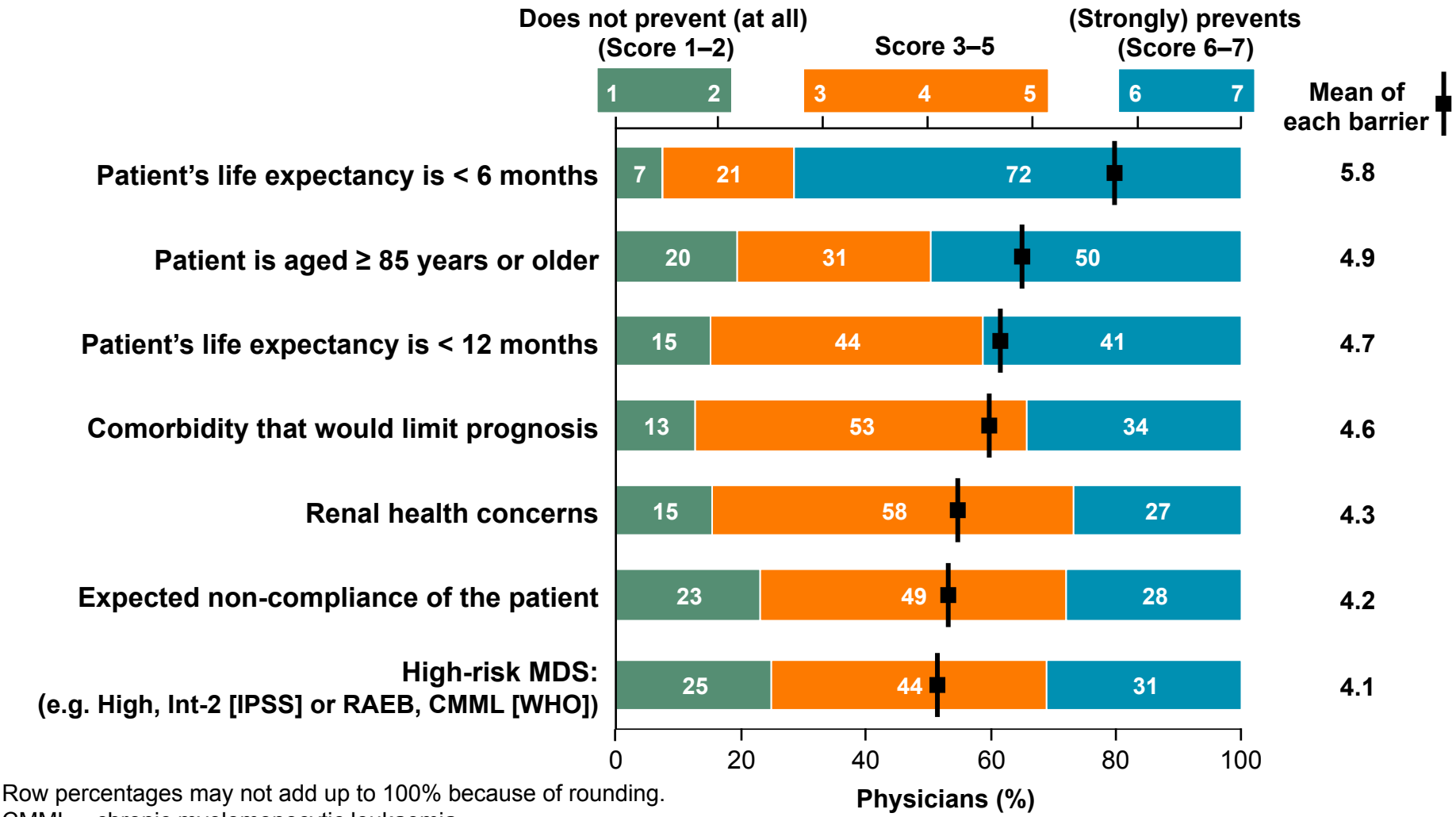

POPEYE
SPINACH

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].

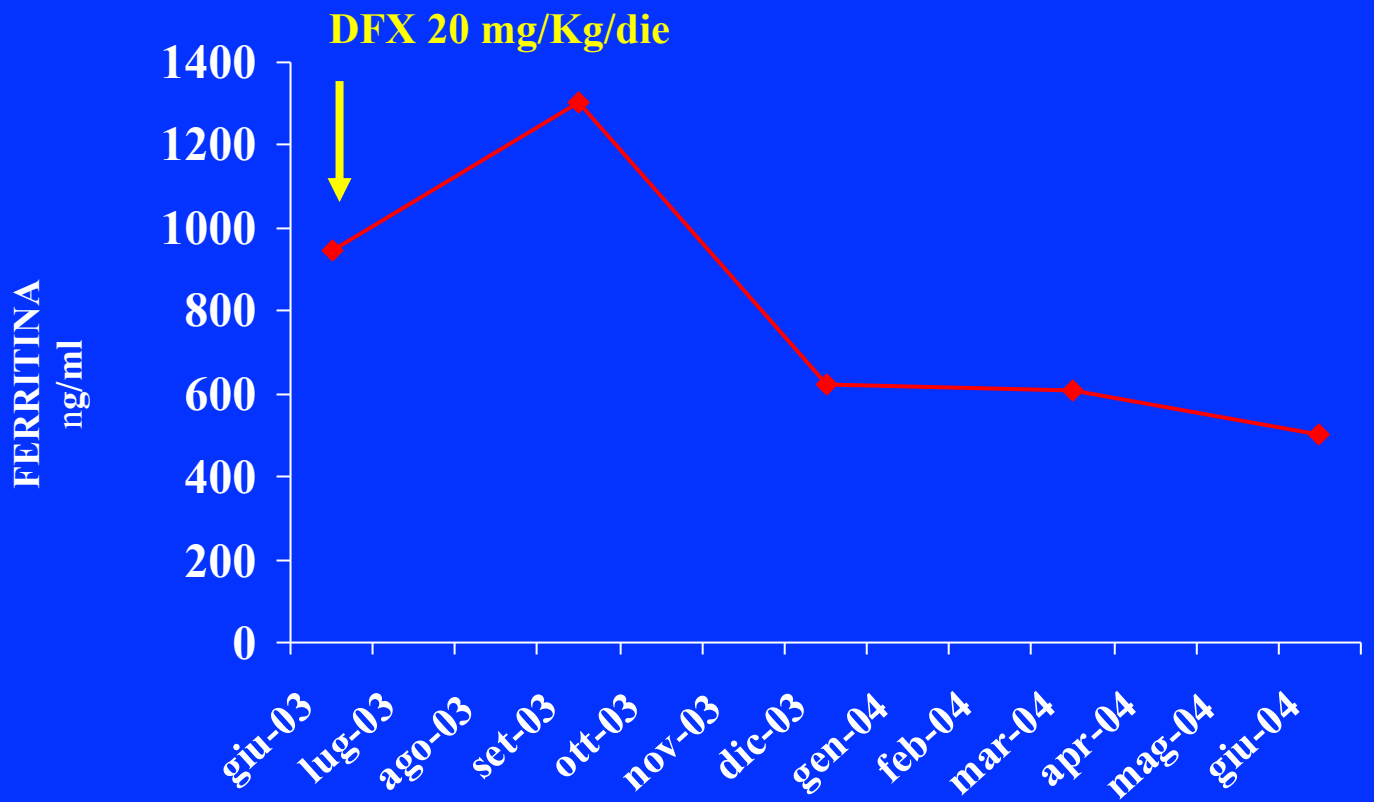
CASO CLINICO N° 1 (1)

- Femmina, 55 anni
- **Giugno 1996 :** Hb 6.5 MCV 126 reticolociti 0.2 %, WBC 4.2 (formula normale), Plts 187
- Aspirato e BOM: midollo ipocellulato, EP ridotta e displastica, MKC numerosi e displastici (ploidia ridotta), GP normale, moderato disomogeneo ↑ linfociti
- Cariotipo: N.V. (materiale scarso)
- EPO: 39
- Diagnosi presuntiva di PRCA , trattata con cortisone e poi ciclosporina , senza risposta (**ottobre 1996:** ancora trasfusione-dipendente)
- **Novembre 1996:** ripete aspirato + cariotipo: quadro morfologico invariato, 8/9 metafasi: **del(5q)(q13q33)**; assenza di piastrinosi (plts 210), WBC normali

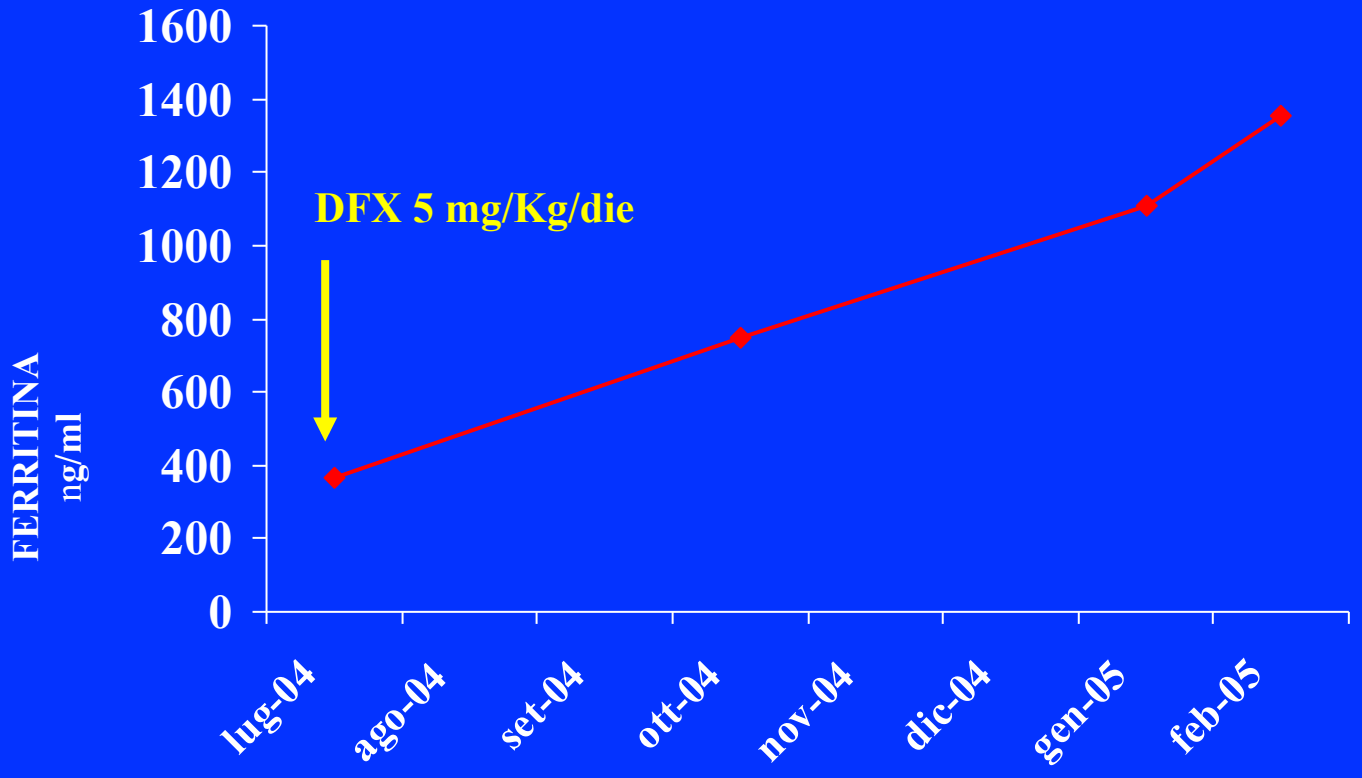
CASO CLINICO N° 1 (2)

- **Ottobre 1996:** inizia EPO, con beneficio solo parziale e transitorio
- **Aprile 1997:** ancora trasfusione-dipendente
- **Maggio 1998:** Inizio DFO (2 g/die i.c., pompa): ferritina 2.200, Ritmo Trasf : 2 GRC/10-14 gg
- **Febbraio 2003:** ferritina 1.100
- **Giugno 2003:** inizia Deferasirox (20 mg/Kg/die) (prot. 108): ferritina: 946 ng/ml; LIC (biopsia epatica): 13
- **Giugno 2004:** ferritina 504 ng/ml; LIC (biopsia epatica): 2.3

CASO CLINICO N° 1: RISPOSTA AL DEFERASIROX (A)

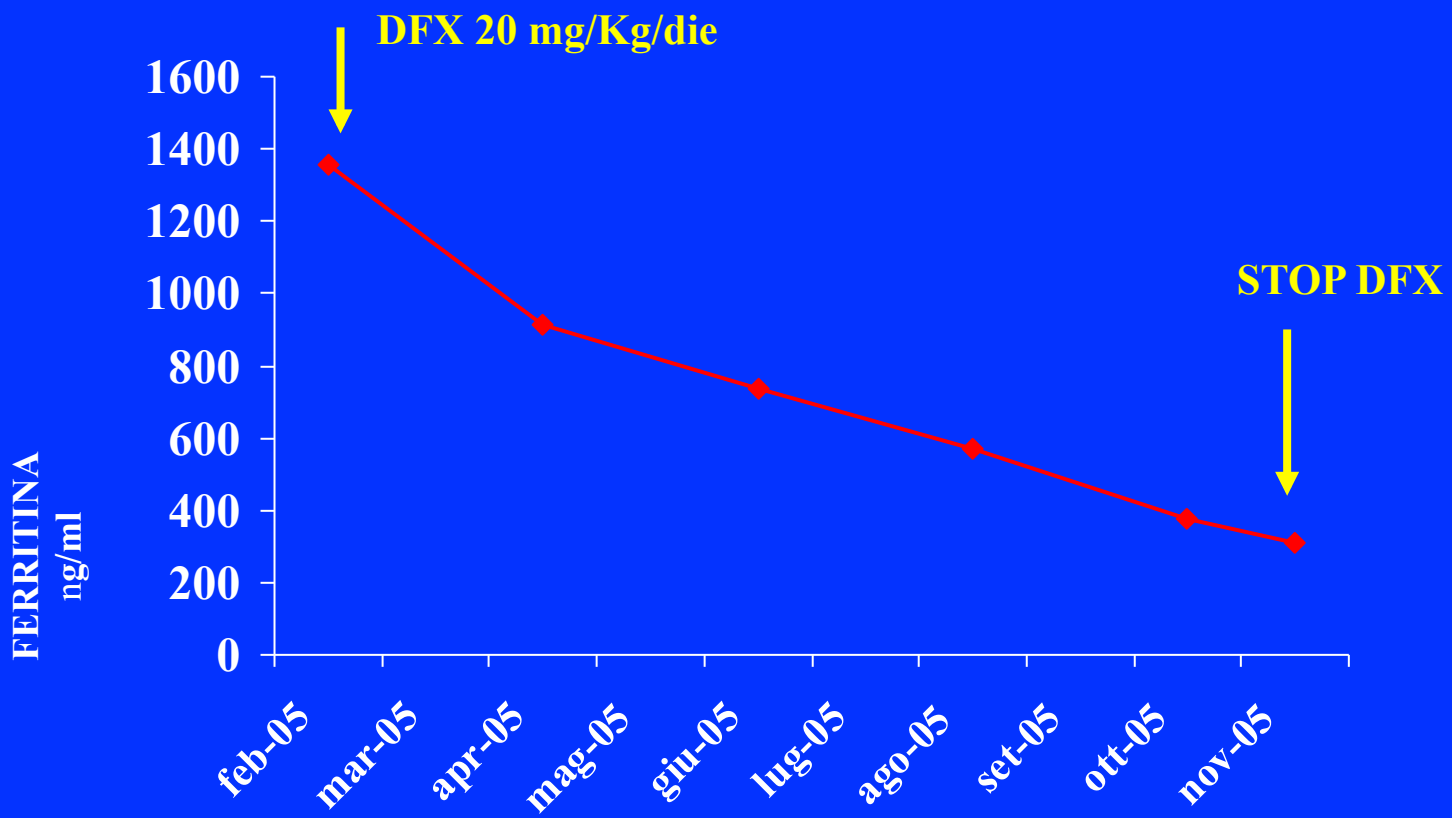


CASO CLINICO N° 1: RISPOSTA AL DEFERASIROX (B)



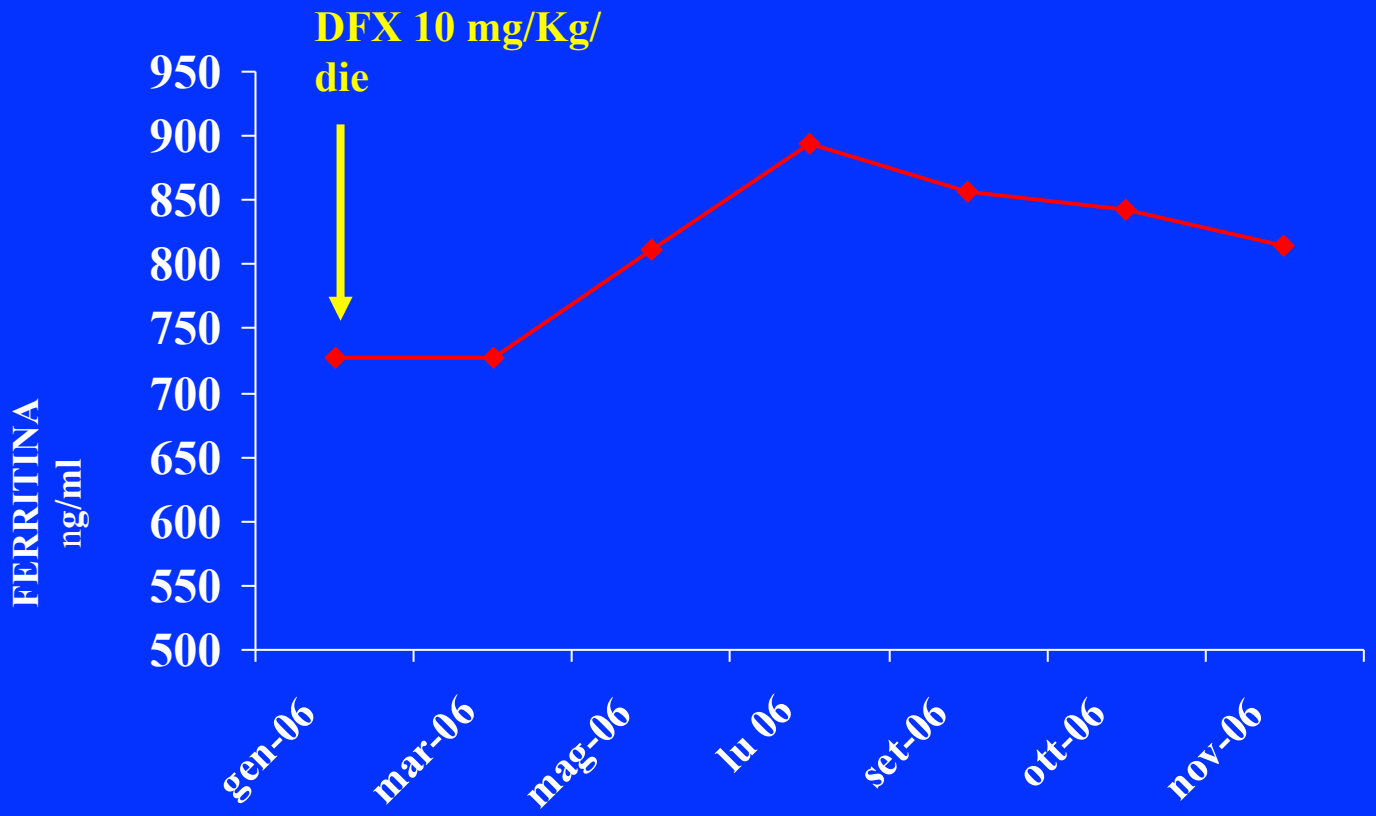
Da luglio 2004 prosegue Deferasirox con riduzione della dose (5 mg/Kg/die) sulla base della LIC (2.3) e della ferritinemia (364 ng/ml): Costante e progressivo incremento della ferritinemia (fino a 1354 ng/ml nel febbraio 2005)

CASO CLINICO N° 1: RISPOSTA AL DEFERASIROX (C)



Da febbraio 2005: nuovo incremento della posologia (20 mg/Kg/die). Progressivo decremento della ferritinemia fino a 311 ng/ml (novembre 2005) : sospende temporaneamente Deferasirox

CASO CLINICO N° 1: RISPOSTA AL DEFERASIROX (D)



Dal gennaio 2006 (ferritina 727 ng/ml) riprende Deferasirox alla posologia intermedia di 10 mg/Kg/die (prot. 108E). Da allora la ferritina si assesta a 700-900 ng/ml (bilancio marziale in pareggio) (ottobre 2006: 842 ng/ml)

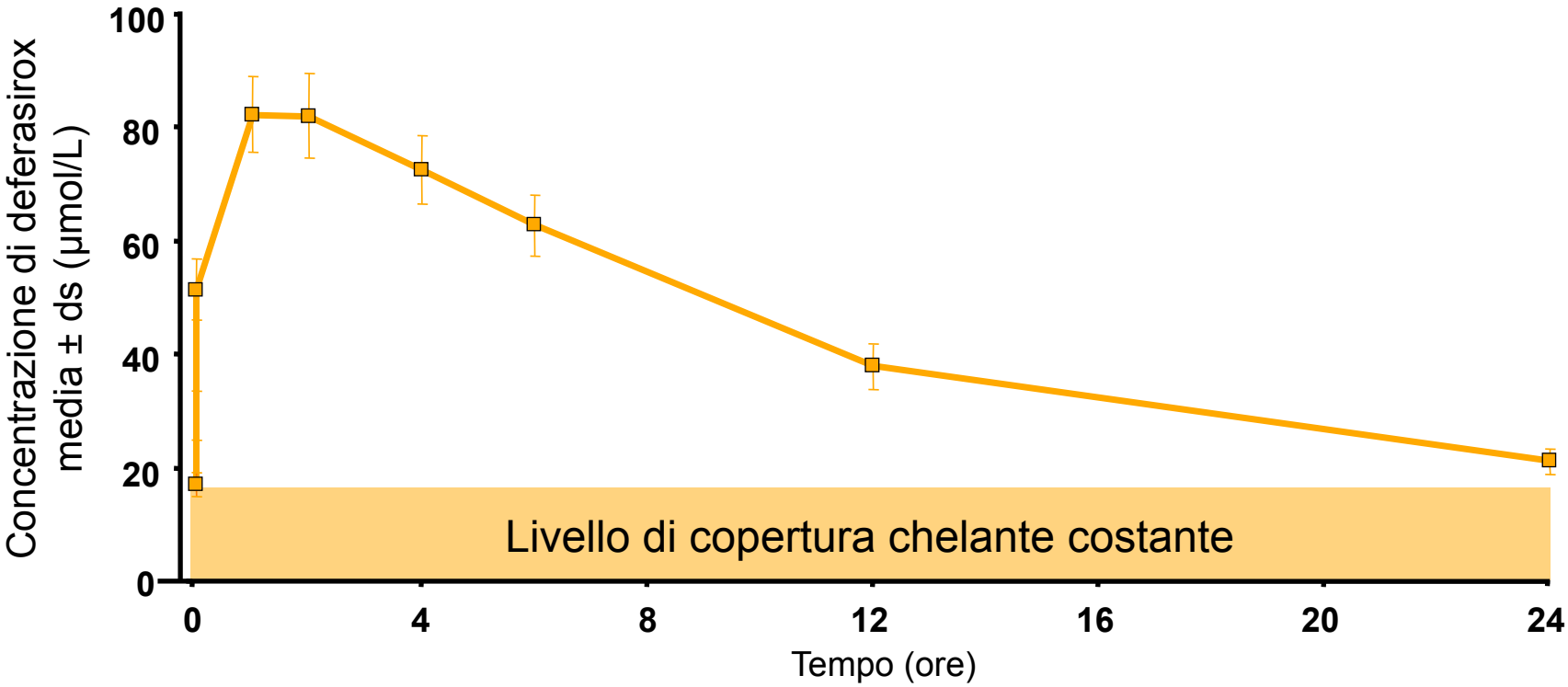
CASO CLINICO N° 1 (3)

- **giugno 2009:** Inizia terapia con **LENALIDOMIDE;**
  CARATTERISTICHE PRE-TERAPIA: Cariotipo: de(5q), +8; Blasti midollari < 2%; N° di citopenie: 1 (anemia); Rischio IPSS: basso (score 0); Ritmo trasfusionale: 4 unità/4 settimane; **ferritina (4/2009): 823 ng/ml**
- **ottobre 2009: 1° RISPOSTA (Hb 12,2);** TIPO DI RISPOSTA (IWG, Cheson 2006): RC; TEMPO ALLA 1° RISPOSTA : 3° mese; DURATA DELLA RC EMATOLOGICA: 76 mesi (ottobre 2009- febbraio 2013); DURATA DELLA CCR: : 18 mesi (luglio 2010-gennaio 2012)
- **ottobre 2009:** sospensione di DFX (cessazione delle trasfusioni, ferritina 791 ng/ml)
- **luglio 2010:** (dopo 12 mesi di terapia): remissione citogenetica completa (CCR)
- **luglio 2011:** sospensione della lenalidomide
- **aprile 2016 :** relapse (Hb 8,8): ripresa della lenalidomide
- **luglio 2016:** Hb 11,1 ; aprile 2017 Hb 12,6
- **SOPRAVVIVENZA: 251 mesi dalla diagnosi**

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

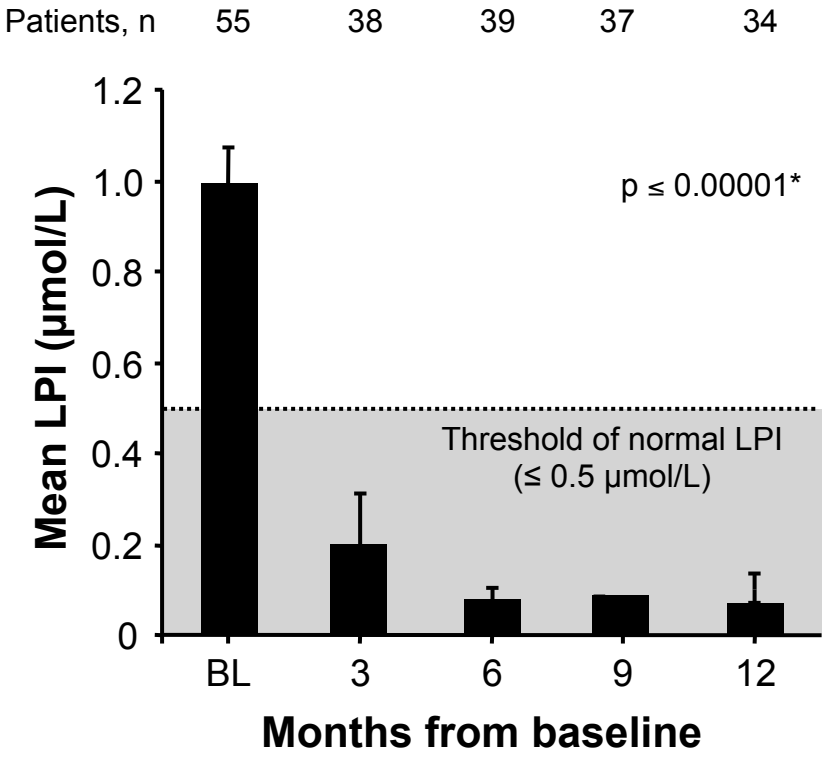


AUC dopo monosomministrazioni giornaliere ripetute di 20 mg/kg/die

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

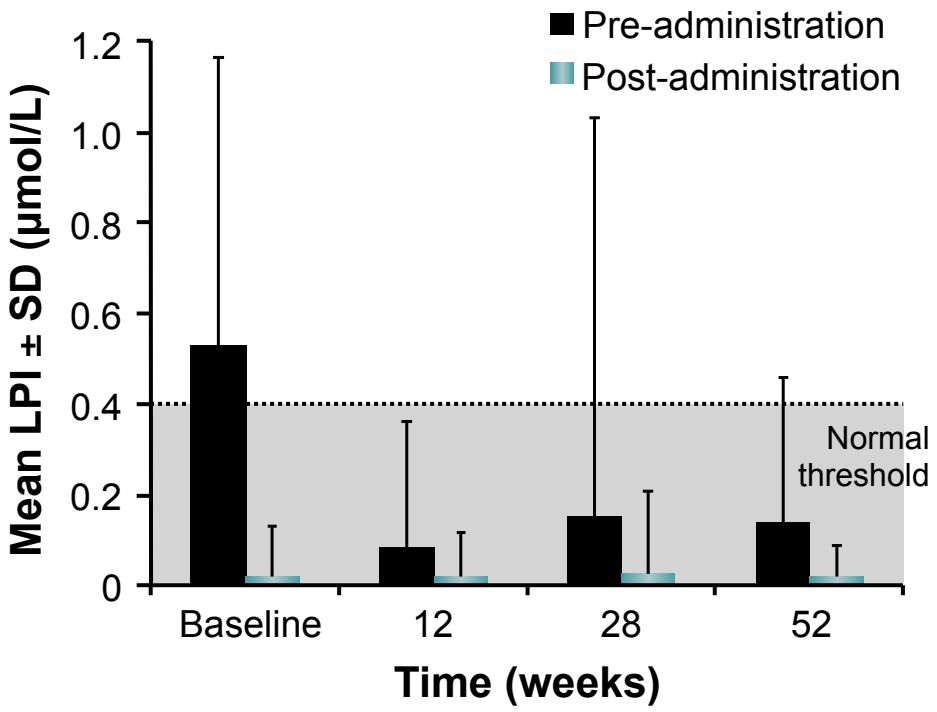
Effect of deferasirox on LPI in MDS

US03 study[1]



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

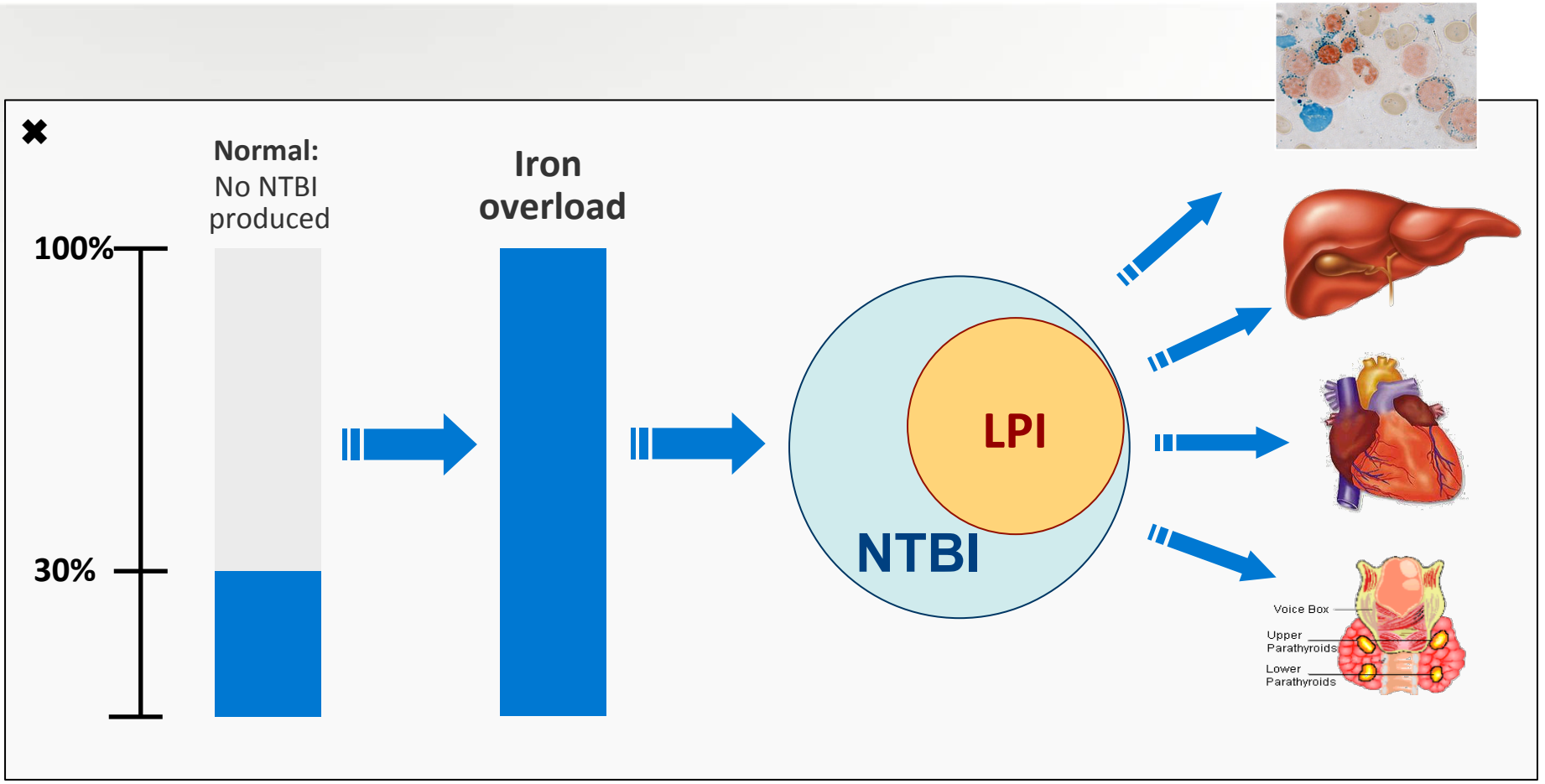
EPIC study – MDS cohort [2]



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)



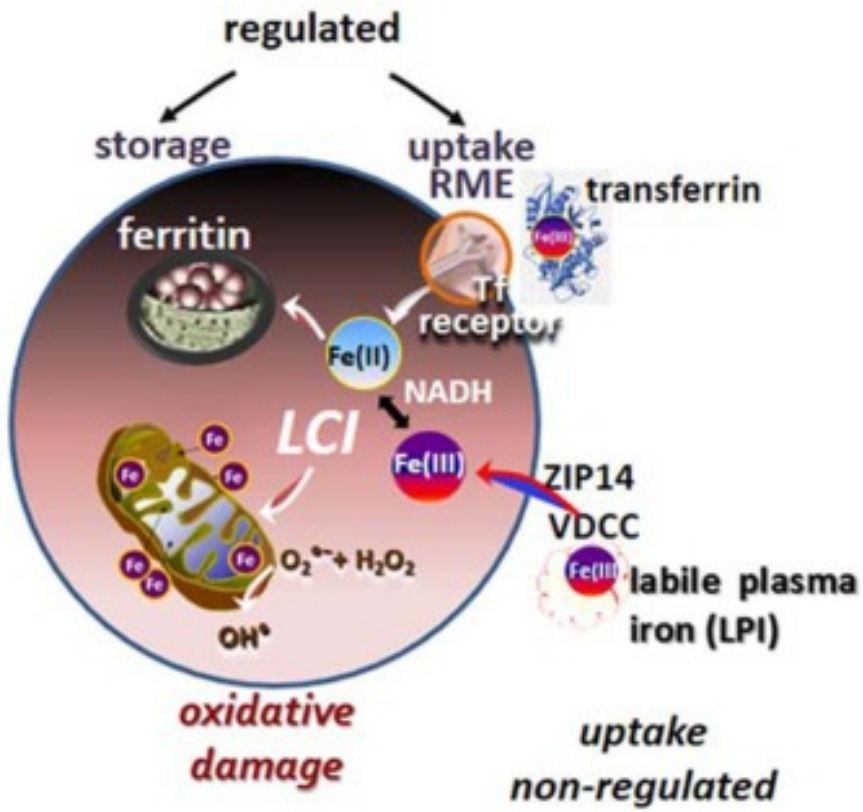
NTBI appears when plasma iron exceeds transferrin binding capacity (saturation > 60–70%)

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.

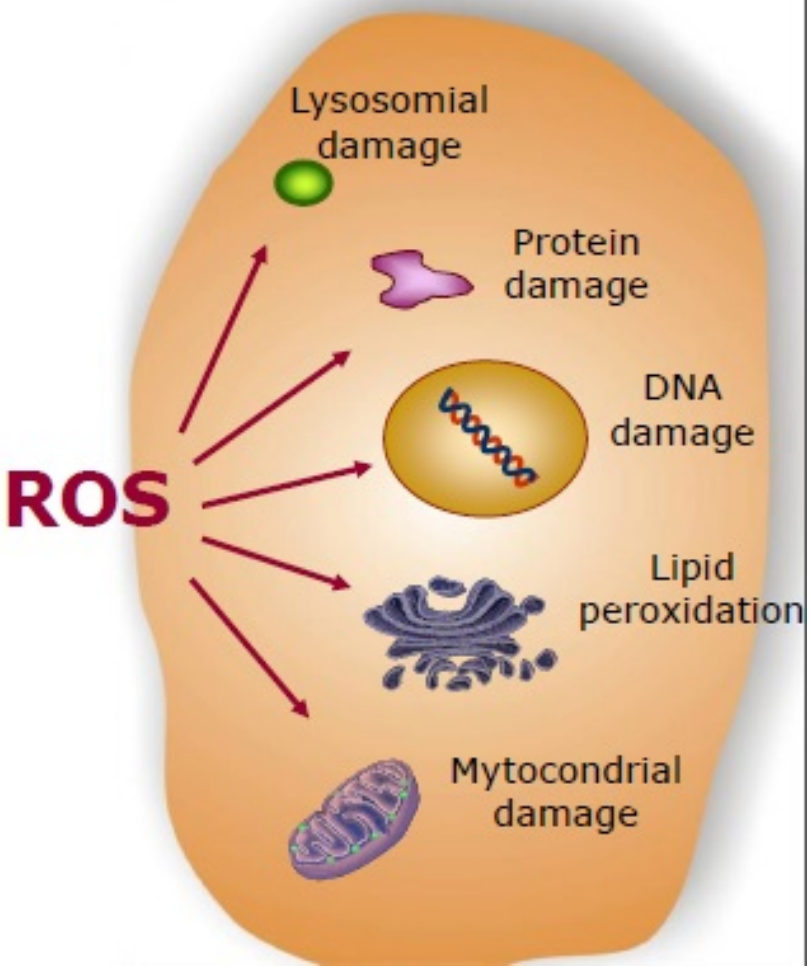
Fe toxicity tissue =

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

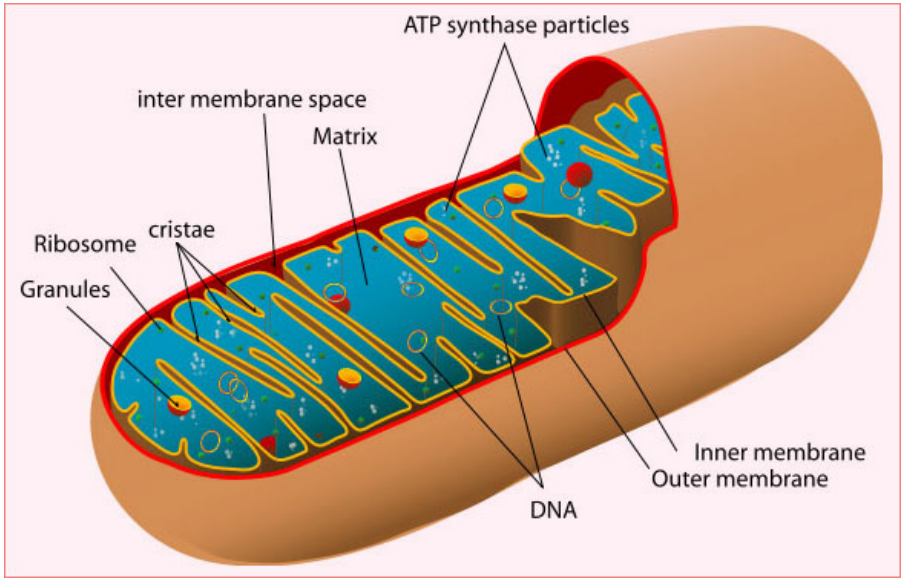
Figure adapted by Jomova et al. Toxicology. 2011:283:65

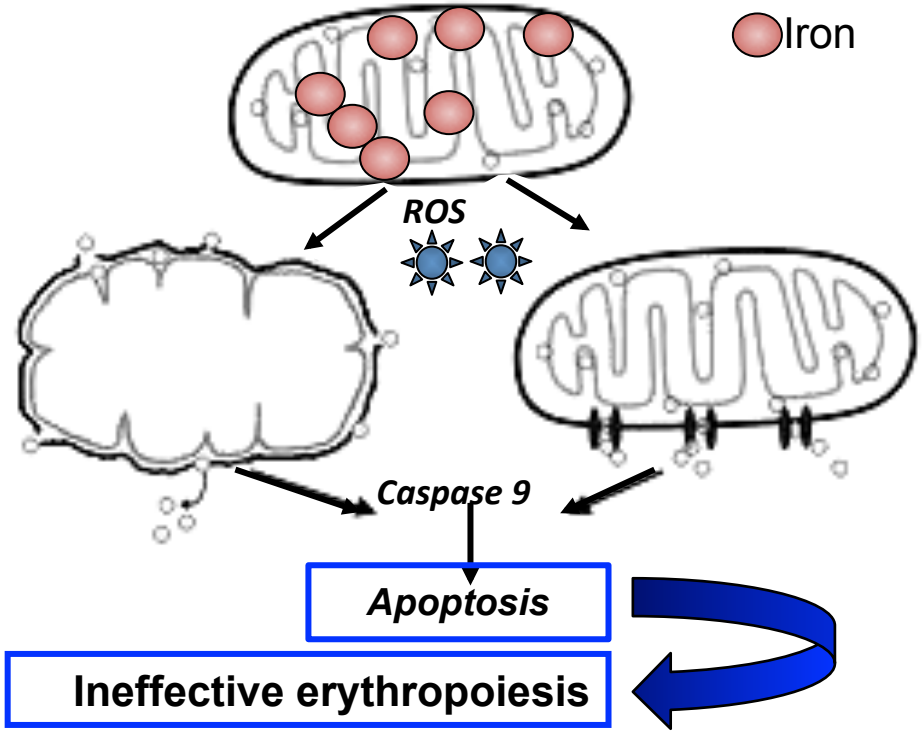
ROS Promote Apoptosis through Activation of the Caspase Cascade

Iron is also a potentially toxic metal

Labile iron can catalyze the production of toxic radicals:

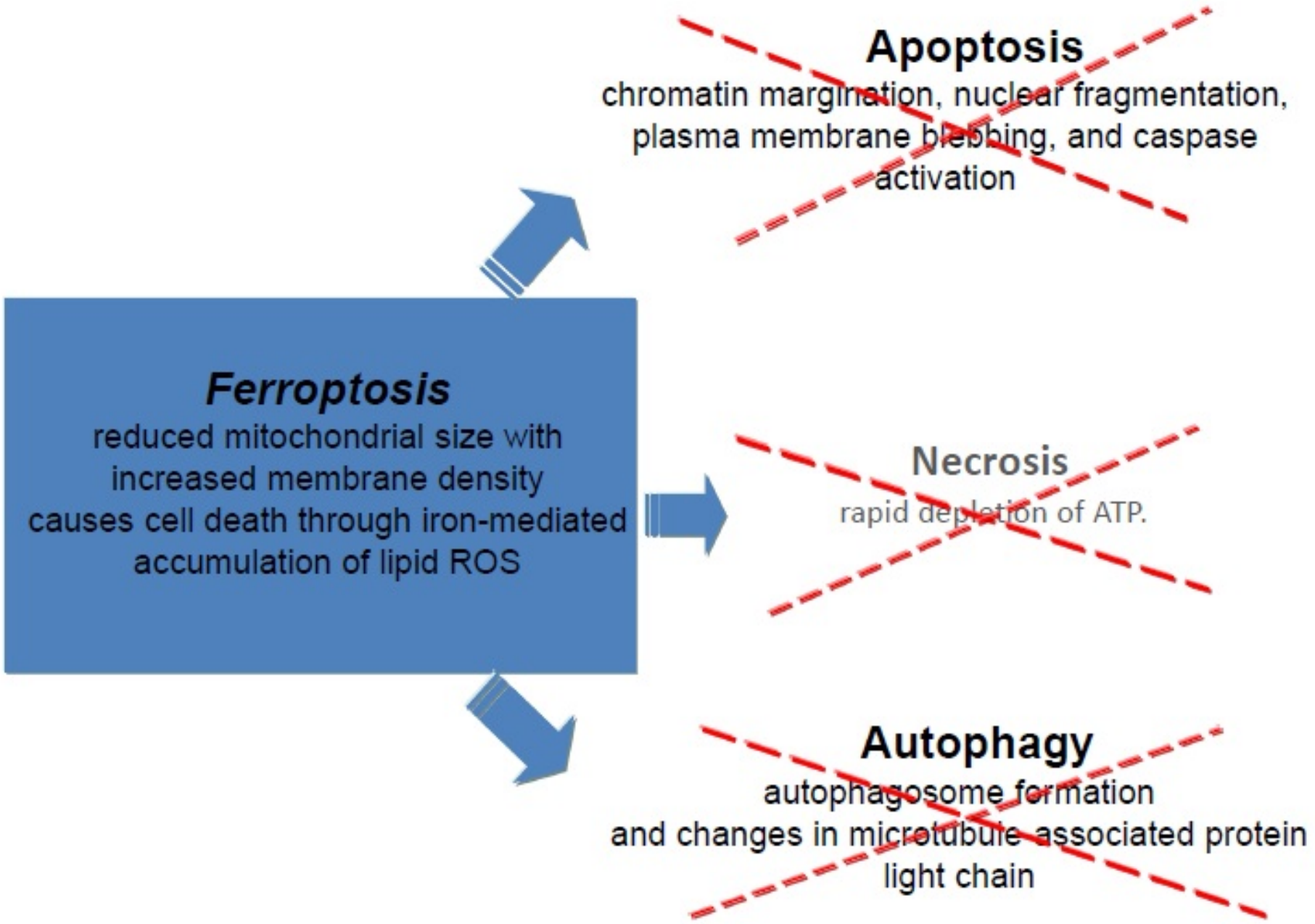
$$O_2^{\bullet -} + H_2O_2 \xrightarrow{Fe(II)} O_2 + OH^- + OH^{\bullet}$$ that can damage the cells





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

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



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.

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]

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[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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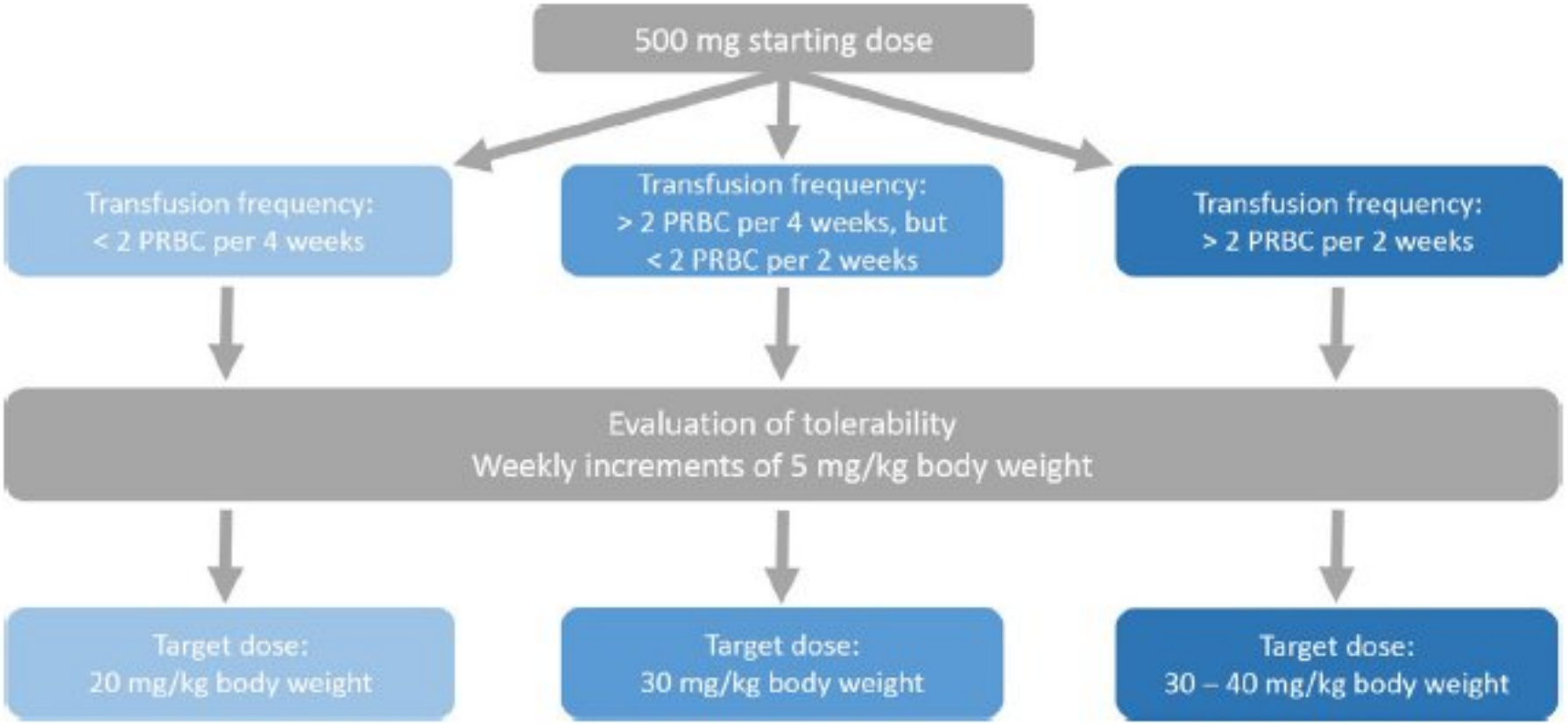
Nolte, Leuk Res 2015

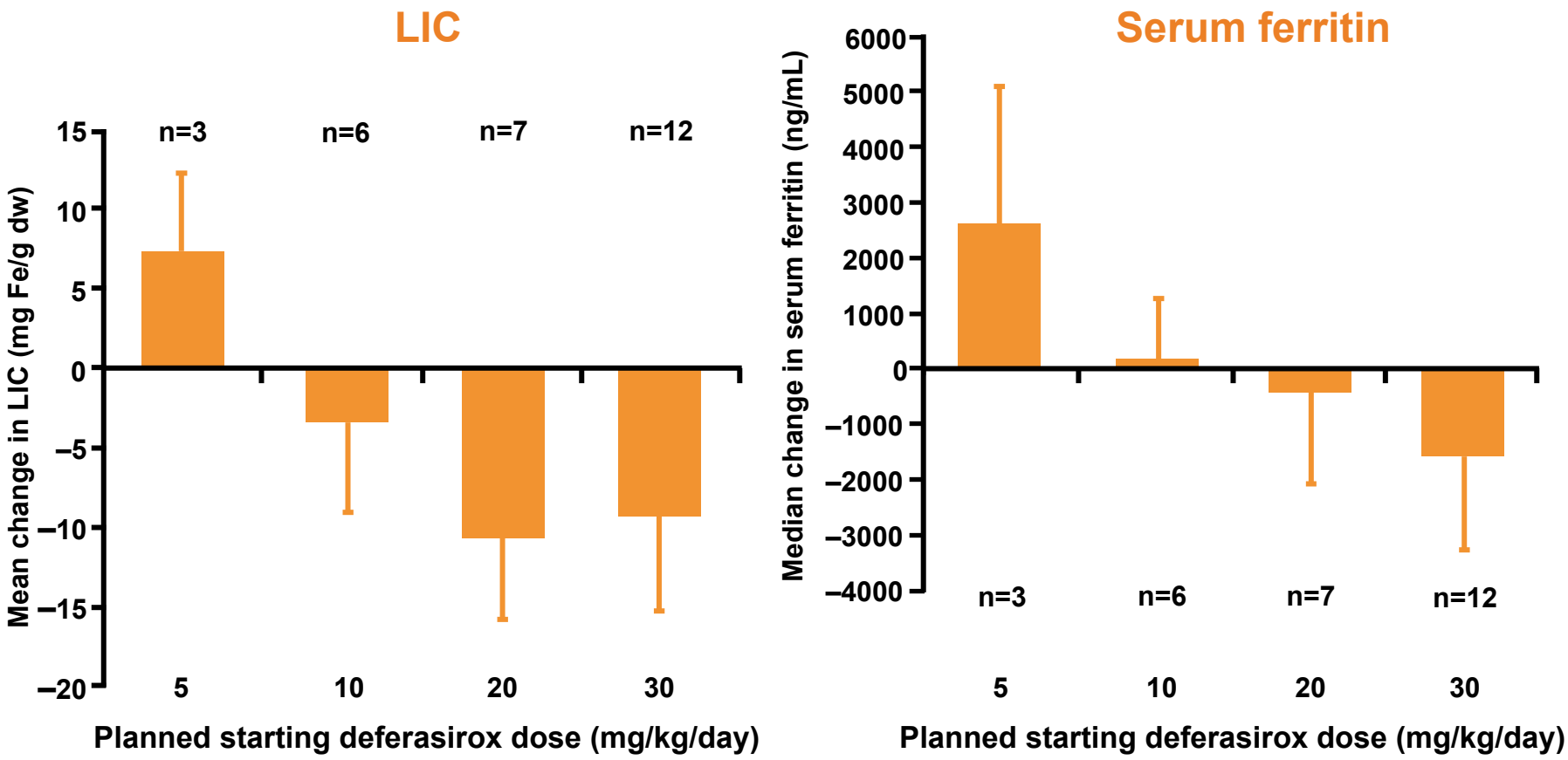


Nolte, Leuk Res 2015

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%)

Deferasirox therapy in MDS induces dose-dependent changes in iron burden (47 MDS pts)



In patients with MDS, iron balance was achieved with 10 mg/kg/day and negative iron balance with 20 and 30 mg/kg/day

Porter J *et al*. *Eur J Haematol* 2008;80:168–176

Study 108

Study 108 – MDS patients
Safety and Tolerability

- 29 MDS patients (61.7%) completed the study
- Study discontinuation
  - 6 patients withdrew consent,
  - 1 patient no longer required study drug
  - 7 patients withdrew due to AEs
    - only one of these AEs – a case of recurrent nausea and vomiting – was considered drug-related
- AEs, *regardless of relationship to deferasirox*, were reported by 45 patients (95.7%). Most AEs were *mild or moderate* in intensity.
- Most common AEs thought to be *related to deferasirox* included transient, mild-to-moderate *diarrhoea* (10/47; 21.3%), *nausea* (7/47; 14.9%) and *vomiting* (6/47; 12.8%)
- Incidence of diarrhea appeared to be dose-dependent

Porter J, Eur J Haematol, 2008, 80: 168-176

Study 108 – MDS patients
Safety and tolerability
Serum creatinine

Mild non-progressive increase of serum creatinine was observed:

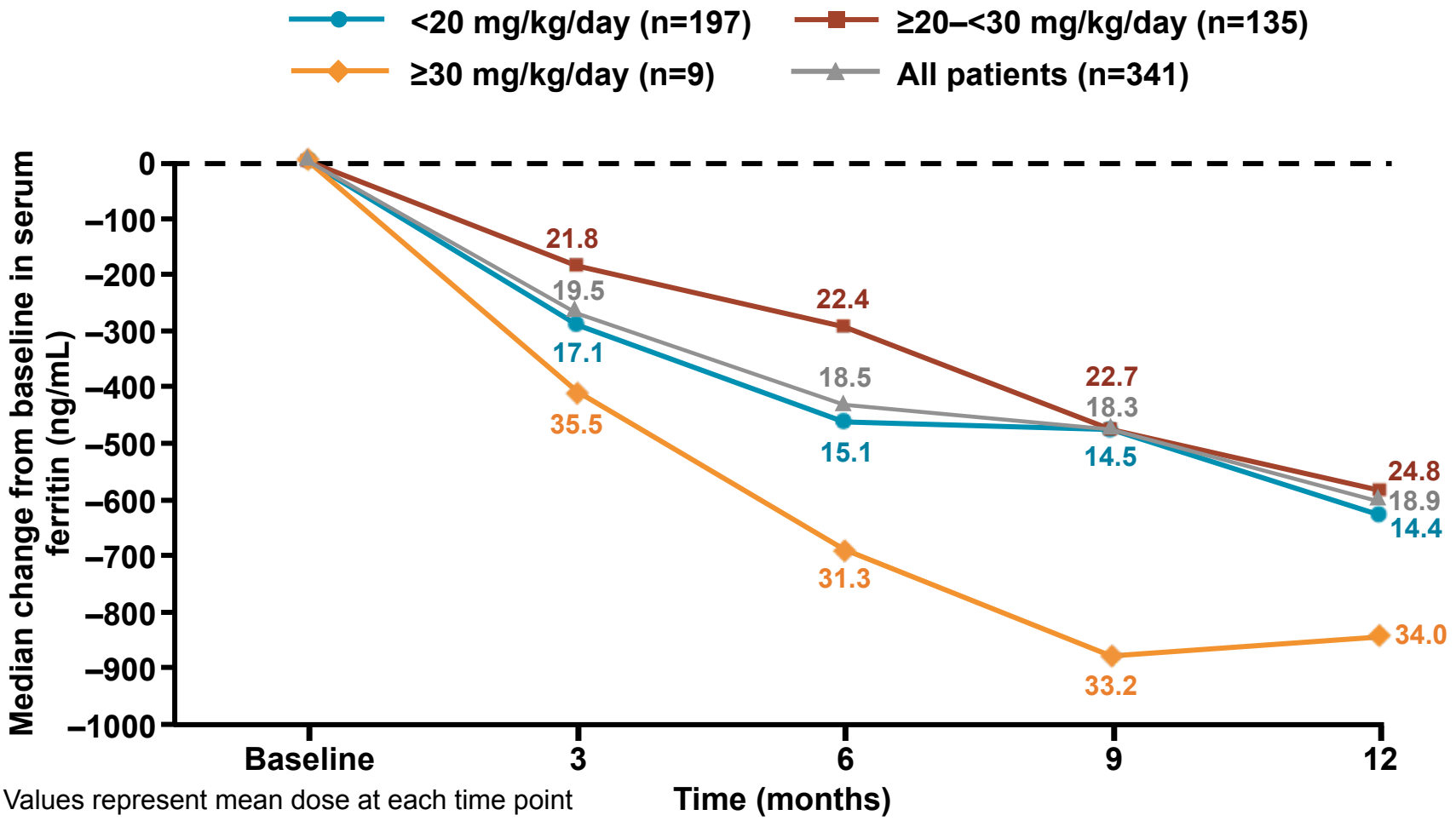
- No. of patients with creatinine > 33%, but < ULN, at ≥ 2 consecutive post-baseline visits 8 (17.0%)
  - 4 patients received 20 mg/kg/day
  - 4 patients received 30 mg/kg/day

- No. of patients with creatinine > 33% and > ULN, at ≥ 2 consecutive post-baseline visits 9 (9.1%)
  - 4 patients received 20 mg/kg/day
  - 5 patients received 30 mg/kg/day

- The values NEVER exceeded twice the ULN in ANY patients

Porter J, Eur J Haematol, 2008, 80: 168-176

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



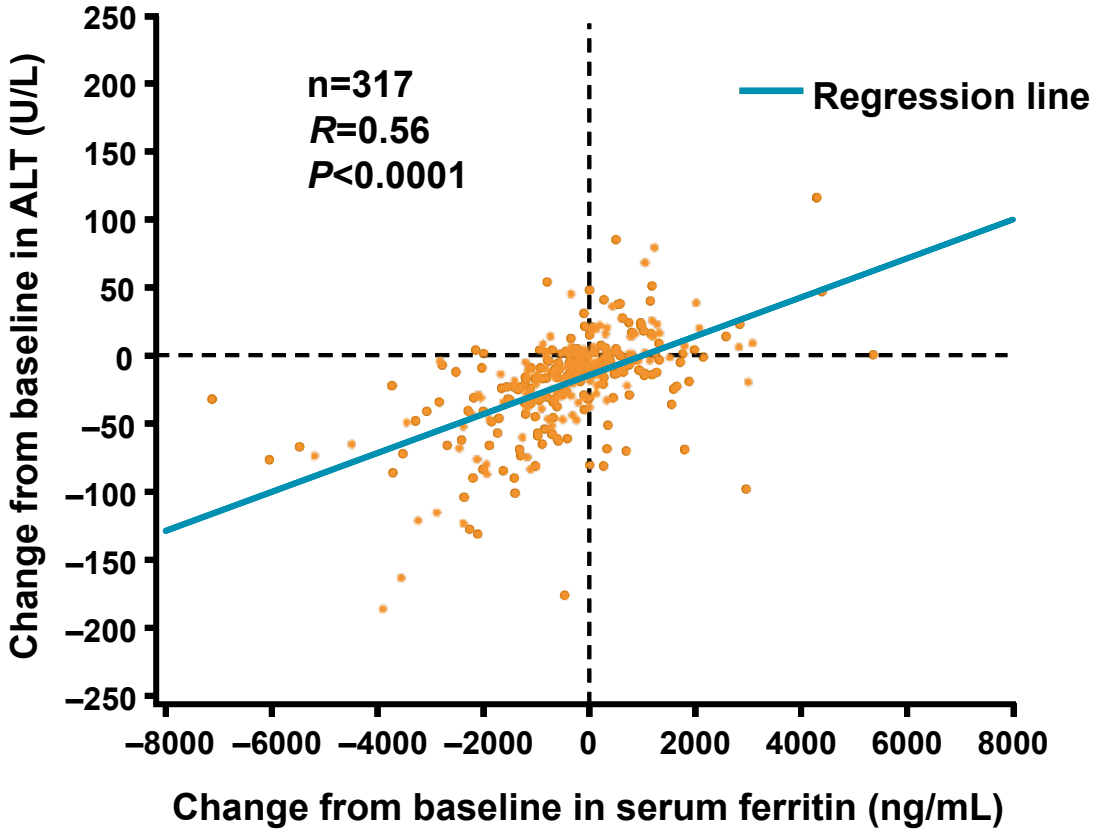
Values represent mean dose at each time point

Gattermann N *et al*. Presented at ASH 2008 [*Blood* 2008;112(11):abst 633]; Gattermann N *et al*. *Leuk Res* 2010;34:1143–1150.

Study 2409

Correlation between decreased serum ferritin and improved ALT during deferasirox treatment in iron-overloaded patients with MDS (2)

Correlation between change in serum ferritin and change in ALT



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

Study 2409

Leukemia Research 34 (2010) 1560–1565

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

Prospective assessment of effects on iron-overload parameters of deferasirox therapy in patients with myelodysplastic syndromes

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ABSTRACT

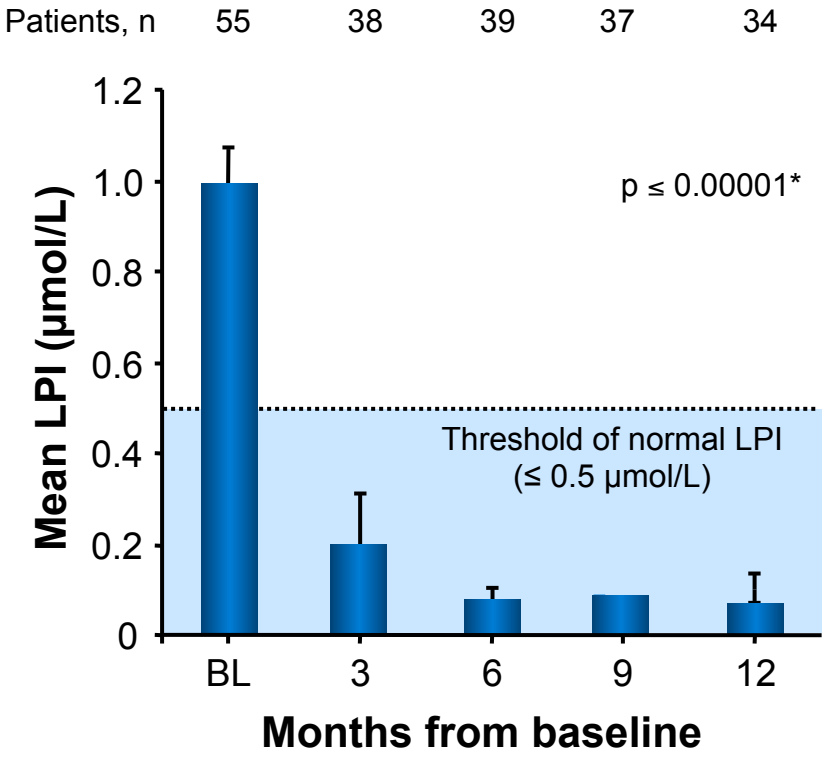
We report the first prospective study evaluating the effects of deferasirox on liver iron concentration (LIC), labile plasma iron (LPI) and pharmacokinetics (PK) along with serum ferritin values in patients with IPSS Low- and Intermediate-1 risk myelodysplastic syndromes (MDS) and evidence of iron overload. Twenty-four heavily transfused MDS patients were enrolled in a planned 52 weeks of therapy. PK studies showed dose-proportional total drug exposure. Data demonstrated that deferasirox was well tolerated and effectively reduced LIC, LPI and serum ferritin in the iron-overloaded patients with MDS who completed 24 and 52 weeks of therapy despite ongoing receipt of red blood cell transfusions.

Deferasirox reduces serum ferritin and LPI in RBC transfusion-dependent patients with MDS *(List, JCO 2012)*

- Studio prospettico multicentrico, MDS con IPSS basso o INT-1
- 176 paz arruolati, 173 trattati
- ↓ ferritina del 23% dopo 12 mesi di DFX (53% dei paz), del 36,7% dopo 24 mesi (28.3% dei paz), e del 36,5% dopo 36 mesi (19.1% dei paz)
- ↓ ferritina correlata con ↓ ALT ($p < .001$)
- 68 paz (39.3%): ↑ LPI a baseline, in tuti i casi LPI normale entro 13 settimane
- 51 paz (28%): Hematologic Improvement (IWG 2006)
- In 3 aa: 138/173 paz (79.8%) hanno interrotto DFX, 43 paz (24.8%) per AE o progressione, e 23 (13.2%) per anomalie di laboratorio
- AE più frequenti: disturbi gastrointestinali e ↑ creatinina
- Decessi: 28 (nessuno imputabile a DFX)

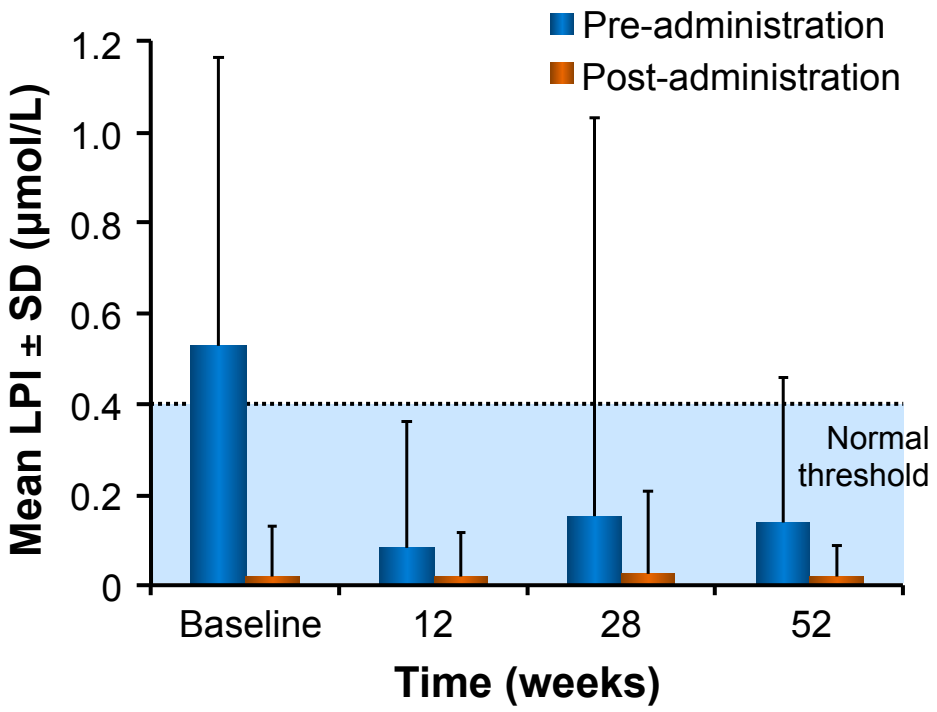
Effect of deferasirox on LPI in MDS

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.

EUROPEAN JOURNAL OF Haematology

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ORIGINAL ARTICLE

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

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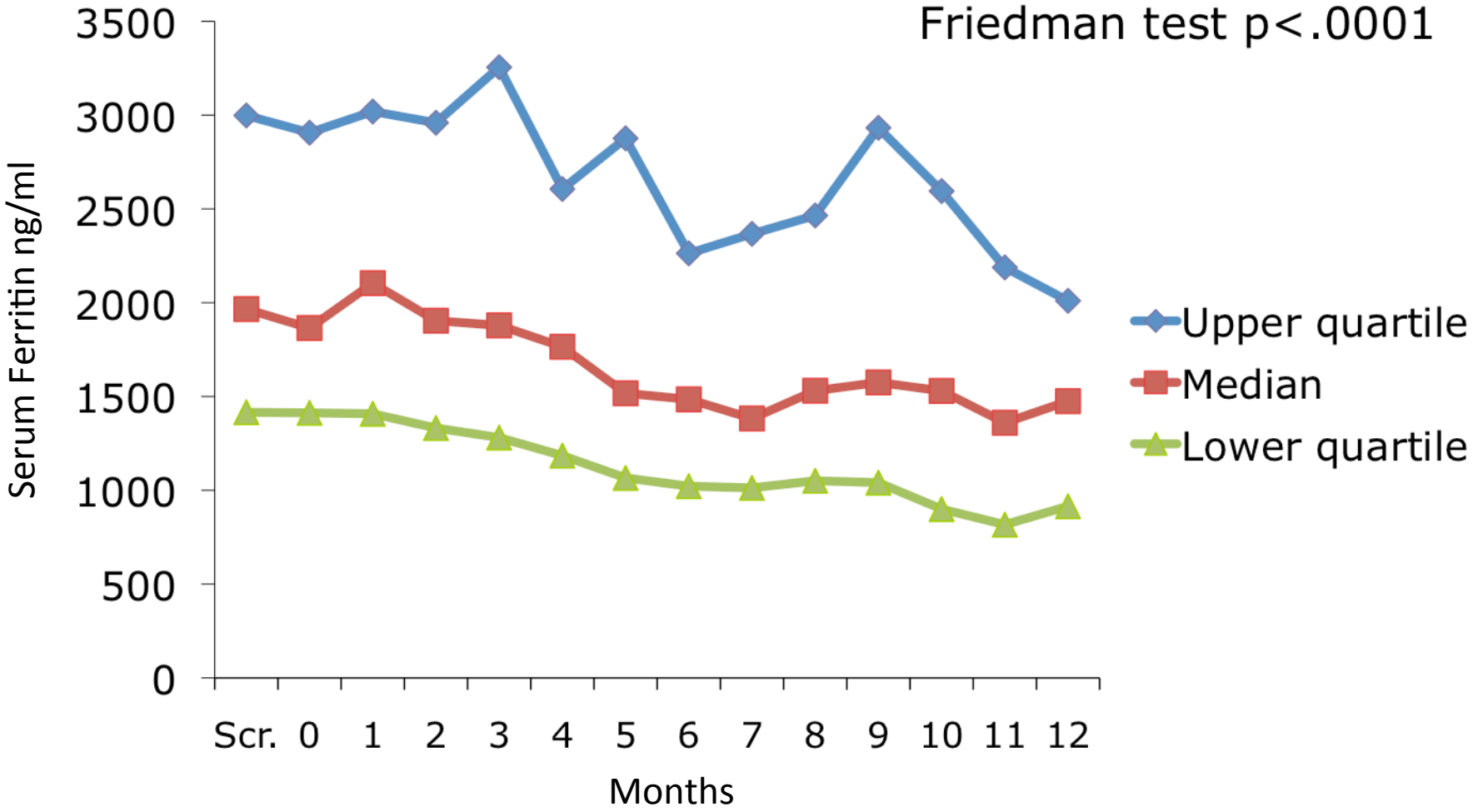
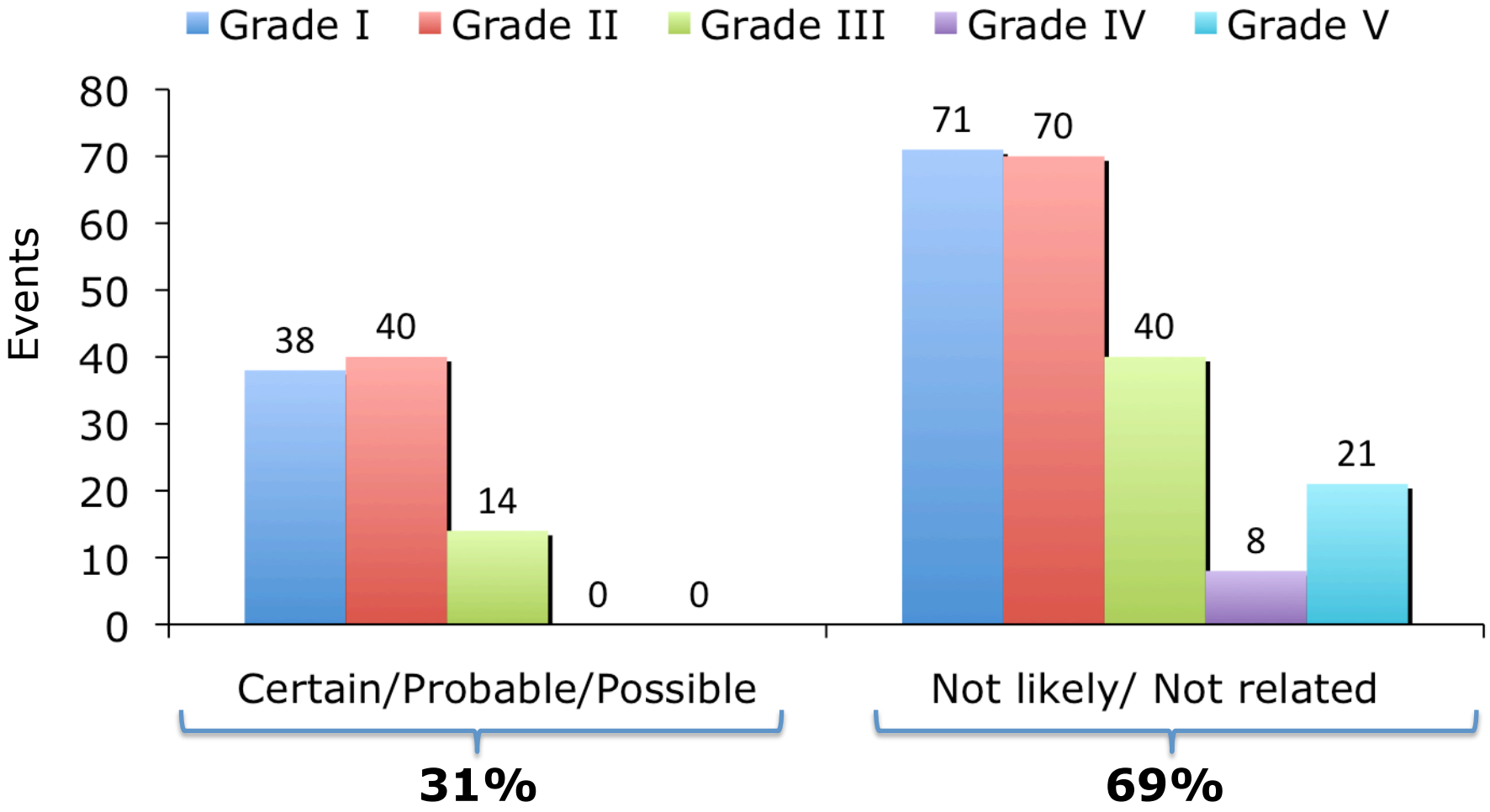
Angelucci, Eur J Haematol. 2014 Jun;92(6):527-36

Activity – Serum ferritin



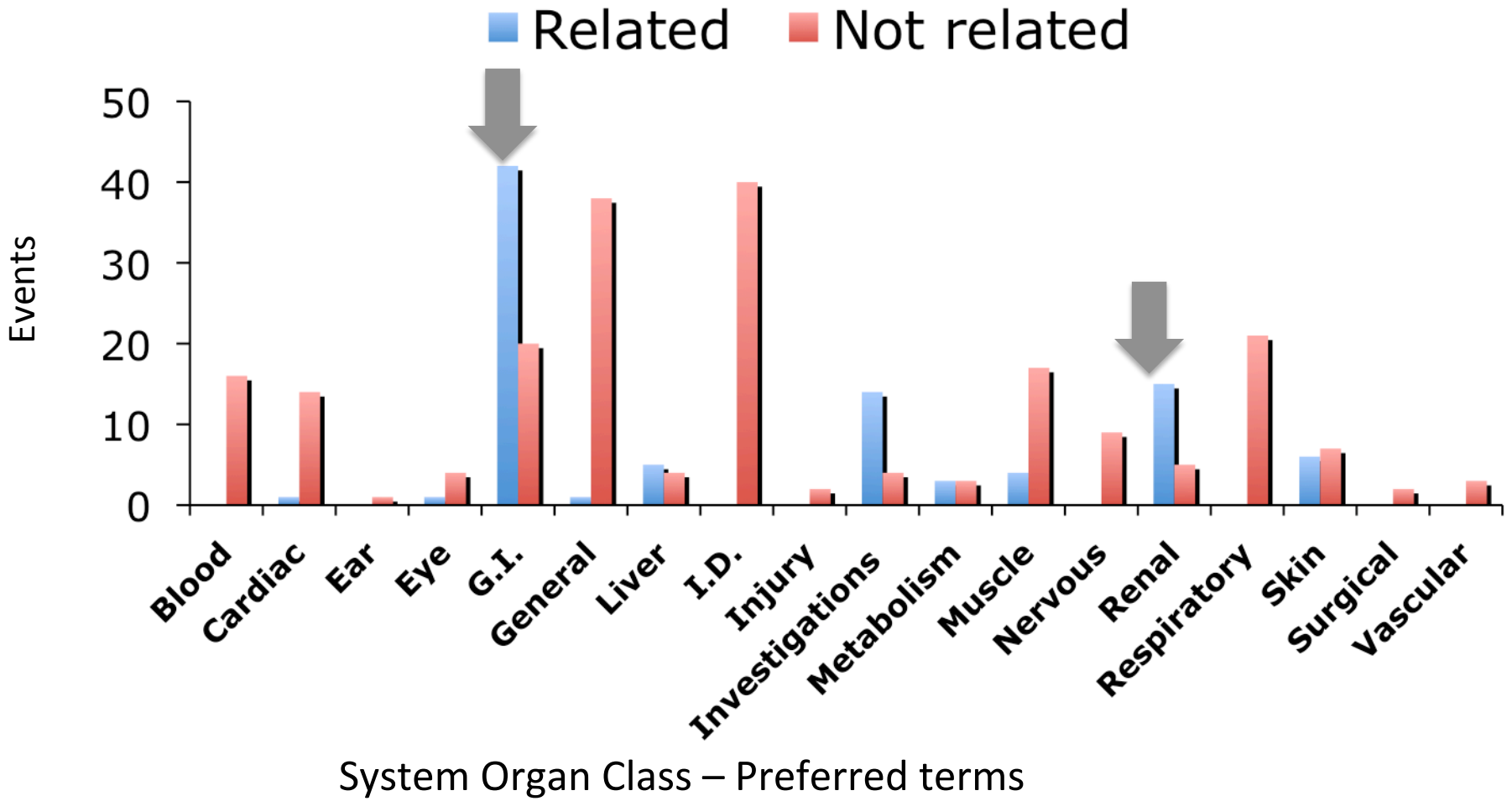
Adverse events

Severity and relationship to Deferasirox.

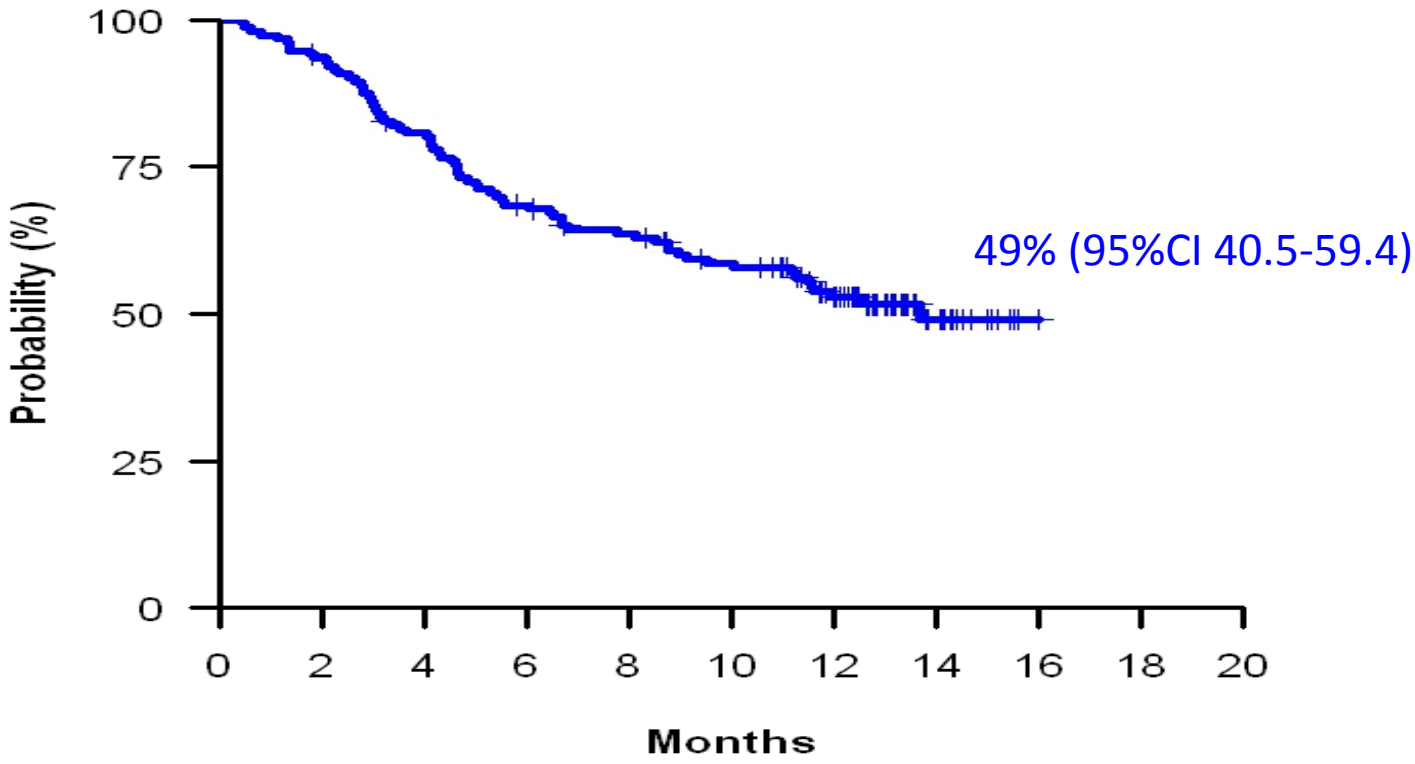


Adverse events

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	

Frequency of adverse events (AEs) during deferasirox treatment

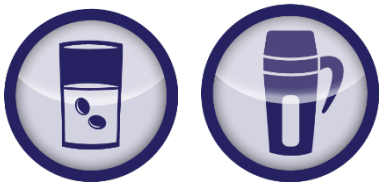
AE	Frequency (% patients)	Observations
Non-progressive increase in serum creatinine	36	Mild, mostly within normal range; dose dependent, often resolve spontaneously; may be alleviated by dose reduction
Gastrointestinal disturbance (nausea, vomiting, diarrhea, abdominal pain)	26	Dose-dependent, mostly 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

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

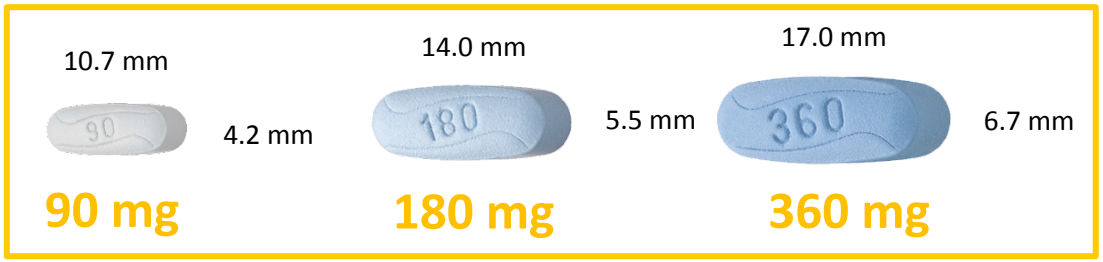
Must be taken on an empty stomach (at least 30 min before food)

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

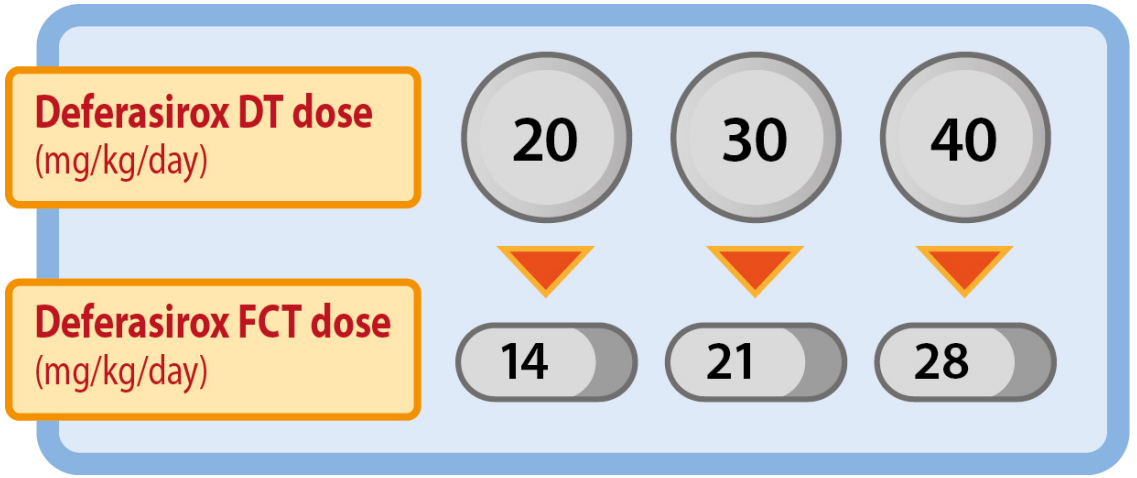
Deferasirox tablets for oral suspension	Nuova formulazione compresse rivestite con film
10 mg/kg/day 20 mg/kg/day* 30 mg/kg/day 40 mg/kg/day	7 mg/kg/day 14 mg/kg/day* 21 mg/kg/day 28 mg/kg/day

Note: * Recommended starting dose.

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

Deferasirox DT dose conversion to deferasirox FCT

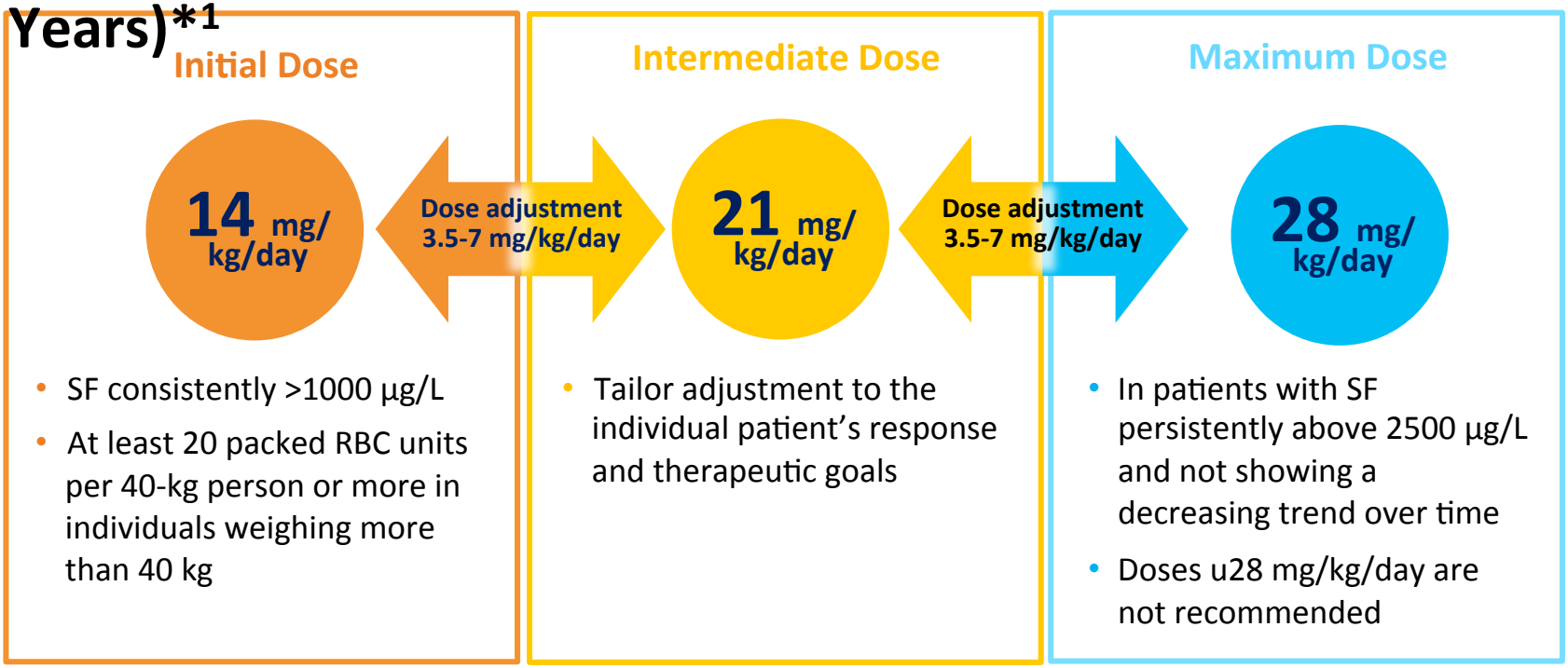
- For patients who are currently receiving chelation therapy with deferasirox DT and converting to deferasirox FCT, the dose of deferasirox FCT should be about 30% lower, rounded to the nearest whole tablet, because of higher bioavailability[1]
- For example, if a patient is currently taking deferasirox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

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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

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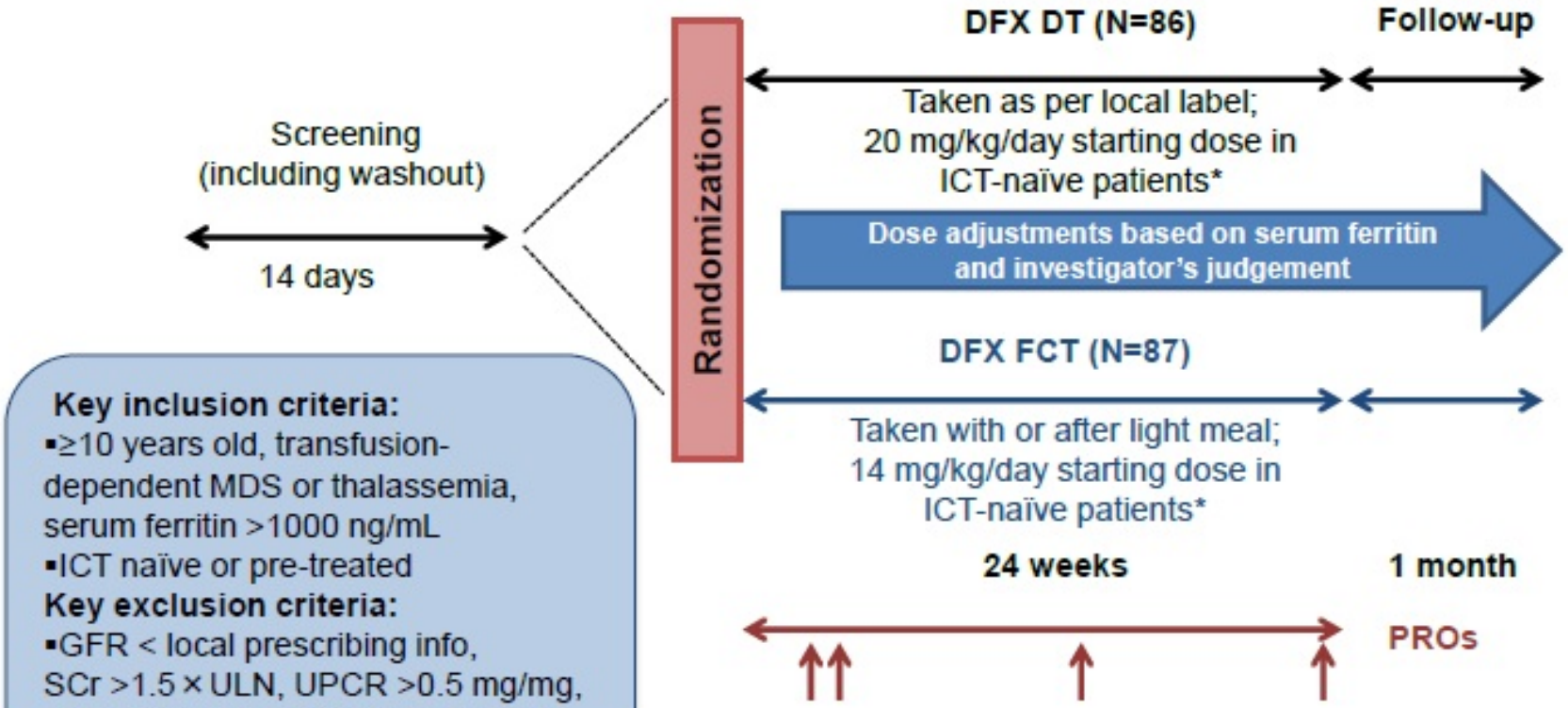
Am J Hematol. 2017;92:420–428.

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]

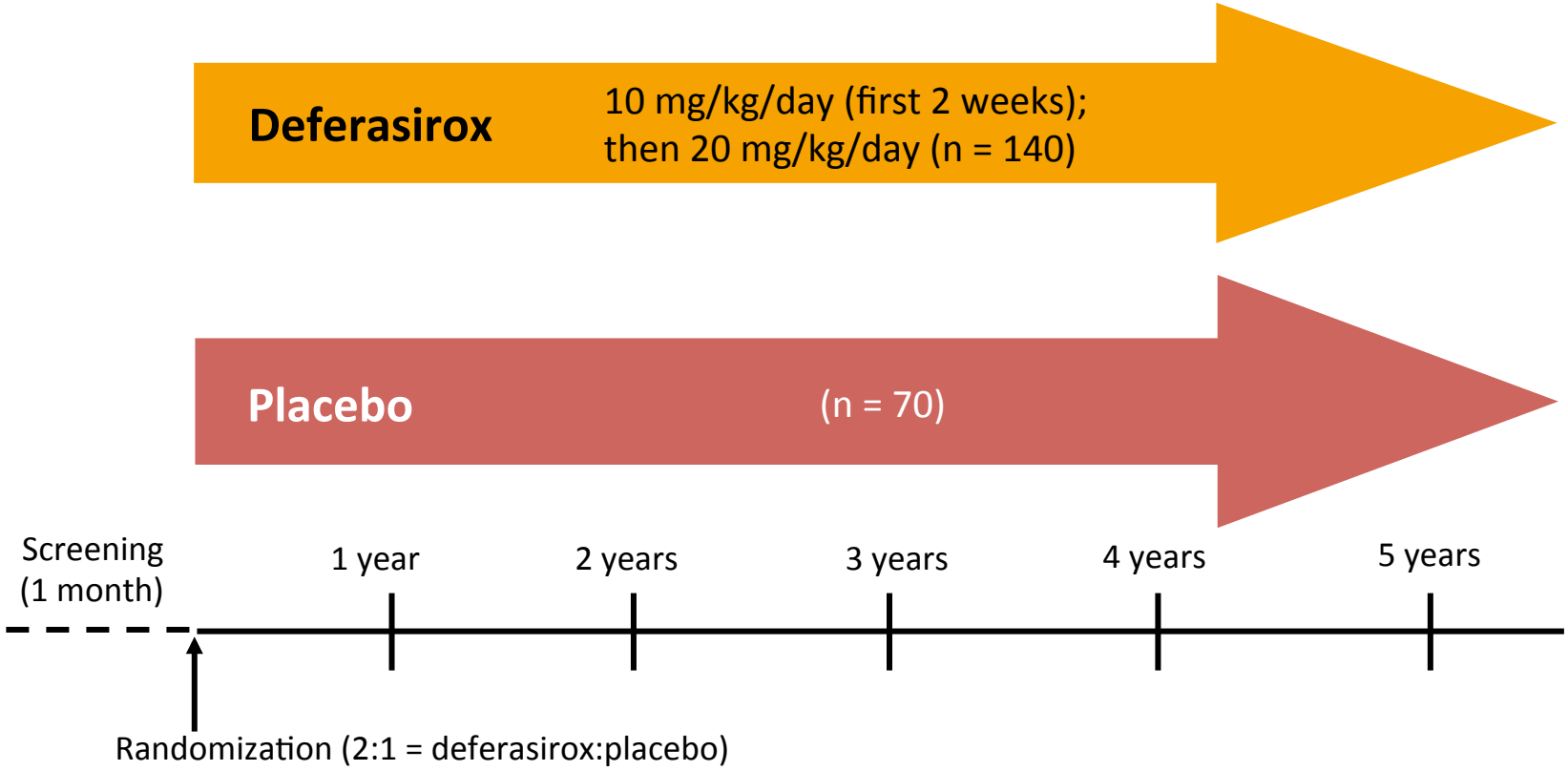
1. Huang VW *et al. International Society for Pharmacoeconomics and Outcomes Research (ISPOR-EU) 19th Annual European Congress, Vienna, Austria October* 2016;PCN210

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

TELESTO: ongoing prospective study of deferasirox in MDS

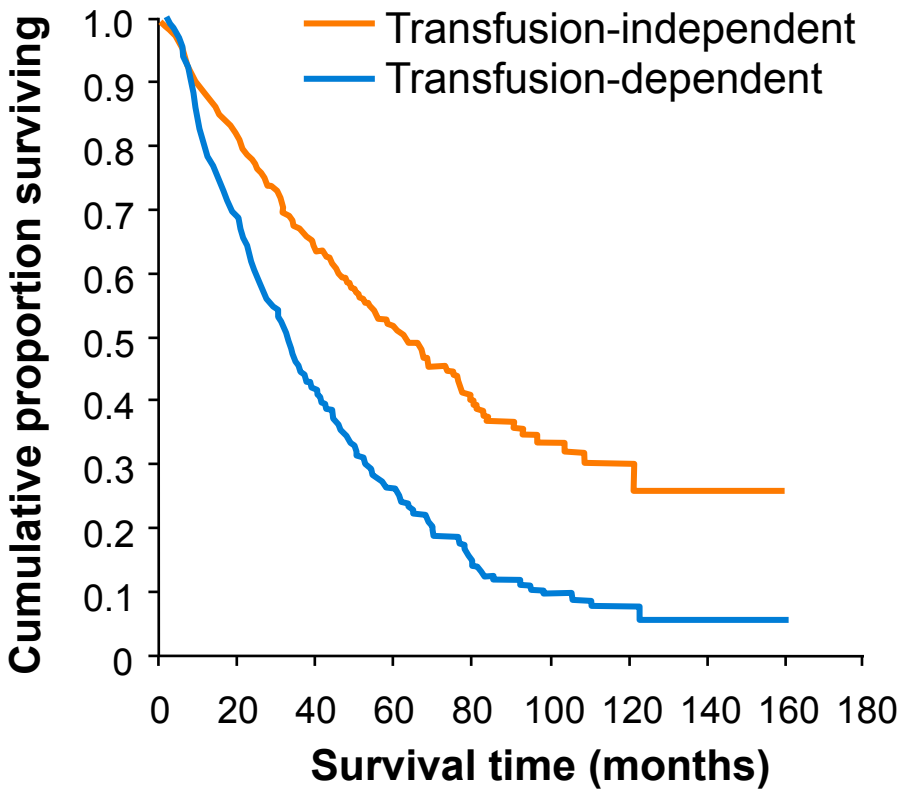
- Prospective, multicentre study to investigate the clinical benefit of chelation therapy with deferasirox in **210** MDS patients
- Primary study end-point: EFS (death, cardiac, and hepatic non-fatal events)



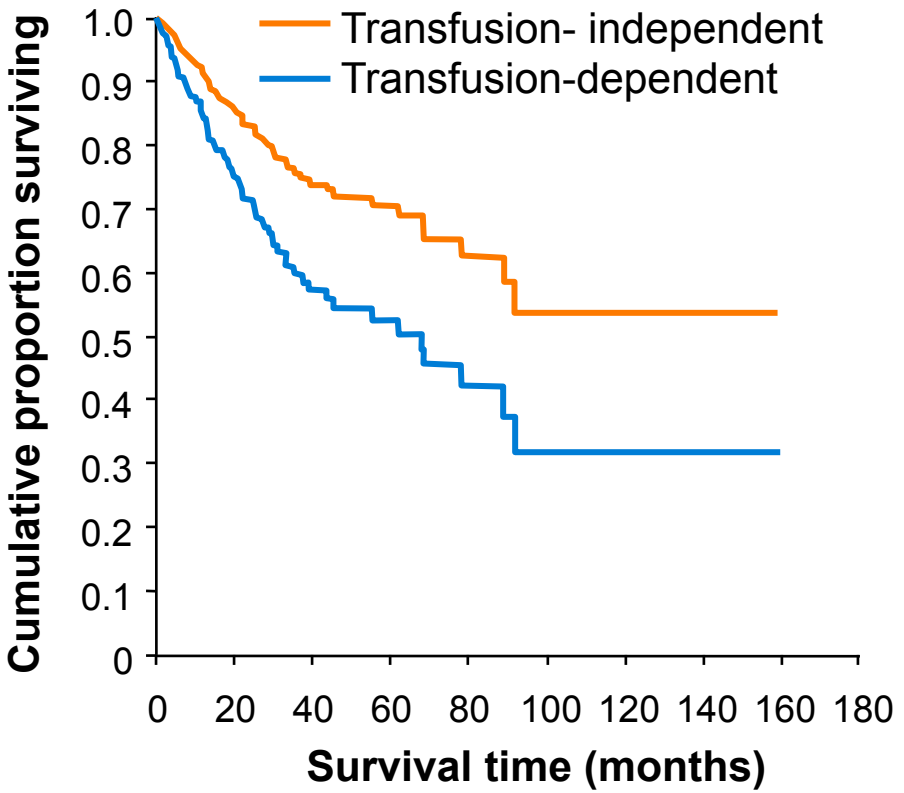
Angelucci E, et al. Blood. 2009;114:abstract 4854.

Survival of MDS patients by transfusion dependence (N = 467)

Overall survival
(HR = 1.91; p < 0.001)



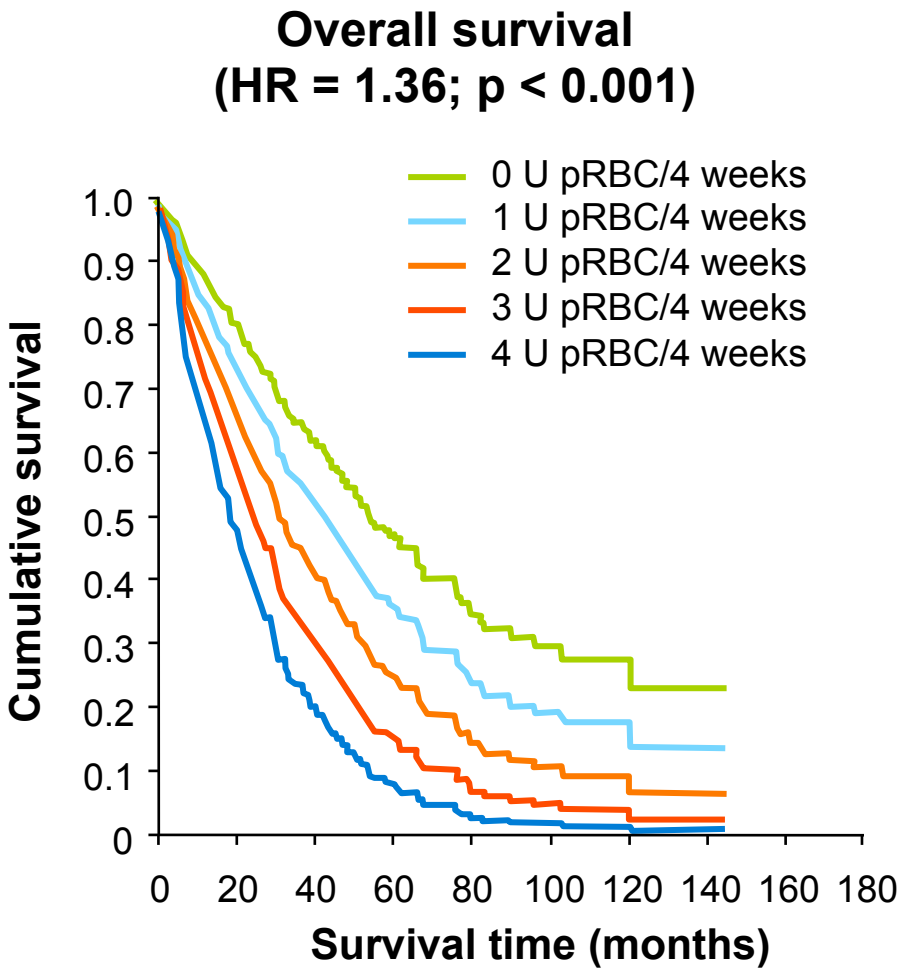
Leukaemia-free survival
(HR = 1.84; p = 0.001)

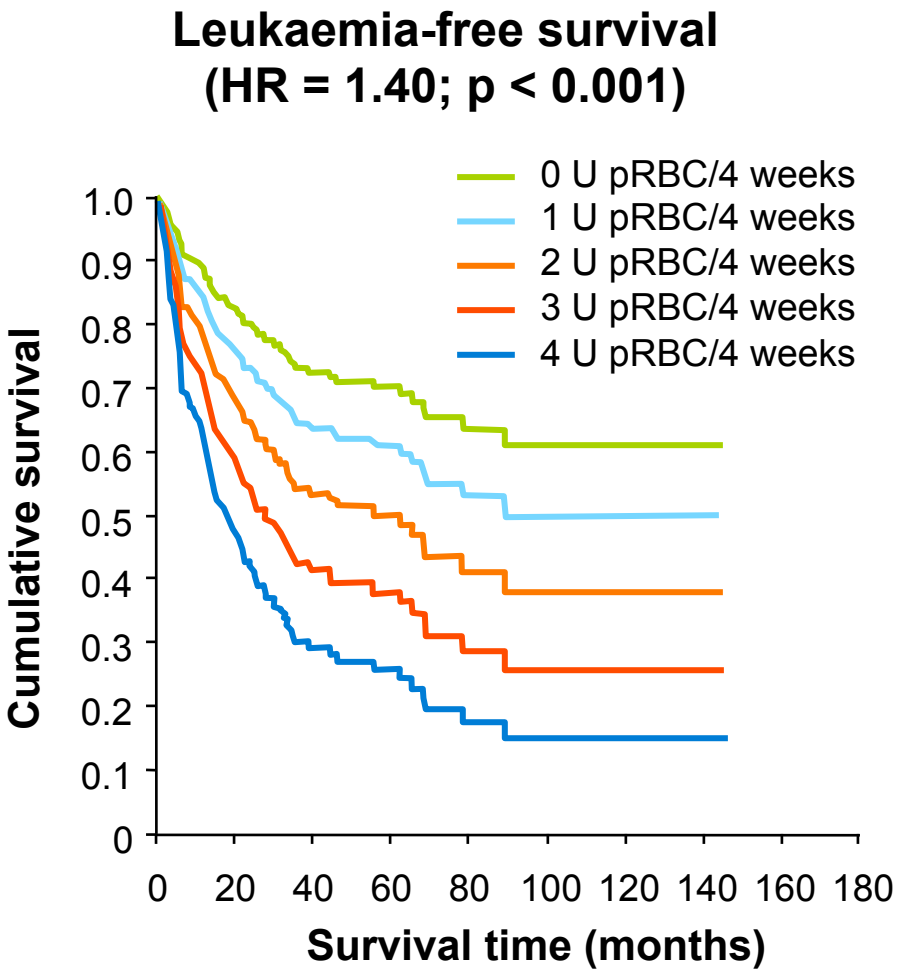


HR = hazard ratio.

Updated data from Malcovati L, et al. J Clin Oncol. 2005;23:7594-603.

Survival of MDS patients by severity of transfusion requirement

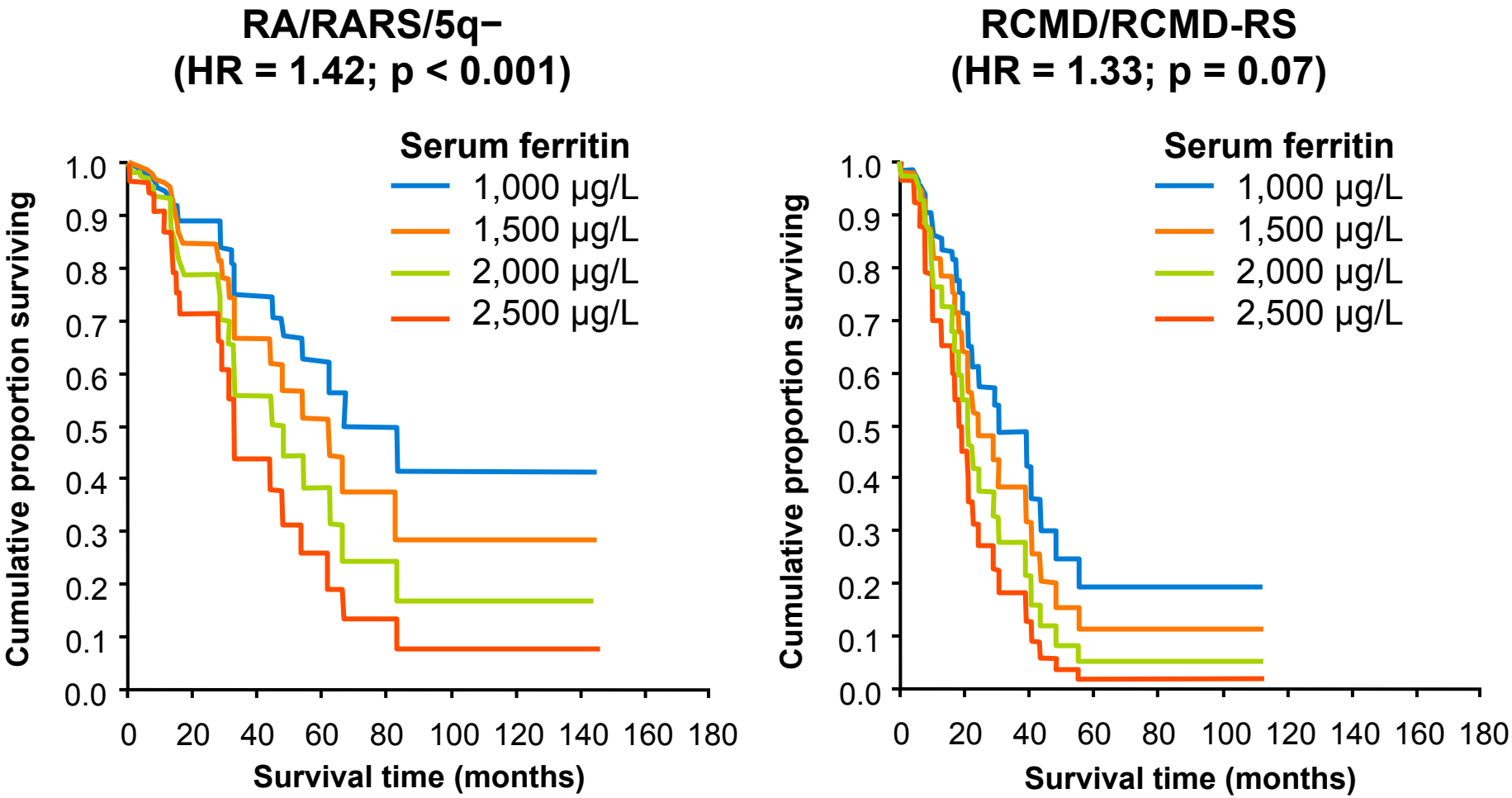




pRBC = packed red blood cells.

Updated data from Malcovati L, et al. Haematologica. 2006;91:1588-90.

Overall survival of transfusion-dependent patients by serum ferritin level



RA = refractory anaemia; RARS = RA with ringed sideroblasts; RCMD = refractory cytopenia with multilineage dysplasia; RCMD-RS = RCMD with ringed sideroblasts..

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

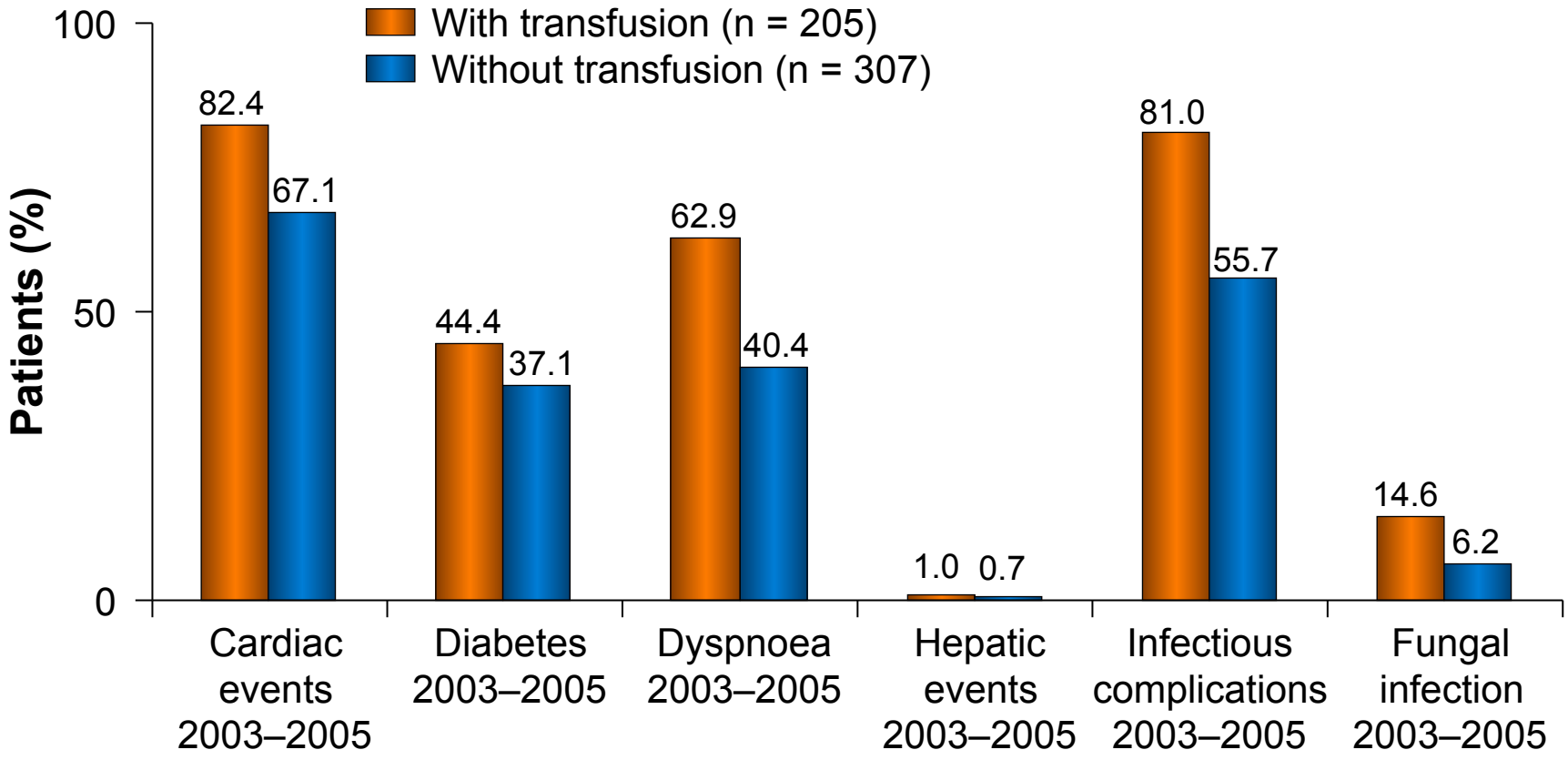
Impact of iron overload and transfusion dependency on cardiac disease and survival in patients with MDS

- Analysis of 455 patients with MDS:
  - Cardiac disease was the most frequent extra-hematological morbidity (25%)
  - Cardiac disease was the main cause (63%) of non-leukemic death
  - Serum ferritin level was significantly associated with the risk of cardiac disease and death (*P*=0.001)

Della Porta MG *et al*. *Blood* 2008;112(11):abst 2677

Prevalence of comorbidities in transfusion-dependent MDS

(retrospective review of 2003 Medicare Files: new MDS pts with 3-year follow-up)



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

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

frontiers in
PHARMACOLOGY

REVIEW ARTICLE
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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

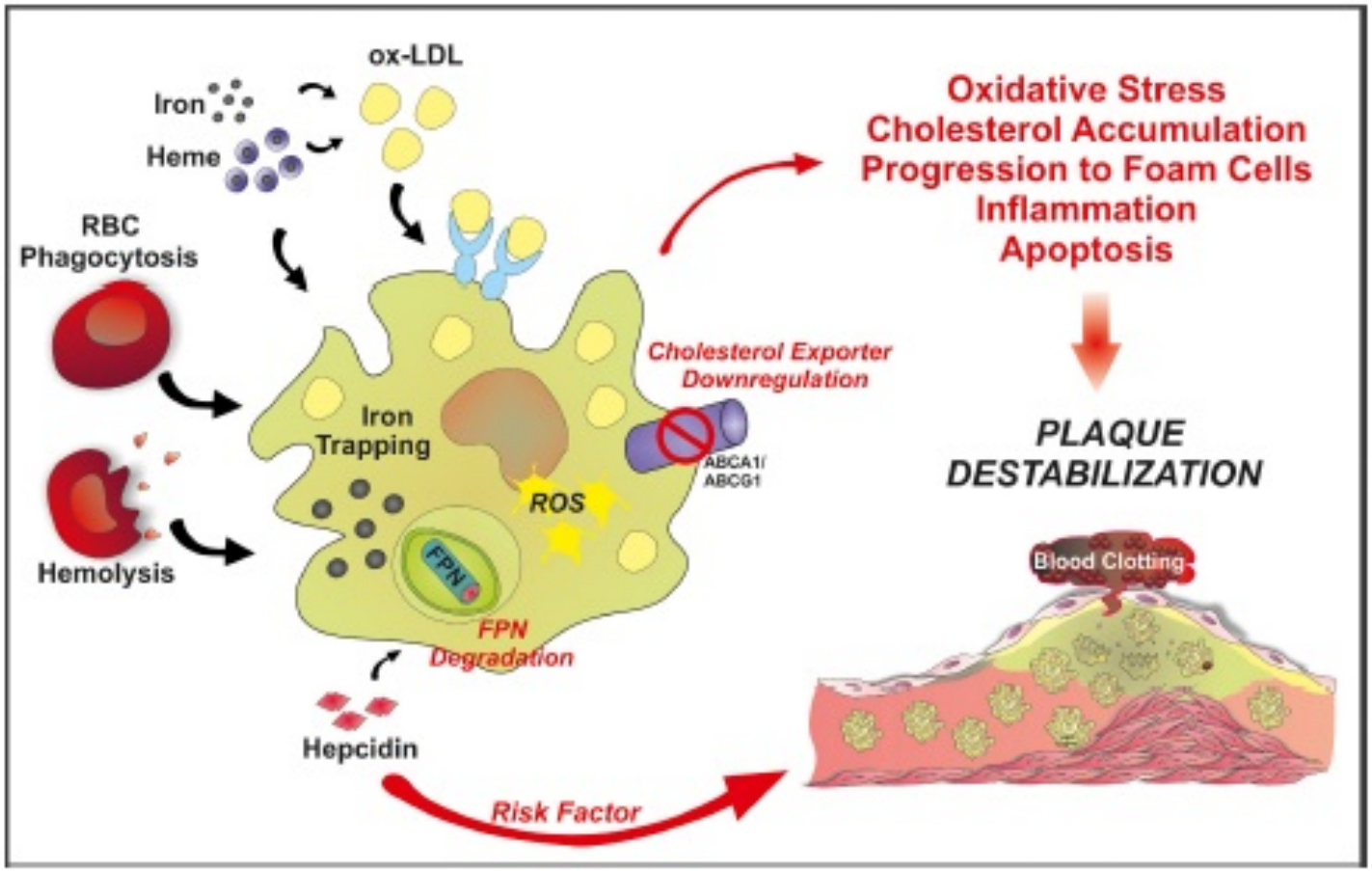

FIGURE 2 | Schematic overview of the "refined iron hypothesis": a role for macrophage-retained iron in atherosclerosis. Iron can accumulate in macrophages as inorganic iron and Hb-iron, upon erytrophagocytosis or hemolysis. Once stored in the cell, iron can be made available to the bloodstream via FPN-mediated 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.

Iron Overload in MDS Prognostic for OS and Risk of AML Transformation

- Transfusion dependency is a known prognostic factor in MDS[1]
- Development of iron overload may influence outcome
- Study of large series (N = 2994) of patients with de novo MDS (FAB criteria)[2]
- Median OS significantly worse with baseline transfusion dependency (*P* < .001)
  - Transfusion-dependent at diagnosis: 19 mos
  - Transfusion-dependent during evolution: 60 mos
  - Not transfusion dependent: 96 mos

Prognostic Factor	HR*	*P* Value
OS		
▪ Iron overload	2.1	< .0001
▪ Transfusion dependency	7.2	< .0001
LFS		
▪ Iron overload	1.6	.04
▪ Transfusion dependency	2.9	< .0001

*Multivariate analysis on cases with complete transfusion and serum ferritin records (n = 731).

1. Malcovati L, et al. J Clin Oncol. 2007;25:3503
2. Sanz G, et al. ASH 2008. Abstract 640.

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].

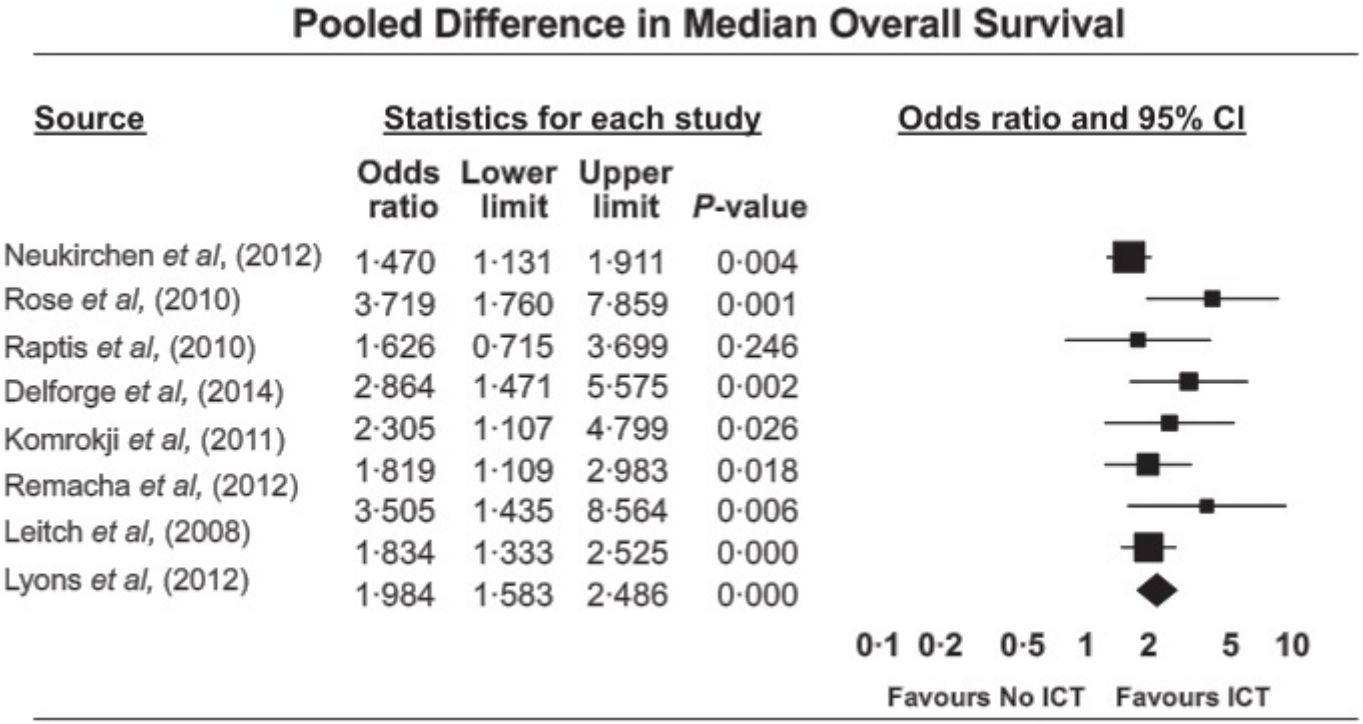
Multiple lines of evidence suggest ICT may improve OS in transfusion-dependent MDS

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)

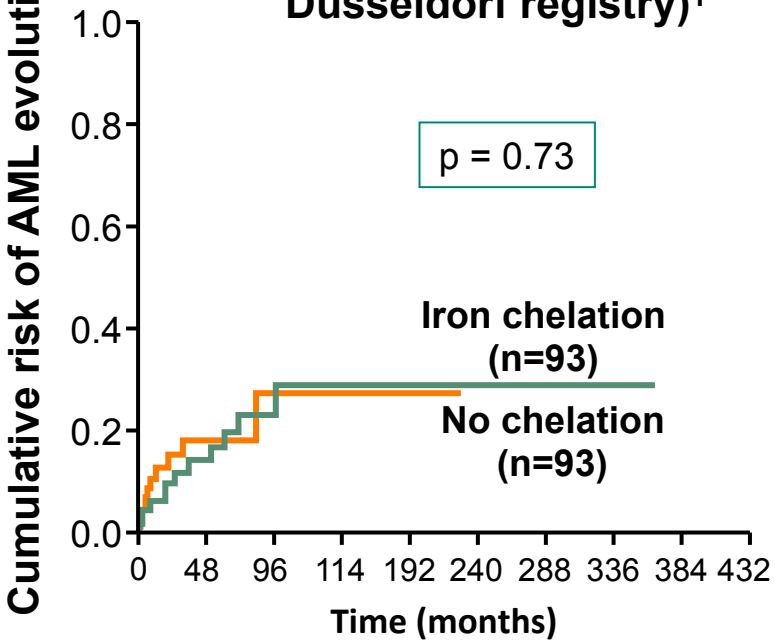
- **Methods:** 8 observational studies, , 1562 pts, median sample size: 153 (78-534)
- **Results:** ICT associated with longer survival (mean difference: 61.2 months)



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

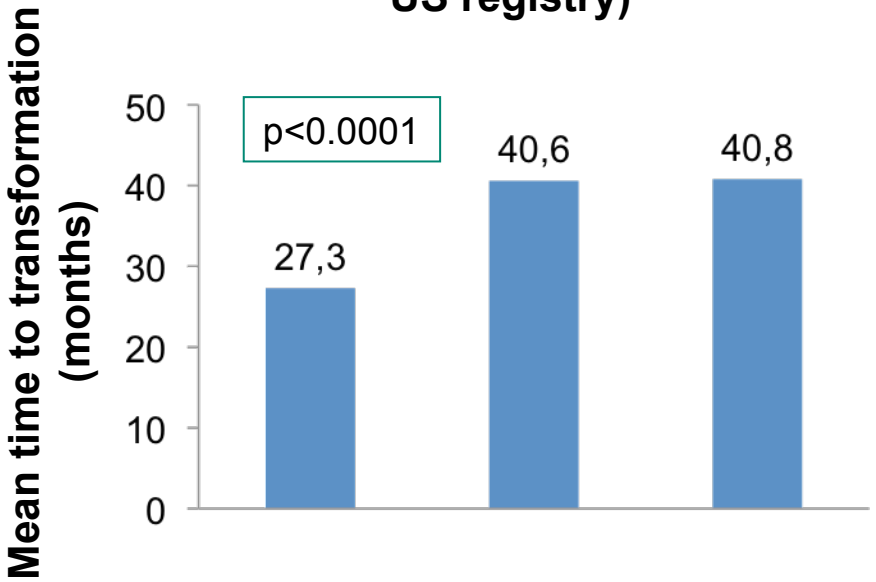
Iron Chelation and AML Transformation: Clinical Data

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]



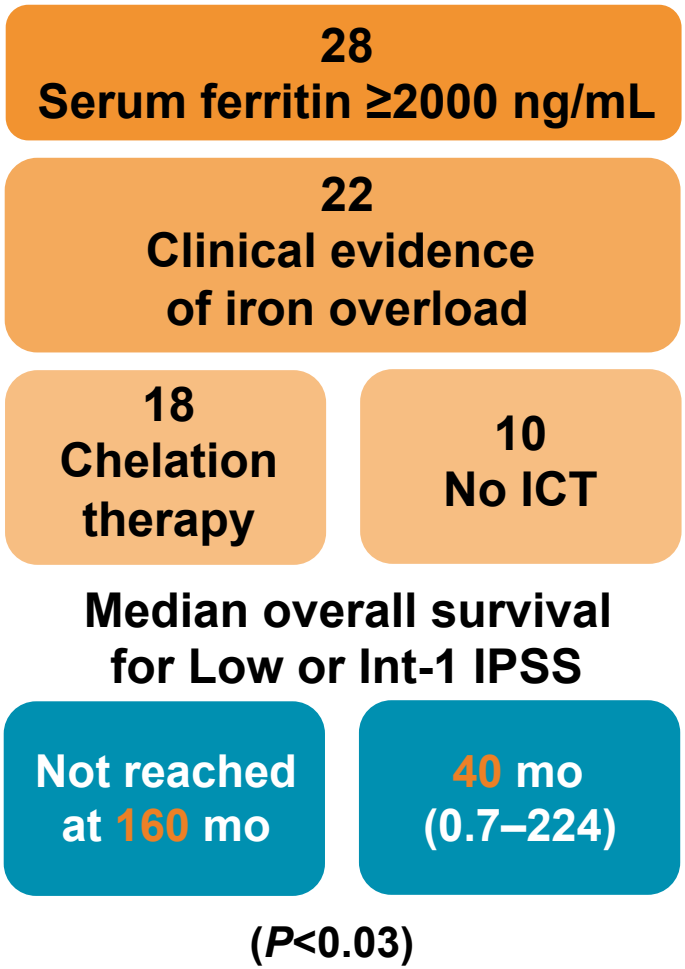
	Non-chelated n=337	All Chelated n=263	Chelated ≥6 months n=191
AML transformation n (%)	30 (8.9)	12 (4.6)	10 (5.2)

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

Improved survival in patients with MDS receiving chelation therapy

Retrospective review of 178 patients

(36 RA, 42 RARS, 28 RAEB, 16 RAEB-T or AML, 25 CMML, 31 other)



ICT, iron chelation therapy

Leitch HA. *Clin Leukemia* 2008;2:205–211

Vancouver: the association between iron chelation therapy and overall survival in non-RARS is stronger than in RARS MDS patients

Retrospective analysis of 268 patients with lower-risk MDS receiving iron chelation therapy

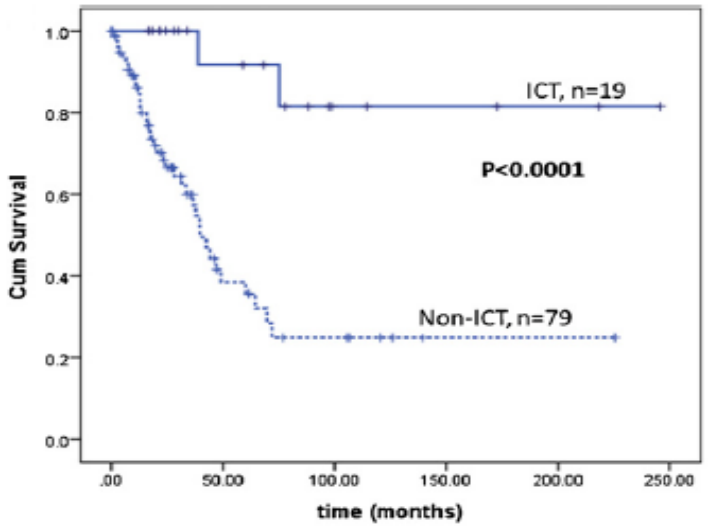
	Non-RARS (n = 129)			RARS (n = 53)		
	No ICT	ICT	p value	No ICT	ICT	p value
Projected median overall survival, months	44	NR	< 0.0001	99	134.4	< 0.0001
5-year overall survival, %	39.2	91.7	0.04	72.4	76.3	NS

Leitch H, et al. Blood. 2011;118:[abstract 1732].

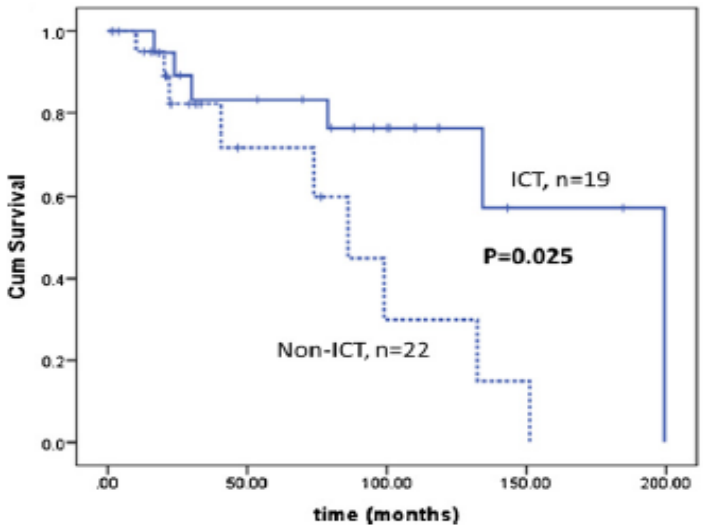
Impact of ICT on OS in non RARS MDS pts

Iron chelation therapy	38(21)
DFX	19(10)
DFO	9(5)
DFO followed by DFX	9(5)
DFX followed by DFO	1(0.5)

Non RARS MDS pts



RARS MDS pts

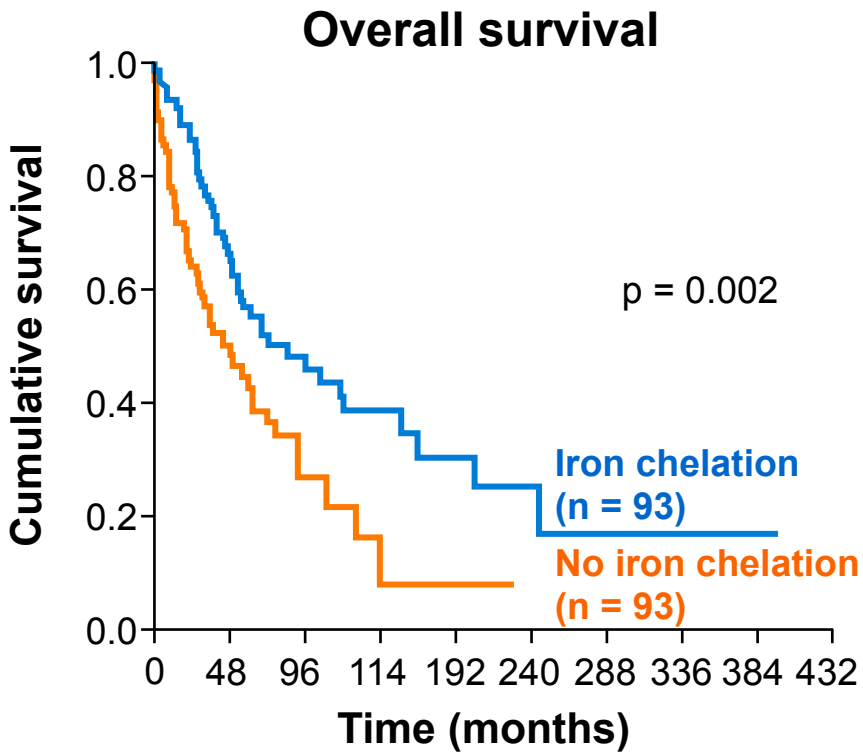


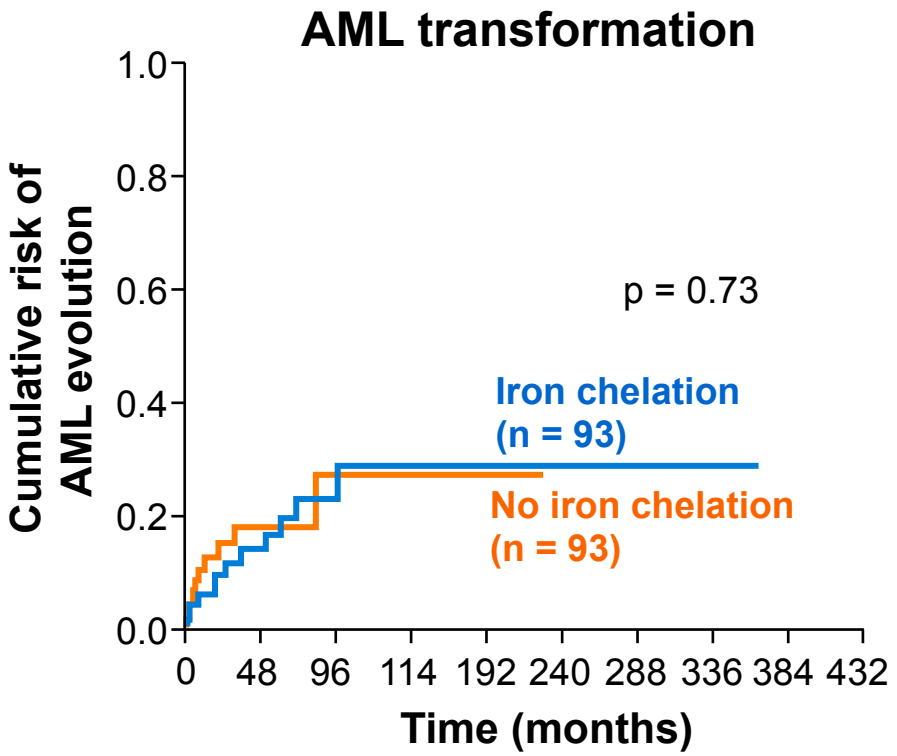
Significant survival improvement in non RARS pts who received ICT
(median OS not reached vs 44 mos of pts without ICT, P<0.0001)

Median OS of RARS pts with ICT was 134.4 mos versus 73.8 mos in pts without ICT (P<0.025)

Leitch HA. Leukemia Research 2012;36(11):1380-6

Iron chelation therapy improves survival in MDS patients: matched-pair analysis (n = 186)





Median cumulative survival
Chelation: 75 months
No chelation: 49 months

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

Fox F, et al. Blood. 2009;114:[abstract 1747].

Iron chelation therapy improves survival in heavily transfused lower-risk MDS

- 165 patients with MDS in France, 97 of whom had Low- or Int-1 MDS
- 53 patients (55%) received chelation therapy for at least 6 months:
  - 28 overnight sc DFO, 5 deferiprone alone, 4 deferiprone + DFO, 4 deferasirox, 7 bolus DFO, 5 iv DFO
- Mean serum ferritin levels were 541, 1491 and 2788 ng/mL at diagnosis, onset of chelation and last evaluation, respectively
- No significant differences between the two groups in total number of comorbidities or the number of patients with iron-related comorbidities

	No iron chelation therapy (n=44)	Iron chelation therapy (n=53)	Total (n=97)	*P*-value
WHO classification				ns
IPSS, n(%)				
Low	15 (34.1)	30 (56.6)	45 (46.4)	0.044
Int-1	29 (65.9)	23 (43.4)	52 (53.6)	

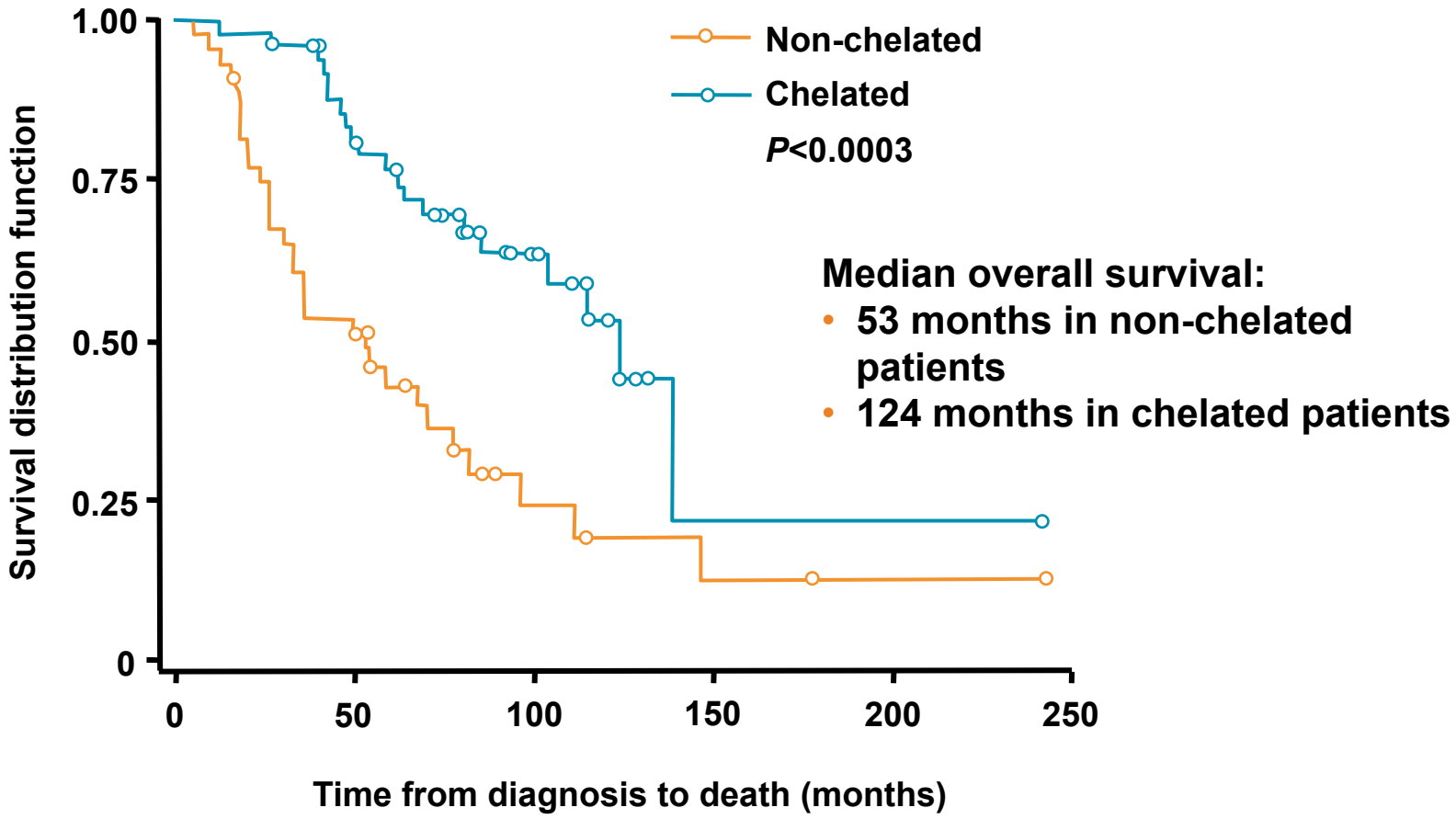
Rose C *et al*. *Leuk Res* 2010;34:864–870

Iron Chelation Therapy and Survival in MDS

- Survey of 170 patients with MDS referred for RBC transfusion at 18 French treatment centers during 1-month period in 2005
  - Assessments: hematologic data, RBC transfusion requirement, iron chelation therapy, and iron overload
  - Cohort survival prospectively followed and reanalyzed on May 15, 2007
- Standard iron chelation therapy
  - Subcutaneous deferoxamine 40 mg/kg/day for 3-5 days/week: n = 41
  - Deferiprone 30-75 mg/kg/day: n = 5
  - Subcutaneous deferoxamine + deferiprone: n = 5
  - Deferasirox 20-30 mg/kg/day: n = 6
- Low-dose iron chelation therapy
  - Subcutaneous deferoxamine bolus 2-3 g/week: n = 12
  - Intravenous deferoxamine 50-100 mg/kg once after RBC transfusion: n = 7

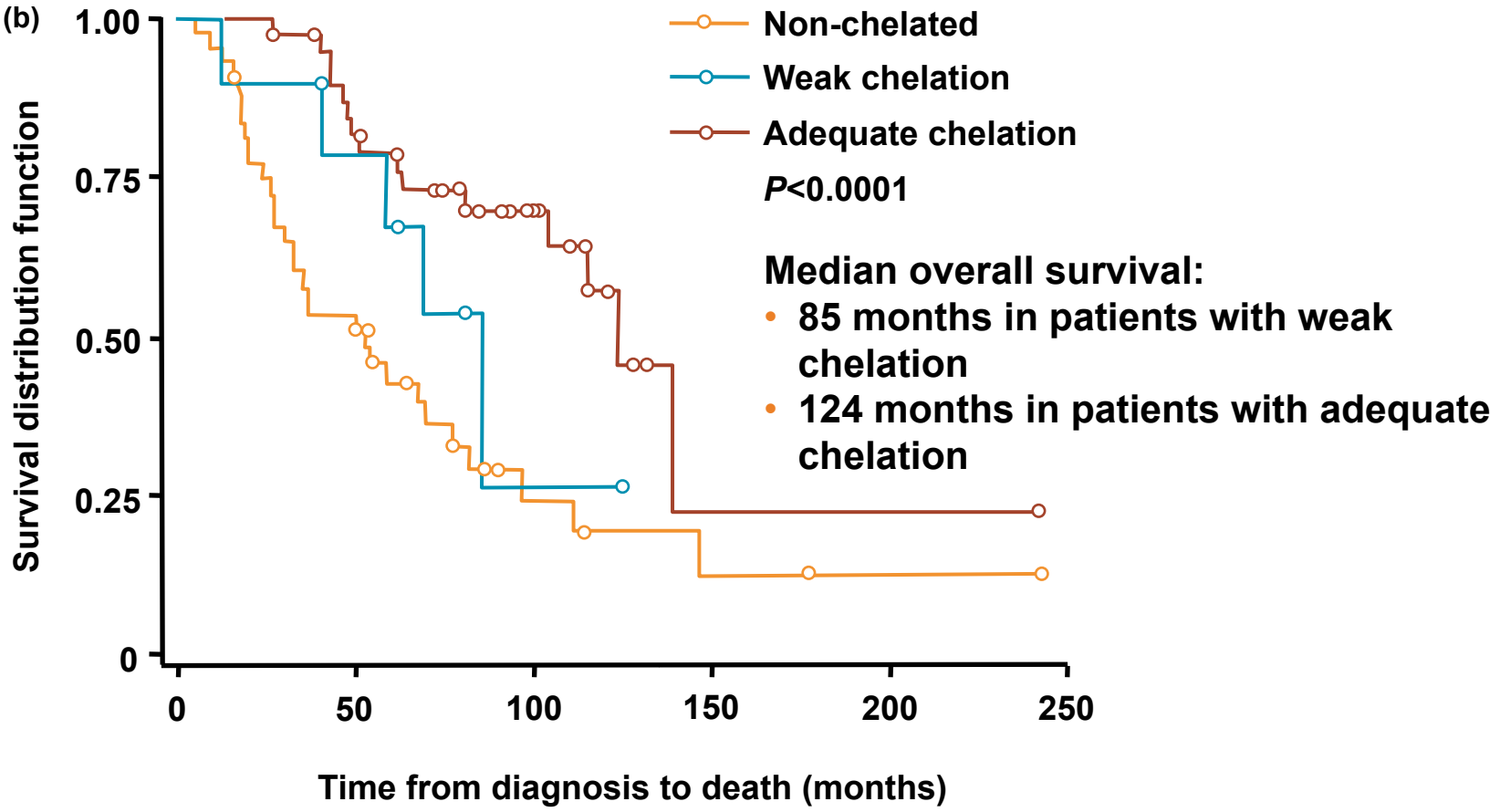
Rose C *et al. Leuk Res* 2010;34:864–870

Improved survival in patients with MDS receiving chelation therapy: Kaplan-Meier survival



Rose C *et al*. *Leuk Res* 2010;34:864–870

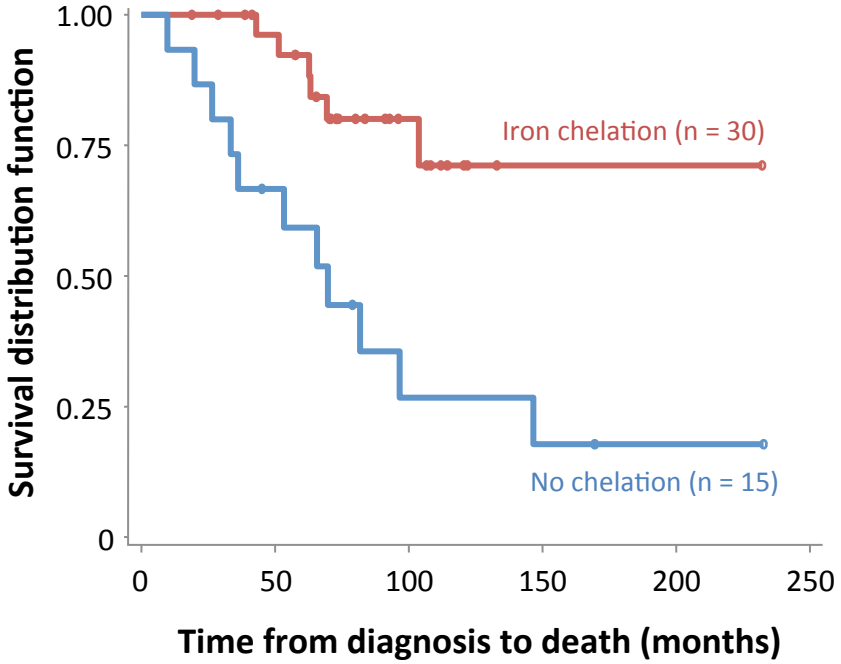
Improved survival in adequately chelated patients with MDS



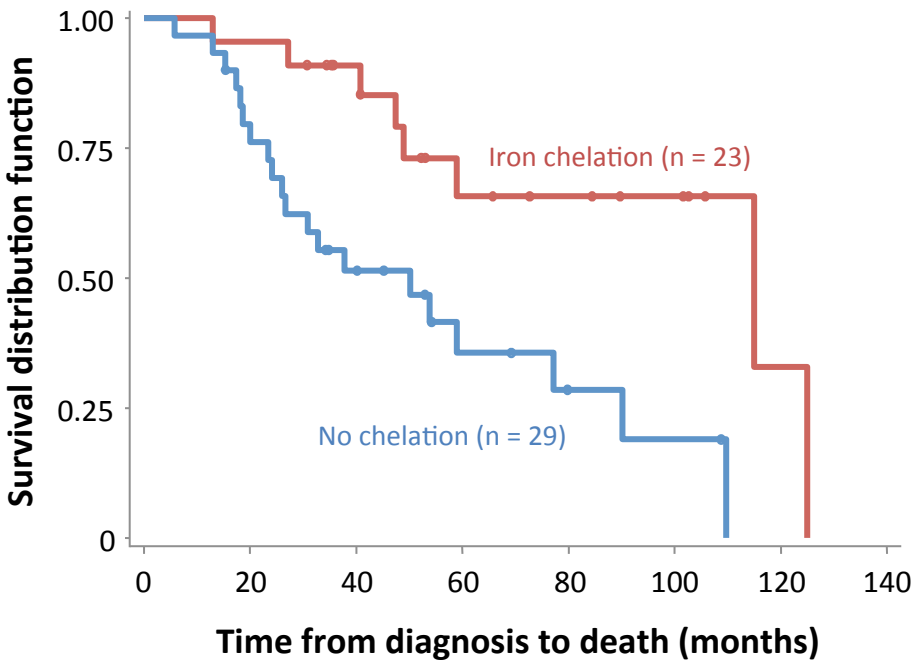
Rose C *et al*. *Leuk Res* 2010;34:864–870

Multiple lines of evidence suggest ICT may improve OS in MDS: GFM study

IPSS = Low
Median: not reached vs 69 months ($p < 0.002$)



IPSS = Int-1
Median: 115 vs 50 months ($p < 0.003$)



Results were the same regardless of sex and age.

GFM, Groupe Francophone des Myélodysplasies;
IPSS, International Prognostic Scoring System.

Rose C, et al. Leuk Res. 2010;34:864-70.

Moffitt Cancer Center: impact of iron chelation therapy on overall survival and AML transformation in lower-risk MDS patients

Retrospective assessment of IPSS Low/Int-1 risk MDS patients with serum ferritin ≥ 1,000 µg/L

	ICT (n = 45)	No ICT (n = 52)	p value
Mean serum ferritin, µg/L	2,680	3,038	0.77
WHO subtype , n (%)			
RARS	11 (24.4)	10 (19.2)	
non-RARS	34 (75.5)	42 (80.8)	
IPSS risk group, n (%)			
Low	15 (33)	9 (17.3)	0.07
Int-1	30 (66.7)	43 (82.7)	
Median overall survival, months	**59**	**34**	**0.013**
AML transformation rate (%)*	**15.6**	**21.2**	**0.33**

*Following adjustment for age > 60 years and MDS Anderson risk score.

Iron chelation therapy was associated with improved overall survival and a trend to lower AML transformation in patients with Low-/Int-1-risk MDS and serum ferritin ≥ 1,000 µg/L

ICT = iron chelation therapy.

Komrokji RS, et al. Blood. 2011;118:[abstract 2776].

Düsseldorf registry: impact of ICT on clinical outcomes in lower-risk MDS patients

- **Methods. Lower risk MDS diagnosed since 1990**, with serum ferritin measurements, who were not chelated or who had received deferasirox and/or deferoxamine (DFO). Transfusion-dependent patients were considered to be **chelated if they received ≥6 months of chelation therapy**, cumulatively. Data were evaluated **up to 30 June 2011**
- **Results.** Data from **417 patients** were analyzed in the three groups: transfusion-independent patients (n=43); and transfusion-dependent, non-chelated (n=289) and chelated patients (n=85). Overall 28 patients received deferasirox; 43 received DFO; 14 received deferasirox and DFO. Data on **comorbidities** were collected only at patient entry; cardiac (34.9, 23.2, 22.4%), hepatic (16.3, 4.2, 7.1%) and renal (7.0, 11.8, 8.2%) conditions were present among transfusion-independent, non-chelated and chelated patients, respectively.
- **In non-chelated patients, time to death was 30.0 months , compared with 67 months in chelated patients.**
- Overall, 4.7% of transfusion-independent patients **progressed to acute myeloid leukemia (AML)**. Among transfusion-dependent patients, **16.6% of non-chelated patients and 14.1% of chelated patients** had progressed.

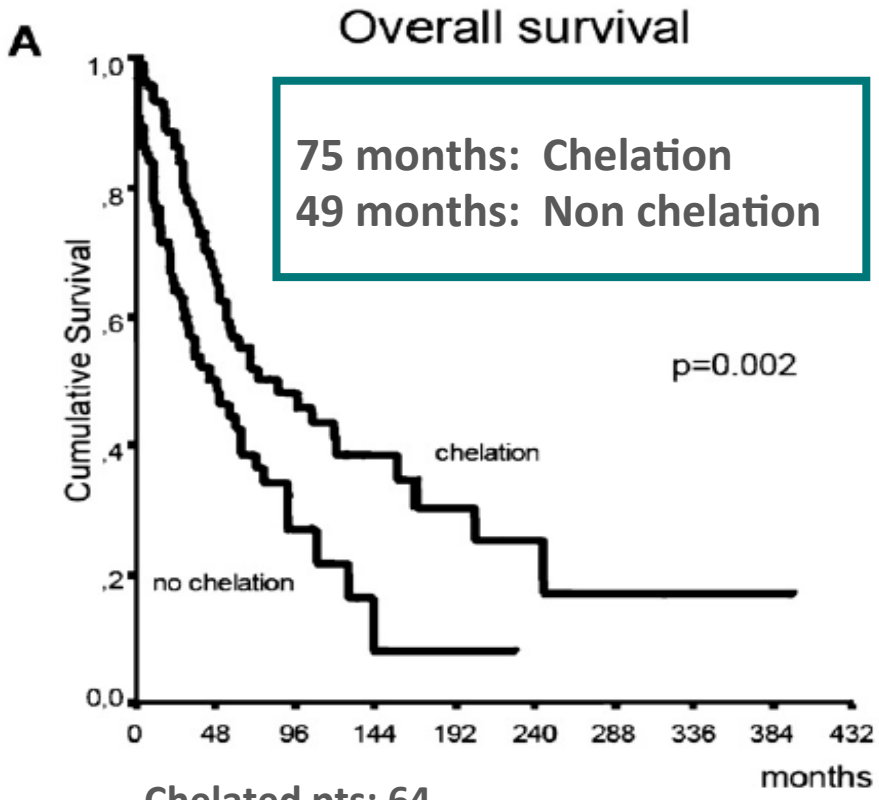
Neukirchen J, et al. Haematologica 2012;97 Suppl 2:abstract 0359

Improved survival in MDS patients receiving iron chelation therapy – A matched pair analysis of 188 patients from the Düsseldorf MDS registry

- **Methods. Matched-pair analysis : 94 patients on long-term chelation therapy and 94 matched patients without it.** All patients had iron overload, defined as serum ferritin (SF) above 1000 ng/ml or a history of multiple transfusions and SF ≥ 500 ng/ml.
- **Results.** Median SF was 1954 ng/ml in chelated and 875 ng/ml in non-chelated patients.
- The difference in **median survival (74 vs. 49 months, respectively; p = 0.002)** supports the idea that iron chelation therapy is beneficial for MDS patients.

Neukirchen J, et al Leuk Res: 36 1067-1070; 2012

Dusseldorf MDS Registry: impact of Deferasirox on OS in MDS pts

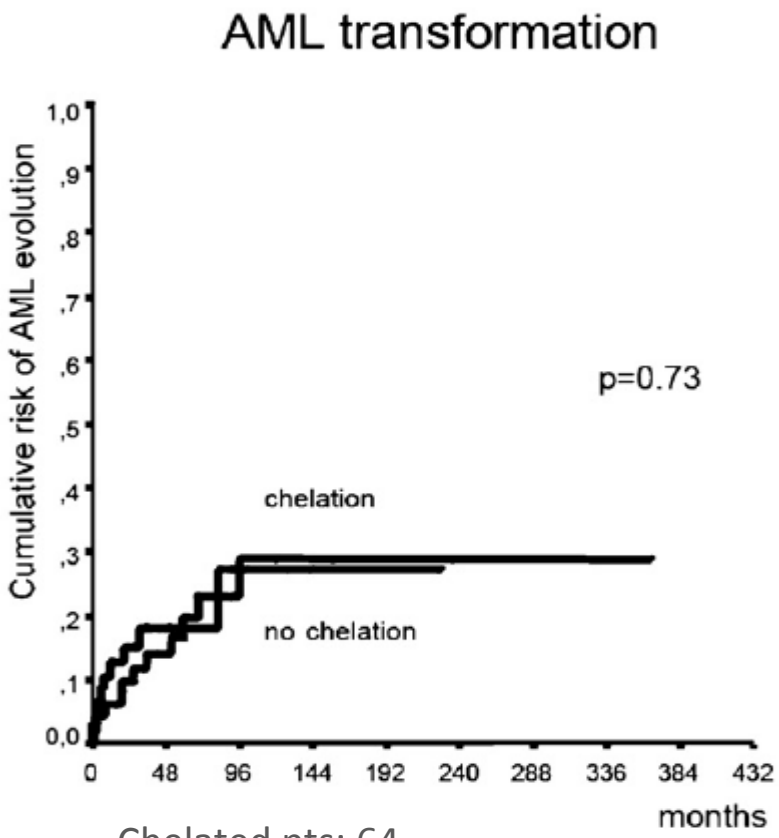


Chelated pts: 64
Not chelated pts: 67
Deferasirox: 47/64 pts
Mean duration Deferasirox tp: 28 months

There was **no significant difference** in median survival between chelated and non-chelated individuals in the cohort of patients with **higher-risk** MDS, whereas a **significant difference was found in the lower-risk** group (p = 0.008).

Neukirchen J. Leuk Res 2012:36(8):1067-70

Dusseldorf MDS Registry:
impact of Deferasirox on LFS in MDS pts



Chelated pts: 64
Not chelated pts: 67
Deferasirox: 47/64 pts
Mean duration Deferasirox tp: 28 months

No significant difference regarding risk of AML evolution

Neukirchen J. Leuk Res 2012:36(8):1067-70

RETROSPECTIVE ANALYSIS ON THE IMPACT OF IRON CHELATION THERAPY ON SURVIVAL AND LEUKEMIA PROGRESSION IN TRANSFUSION DEPENDENT MDS PATIENTS IN BELGIUM

- **Methods.** A **Belgian cross-sectional analysis**, performed in Oct-Dec 2008, identified a **cohort of 193 TD MDS patients. Two years later**, this non interventional, retrospective study allowed to collect and analyze follow-up data from **186 patients of the original cohort.**
- **Results**. Of 186 patients, 38% still alive . MDS patients with low-intermediate1 IPSS scores at diagnosis had a median survival of 87 months. Patients from this group who received **ICT for at least 6 months had a significantly longer median survival than non-chelated patients (126 *vs.* 37 months; *p<0.001*).** This survival difference remained significant when looking only at low IPSS patients (171 *vs.* 37 months; *p<0.001*) or only at intermediate1 patients (126 *vs.* 37 months; *p=0.002*). **AML-free survival was similarly different** between the two groups. In **Cox Proportional Hazard models the use of iron chelation therapy appeared to be the most prominent factor impacting survival**, followed by calculated "transfusion intensity"

Delforge et al, Haematologica 2012 (EHA abstr.)

Multiple lines of evidence suggest ICT may improve OS in MDS: Belgian study

	Chelated ≥ 6 months (n = 62)	No ICT (n = 47)	p value
Total RBC units	144	70	< 0.001
Overall median survival (months)	126	37	< 0.001
Low IPSS	171	37	< 0.001
Int-1	126	37	0.002
Patients died – n (%)	20 (32)	33 (70)	< 0.001

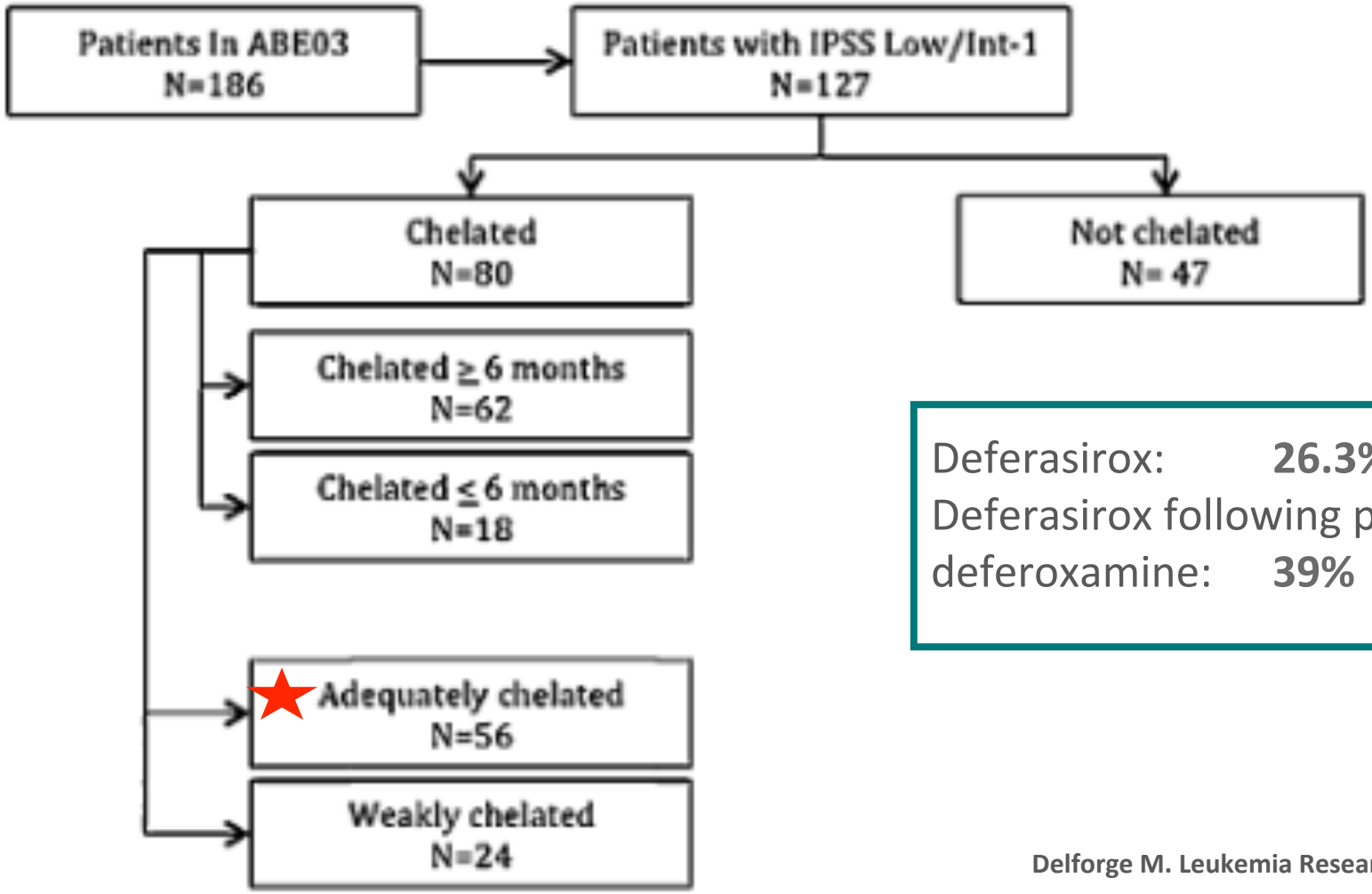
Delforge M, et al. Haematologica. 2012;97 Suppl 1:abstract 0898.

Adequate iron chelation therapy for at least six months improves survival in transfusion-dependent patients with lower risk myelodysplastic syndromes *(Delforge et al, 2014)*

- **Methods:** **Follow-up of a retrospective study**. 127 Low/Int-1 MDS patients from 28 centers in Belgium. Statistical analysis stratified by duration (≥6 versus <6 months) and quality of chelation (adequate versus weak).
- **Results:** Crude **chelation rate was 63% but 88% among patients with serum ferritin ≥1000 g/L.** Of the 80 chelated patients, 70% were chelated adequately mainly with deferasirox (26%) or deferasirox following deferoxamine (39%). **Mortality was 70% among non-chelated, 40% among chelated, 32% among patients chelated ≥6 m, and 30% among patients chelated adequately;** with a trend toward reduced cardiac mortality in chelated patients. Overall, **median overall survival (OS) was 10.2 years for chelated and 3.1years for non-chelated patients (p < 0.001)**. For **patients chelated ≥6 m** or patients classified as adequately chelated, **median OS was 10.5 years**. Mortality increased as a function of average monthly transfusion intensity (HR = 1.08, p = 0.04) but was lower in patients receiving adequate chelation or chelation ≥6 m(HR = 0.24, p < 0.001).

Delforge et al, Leuk Res 38 (2014) 557-563

Adequate ICT ≥ 6 m in TD lower risk MDS pts: impact of Deferasirox on OS

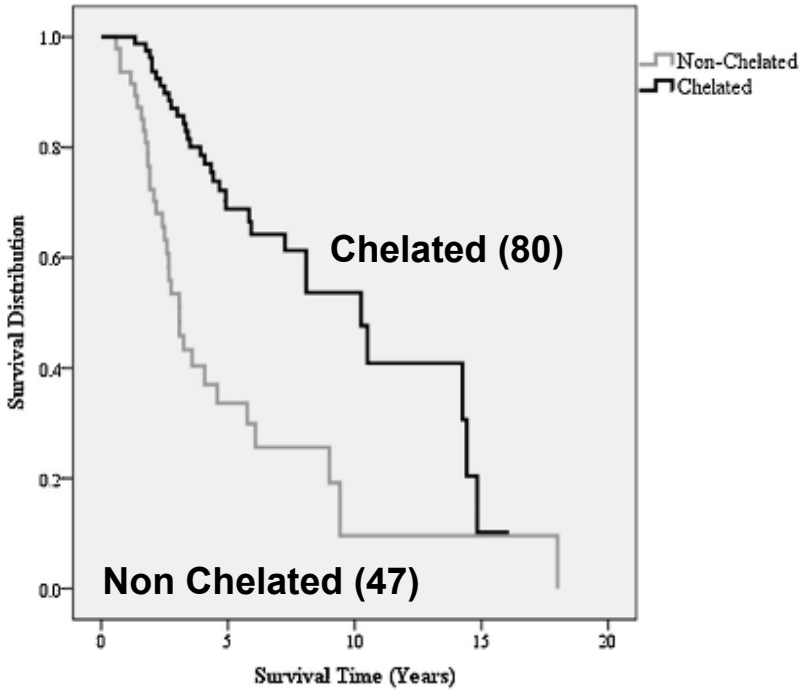


Deferasirox: **26.3%**
Deferasirox following prior deferoxamine: **39%**

Delforge M. Leukemia Research 2014;38:557-563

★ **s.c. deferoxamine infusion on multiple days /week or deferasirox at any dose**

Impact of Deferasirox on OS in MDS pts

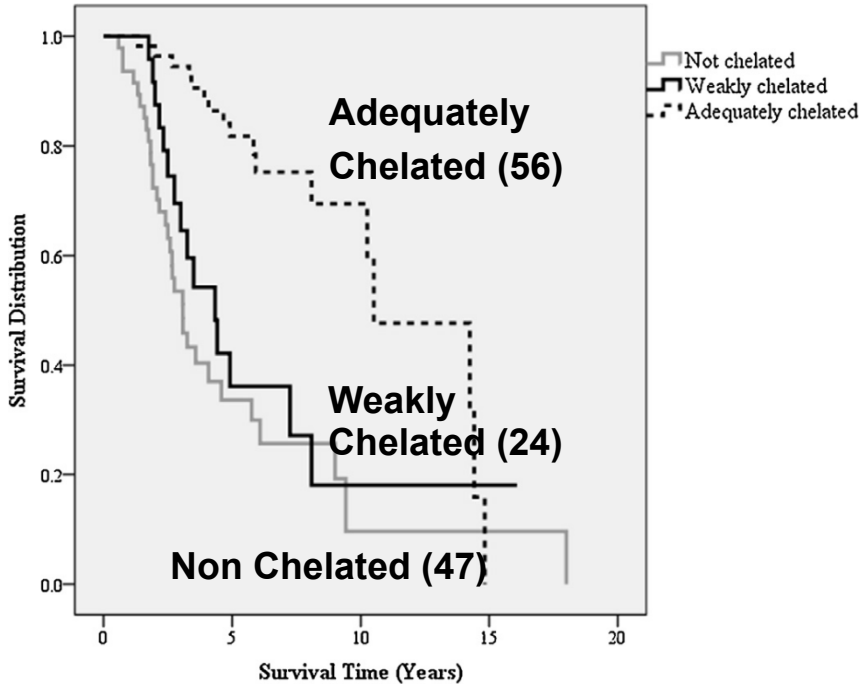


Median OS:

3.1 years: non chelated

10.2 years: chelated

P: < 0.001.



Median OS:

3.1 years: non chelated

4.3 years: weakly chelated

10.5 years: adequately chelated

P: <0.001

Delforge M. Leukemia Research 2014;38:557-563

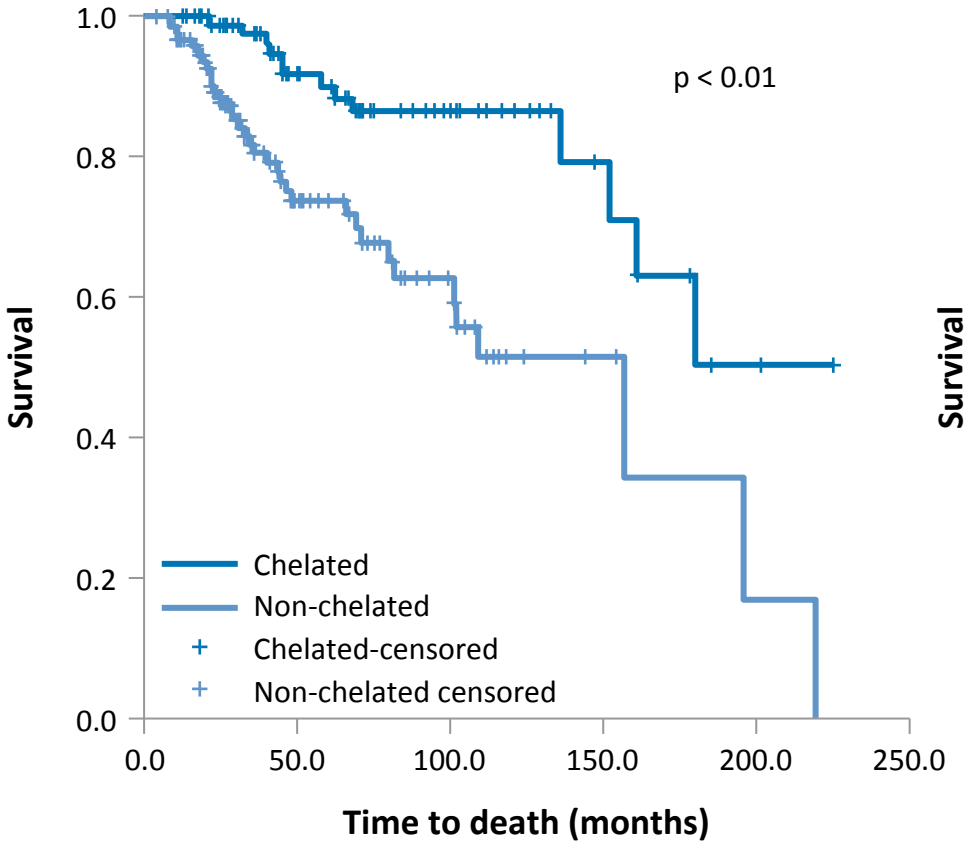
Evolution of iron overload in patients with low-risk myelodysplastic syndrome: iron chelation therapy and organ complications

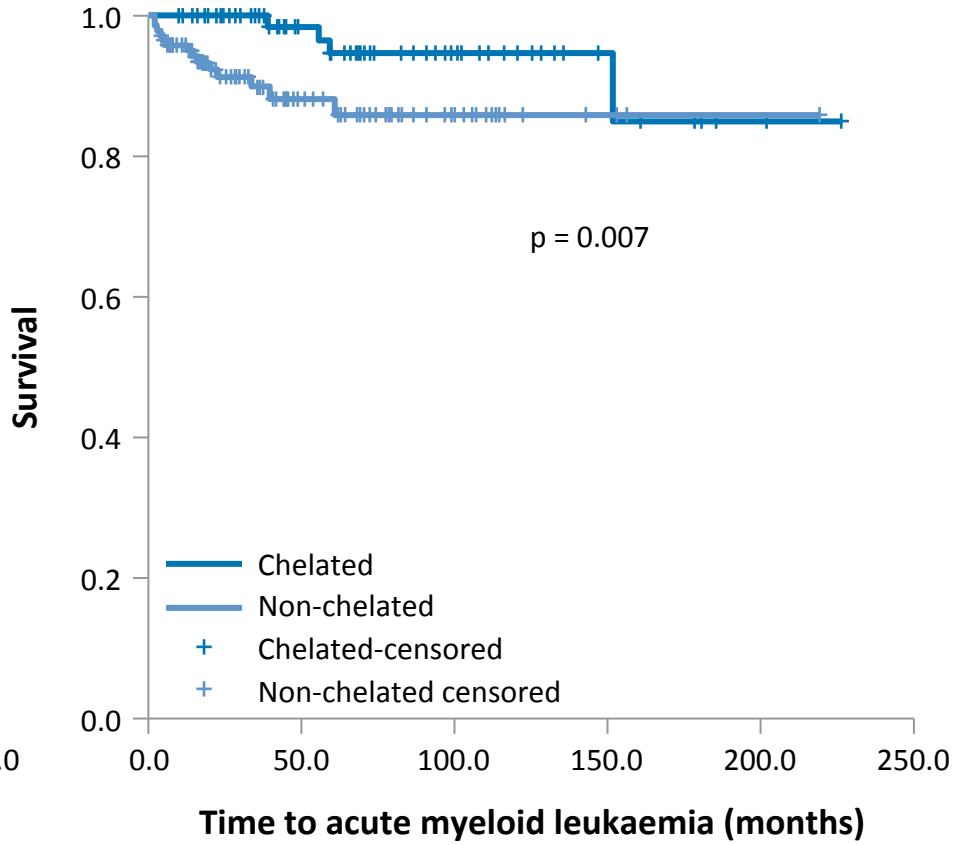
Remacha et al (IRON-2 STUDY GROUP) Ann Hematol 2015

- **Methods.** **Observational retrospective study** (March 2010- March 2011); 47 Spanish hospitals. **263 patients with lower risk MDS), transfusion-dependent, ≥10 PRBC** .
- **Results.** **Cardiac, hepatic, endocrine, or arthropathy complications** appeared/worsened in 20.2, 11.4, 9.9, and 3.8 % of patients, respectively.
- **96 (36.5 %) pts received iron chelation therapy for ≥6 months, (deferasirox: 71.9 %).** **Chelation-treated patients showed longer**
- **overall survival (p<0.001), leukemia-free survival (p=0.007), and cardiac event-free survival (p=0.017) than non-chelated patients.** **In multivariable analyses, age (p=0.011), IPSS (p<0.001), and chelation treatment (p=0.015)were predictors for overall survival**; IPSS (p=0.014) and transfusion frequency (p=0.001) for leukemia-free survival; and **chelation treatment (p=0.040) and Sorror comorbidity index (p=0.039) for cardiac event-free survival.**

Remacha et al, Ann Hematol 2015

IRON2: survival improves with ICT





Remacha AF, et al. Ann Hematol. 2014

EUMDS prospective registry: ICT halves the HR for early mortality in transfused MDS patients with SF > 1,000 µg/L

	Patients, n	Median SF levels	HR (95% CI)	Adjusted HR[a] (95% CI)
Chelation				
No	945	281	1	1
Yes	55	1,779	2.05 (1.15–3.64)	0.36 (0.15–0.88)
Mean number of units				
No chelation	4.6	–	–	–
Chelation	28.9	–	–	–
Chelation and transfusion status				
No transfusion/no chelation	570	345	1	1
Transfusion/no chelation	375	377	4.71 (3.01–7.36)	3.61 (1.96–6.66)
Transfusion/chelation	52	1,838	5.27 (2.71–10.26)	1.47 (0.50–4.31)
Transfusion and SF > 1,000 µg/L	134	–	–	–
No chelation	94	–	1	1
Chelation	40	–	0.75 (0.38–1.51)	0.51 (0.19–1.32)

[a] Adjusted for age at diagnosis, sex, country, WHO category, cytogenetics, number of cytopenia, % blasts, number of transfusions, and SF levels (at registration or start of chelation.

CI, confidence interval.

de Witte T, et al. EUMDS Registry. Presented at ELN 2012.

Deferasirox therapy is associated with reduced mortality risk in a medicare population with myelodysplastic syndromes

Journal of Comparative Effectiveness Research

Aims: Iron overload adversely affects patients with myelodysplastic syndromes (MDS), but benefits of iron chelation therapy have not been clearly demonstrated. We examined the association between deferasirox (DFX) therapy and mortality in transfusion-receiving Medicare patients. **Patients & methods:** MDS patients from 2005 to 2008 were identified using ICD-9 codes from 100% Medicare claims. Patients receiving ≥20 blood units were observed until death or end of study. Marginal structural models were used for estimation. **Results:** 3926 patients (10.1% used DFX) were observed for a mean of 48.8 weeks. Each incremental week of DFX was associated with a significant reduction in mortality risk (hazard ratio [HR]: 0.989; 95% CI: 0.983–0.996; p = 0.001). **Conclusion:** DFX therapy is associated with a reduced mortality risk among older MDS patients who received a minimum transfusion threshold.

Keywords: deferasirox • iron chelation therapy • iron overload • mortality • myelodysplastic syndromes

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J. Comp. Eff. Res. **(2015) 4(4), 327–340**

Impact of Deferasirox on mortality in MDS

Medicare population: DFX associated with reduced mortality risk in MDS patients

- Chelated pts: 544 (Deferasirox: 100%)
- Non chelated pts: 3.682

Risk of death reduced by:

23%: 14-26 weeks of Deferasirox

66%: ≥53 weeks of Deferasirox

Zeidan AM. Blood 2012;120(21):426

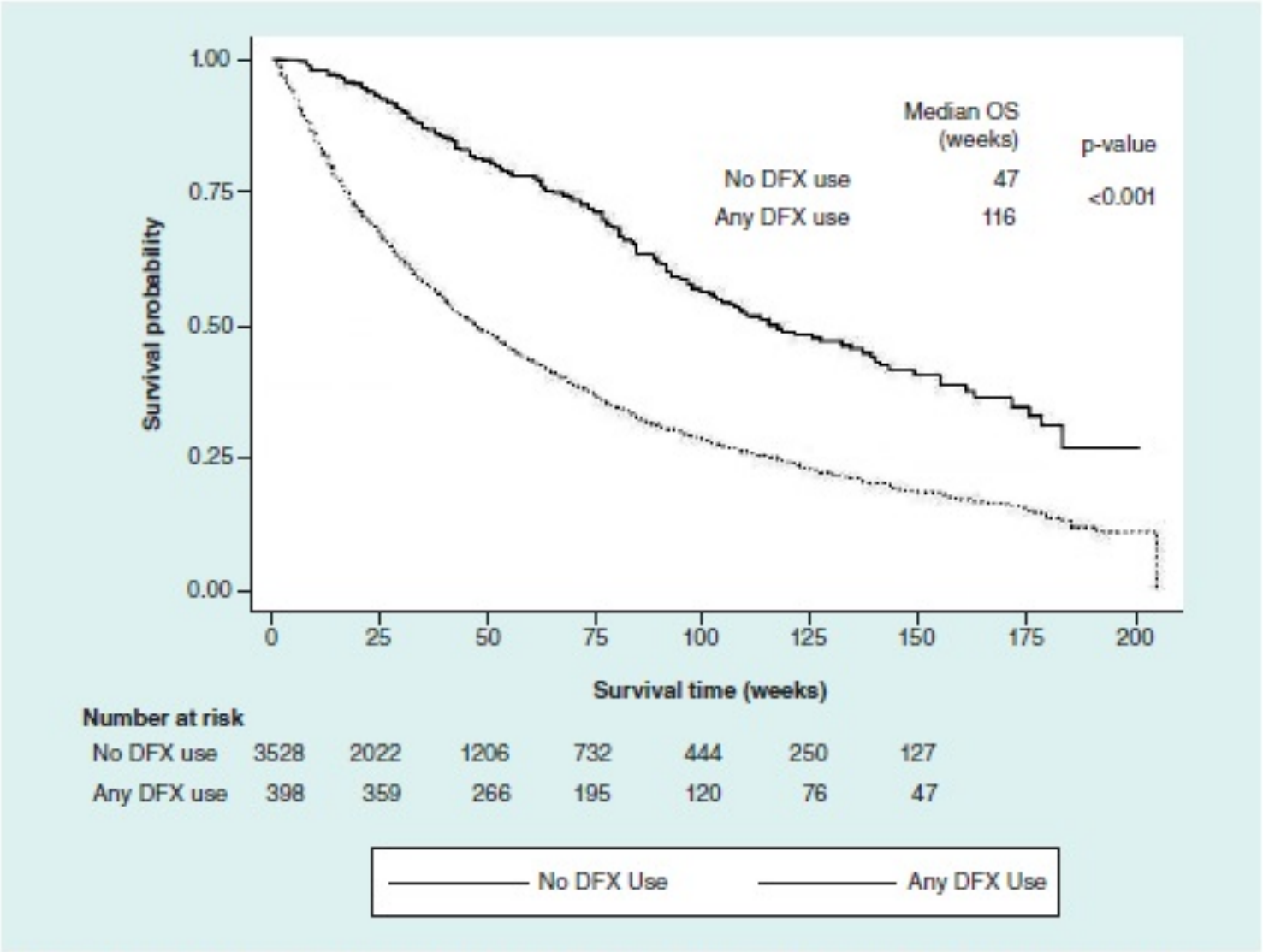


Figure 3. Kaplan–Meier overall survival estimates for patients with myelodysplastic syndromes who received deferasirox therapy and those who did not.

DFX: Deferasirox; OS: Overall survival.

***J. Comp. Eff. Res.* (2015) 4(4), 327–340**

Comparison of 24-month outcomes in chelated and non-chelated lower-risk patients with myelodysplastic syndromes in a prospective registry

Lyons et al, Leuk Res 38 (2014) 149-154

- **Methods**. **5-year, prospective registry** . Enrolled **600 lower-risk MDS pts with transfusional iron overload.** Clinical outcomes were compared between chelated and non-chelated pts.
- **Results**. **At baseline, cardio-vascular comorbidities more common in non-chelated pts**, and MDS therapy was more common in chelated pts.
- **At 24 months, chelation was associated with longer median overall survival (52.2 months vs. 104.4 months; p < .0001) and a trend toward longer leukemia-free survival and fewer cardiac events.**
- No differences in safety between groups.
- Limitations: 1) varying time from diagnosis and duration of chelation; 2) the decision to chelate may have been influenced by pt clinical status.

Lyons et al, Leuk Res 38 (2014) 149-154

Iron chelation and clinical outcomes in patients with lower-risk MDS: registry analysis at 5 years

Objective

- To evaluate the association between chelation and clinical outcomes and also between chelation and OS in lower-risk MDS patients for 5 years

Methods

- Multicentre, prospective study in patients (N = 600, ≥ 18 years of age) with lower-risk MDS and TIO
- Patients were categorized as non-chelated, chelated, and chelated ≥ 6 months, and followed for 5 years

Results

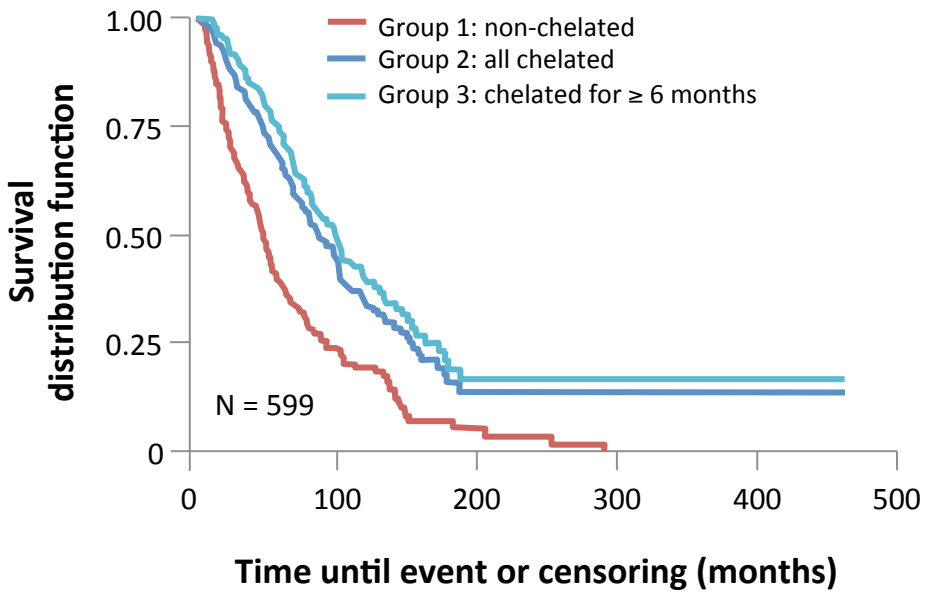
- 599 patients were evaluated (57.8% male) with a median age of 76 (range 21–99) years
  - 61 patients continue in the registry (May 2014); 538 discontinued (400 died, 66 were lost to follow-up, 46 completed study, and 26 discontinued for other reasons)
- At baseline
  - cardiac and vascular comorbidities (CVC) were significantly more common in non-chelated vs chelated patients (52.4% vs 34.3%, $p < 0.0001$, and 59.8% vs 48.0%, $p = 0.0039$, respectively)
  - ECs were numerically greater in non-chelated than in ≥ 6-mo-chelated patients (44.2% vs 35.6%)
- 271/599 patients were chelated
  - deferasirox 69.0% (n = 187)
  - deferoxamine 11.8% (n = 32)
  - deferoxamine and deferasirox 14.8% (n = 40)
  - unknown chelator or chelator name not provided 4.5% (n = 12)

EC, endocrine comorbidities; TIO, transfusional iron overload.

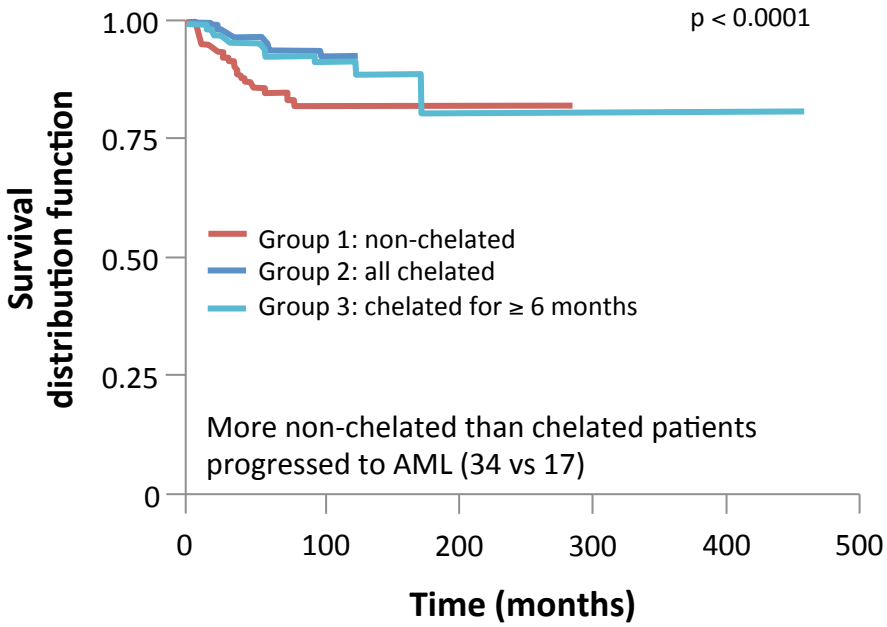
Lyons R, et al. Presented at ASH 2014. Blood. 2014;124:abstract 1350.

US22 prospective registry: OS and AML-free survival significantly greater in chelated patients

Overall survival



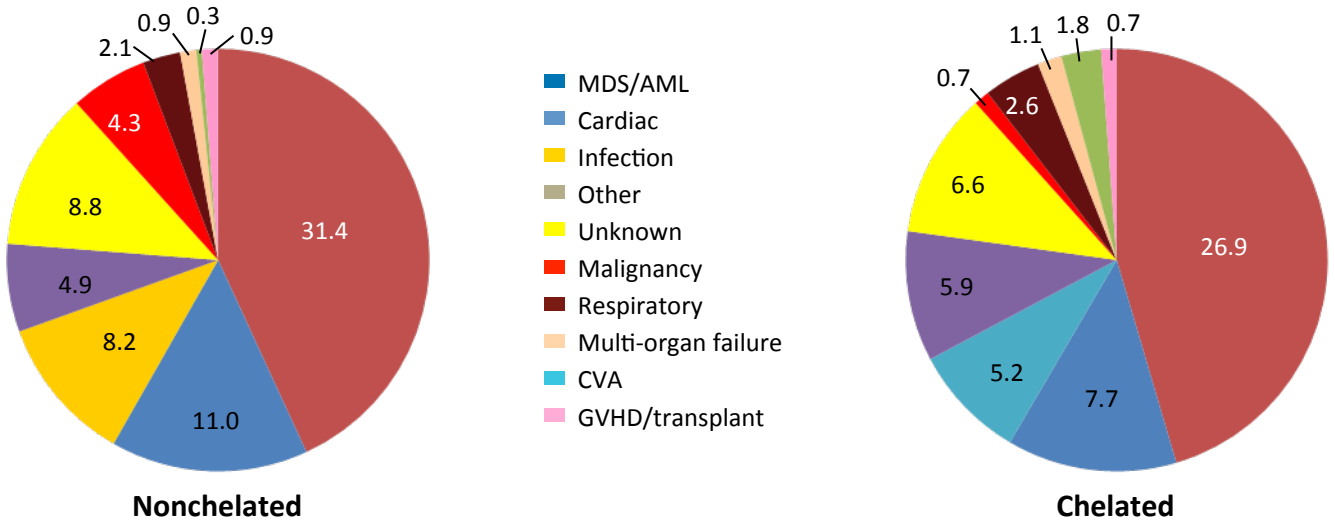
Time to progression to AML



Significantly greater OS and time to AML progression (from date of diagnosis) in chelated than in non-chelated patients (p < 0.0001)

Lyons RM, et al. Blood. 2014;124:abstract 1350.

US22 prospective registry: MDS patients receiving ICT have lower all-cause mortality



Patient characteristic	Non-chelated (N = 328)	Chelated (N = 271)	Chelated ≥ 6 months (N = 202)
Time to death, median (min, max), months	**47.8** (43.4, 53.1)	**88.0** (78.4, 103.0)[a,*]	**100.0** (83.4, 118.2) *
Deaths, n (%)	239 (72.9)	161 (59.4) [a,***]	115 (56.9) [a,**]
Cause of death, n (%)			
MDS/AML	103 (31.4)	73 (26.9)	53 (26.2)
Cardiac	36 (11.0)	21 (7.7)	15 (7.4)
Infection	27 (8.2)	14 (5.2)	14 (6.9)
Other	16 (4.9)	16 (5.9)	10 (5.0)
Unknown	29 (8.8)	18 (6.6)	12 (5.9)
Malignancy	14 (4.3)	2 (0.7)	0 (0.0)
Respiratory	7 (2.1)	7 (2.6)	4 (2.0)
Multi-organ failure	3 (0.9)	3 (1.1)	3 (1.5)
CVA	1 (0.3)	5 (1.8)	3 (1.5)
GVHD/transplant	3 (0.9)	2 (0.7)	1 (0.5)

[a] Versus non-chelated. * p < 0.0001; ** p = 0.0002; *** p = 0.0005.

Lyons RM, et al. Blood. 2014;124:abstract 1350.

Leukemia Research 56 (2017) 88–95

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

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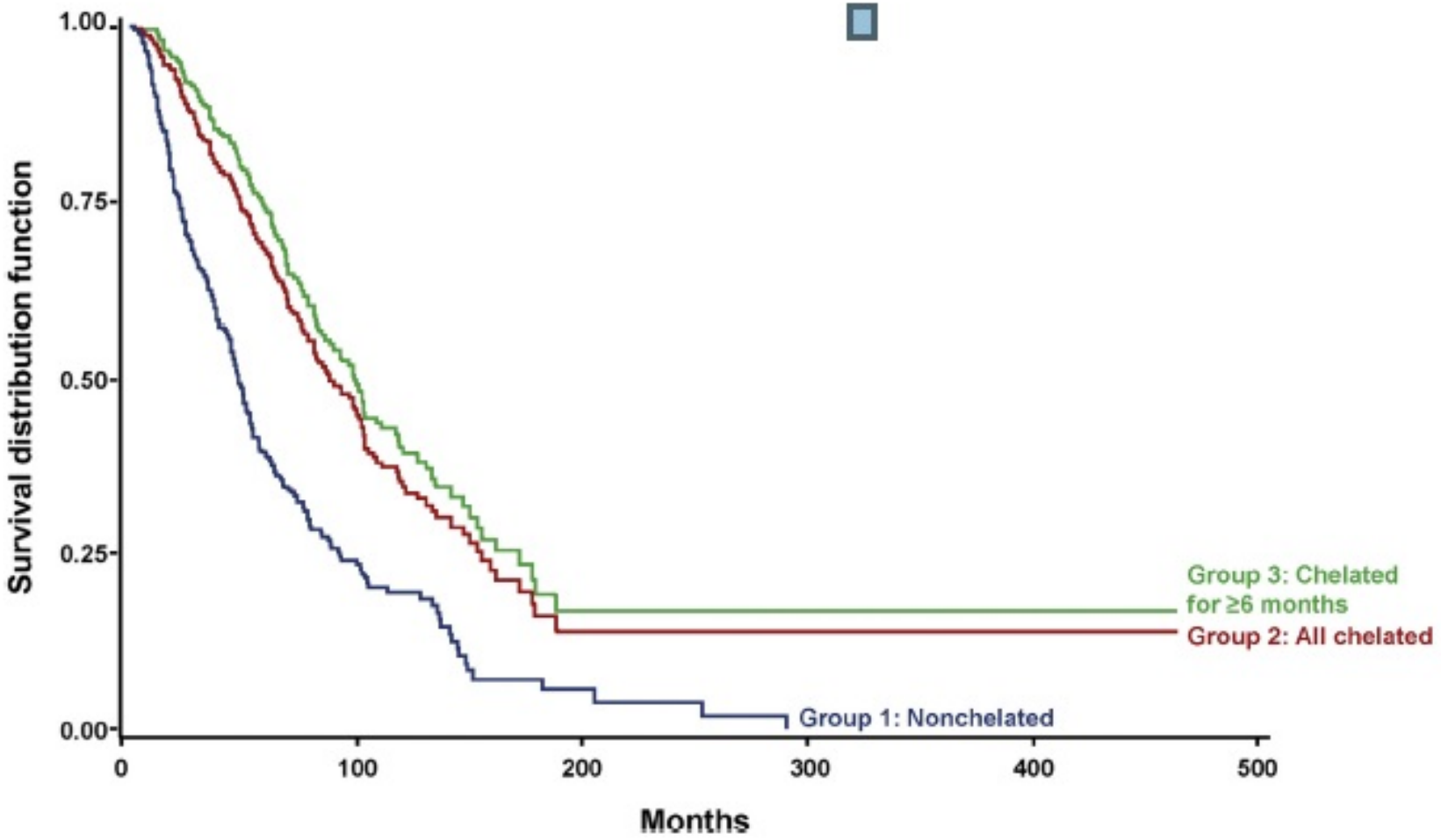


Fig. 1. Overall Survival: All Enrolled Patients. Patients who received iron chelation therapy had longer overall survival compared with nonchelated patients. Kaplan-Meier curves for overall survival show median time to death from myelodysplastic syndrome diagnosis in the nonchelated, chelated, and chelated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

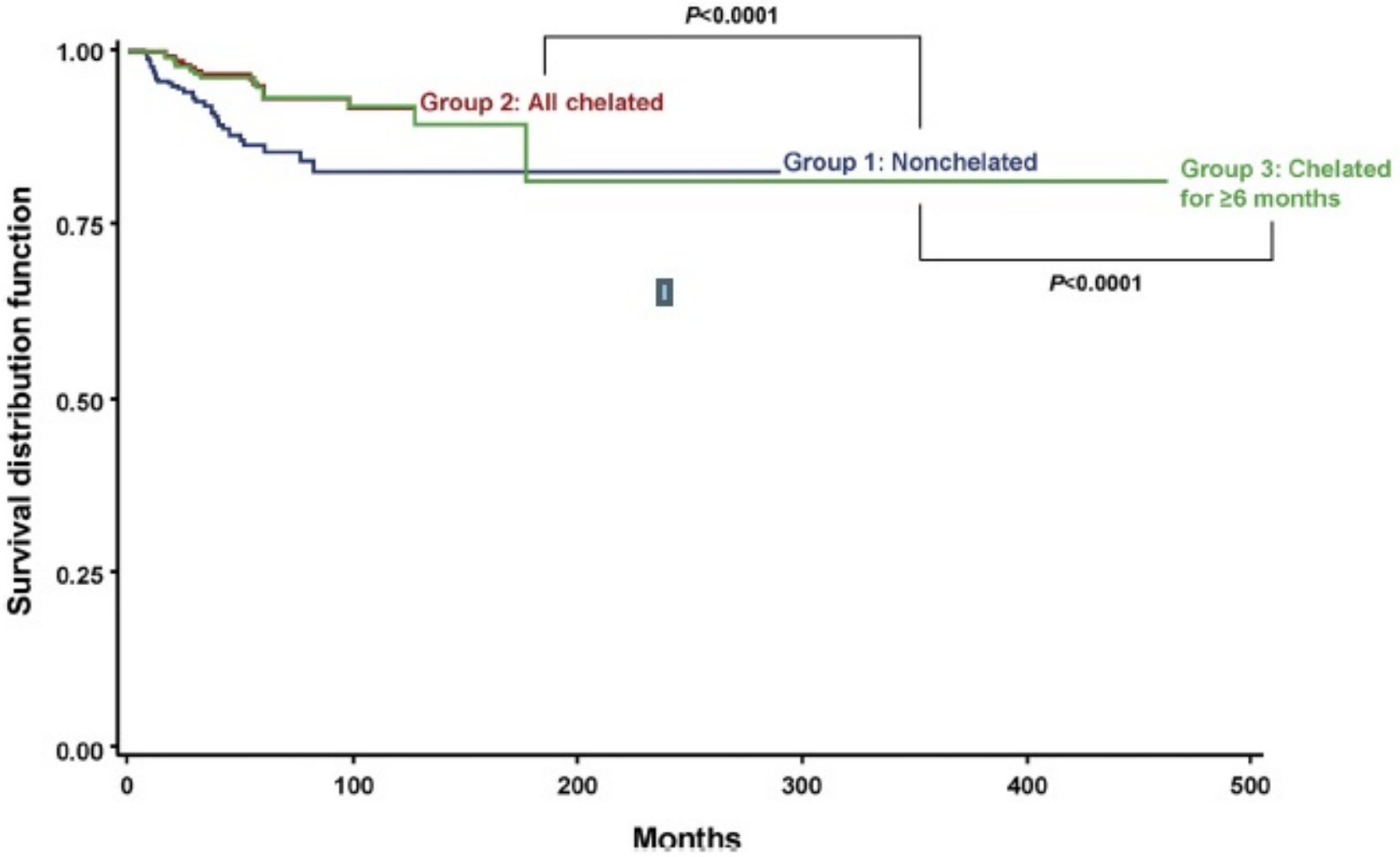


Fig. 3. Progression to Acute Myeloid Leukemia: All Enrolled Patients. Time to progression to acute myeloid leukemia was significantly longer in chelated vs nonchelated patients ($P < 0.0001$). The median time from diagnosis to leukemic progression was 46.7 months in the nonchelated group, 86.3 in the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

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)

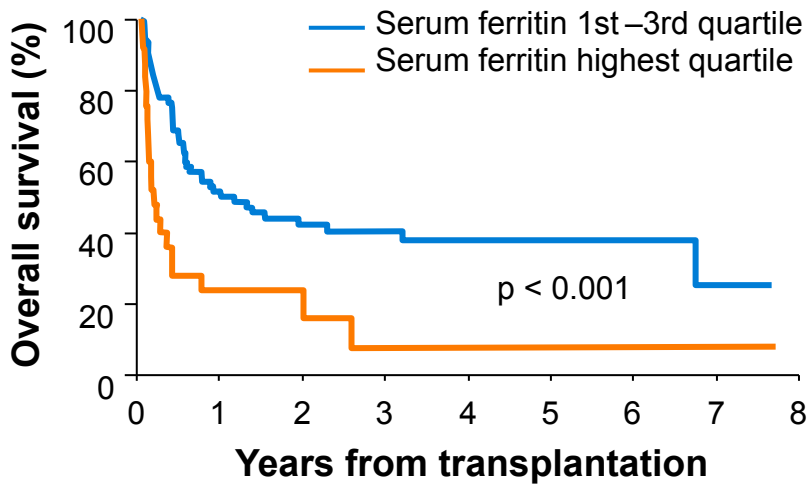
AML, acute myeloid leukaemia; CML, chronic myeloid leukaemia; RIC, reduced-intensity conditioning.

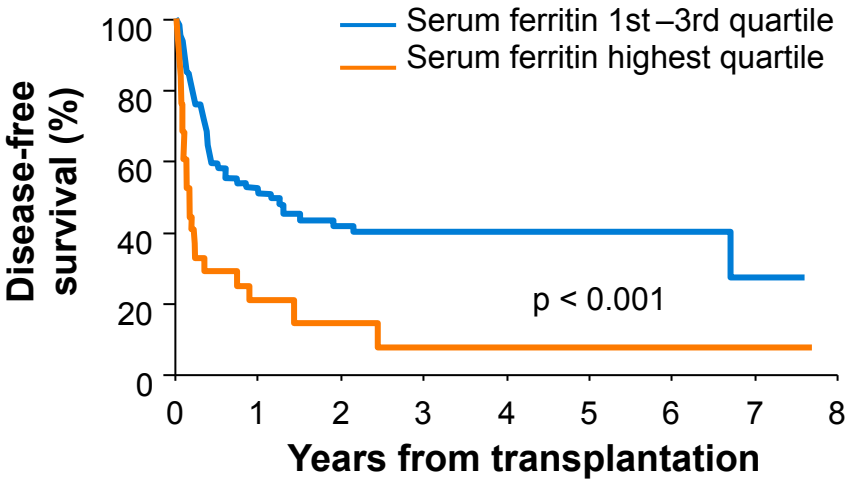
Alessandrino EP, et al. Haematologica. 2010;95:476-84. Armand P, et al. Biol Blood Marrow Transplant. 2007;13:655-64. Kataoka K, et al. Biol Blood Marrow Transplant. 2009;15:195-204. Lee JW, et al. Bone Marrow Transplant. 2009;44:793-7.Platzbecker U, et al. Biol Blood Marrow Transplant. 2008;14:1217-25.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

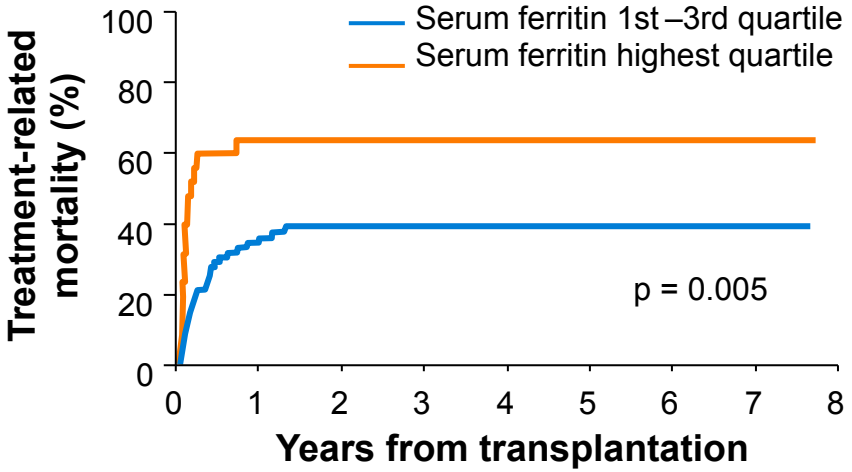
Outcome according to serum ferritin level

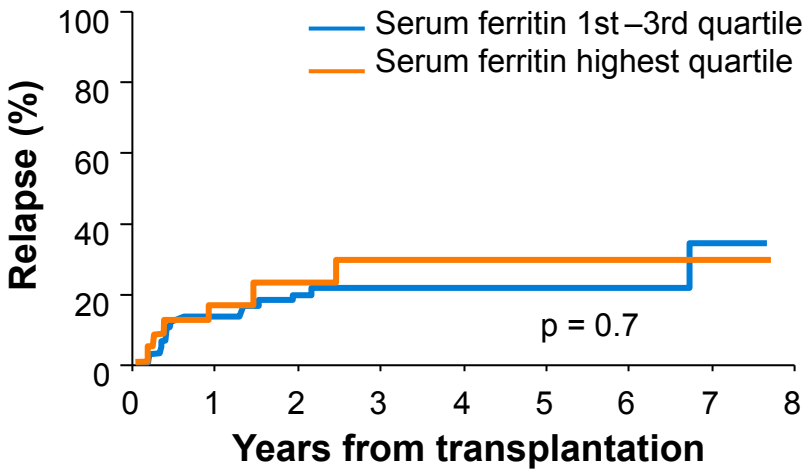
(590 pts: 154 CML, 144 AML, 103 MDS, 74 ALL, 115 other)

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

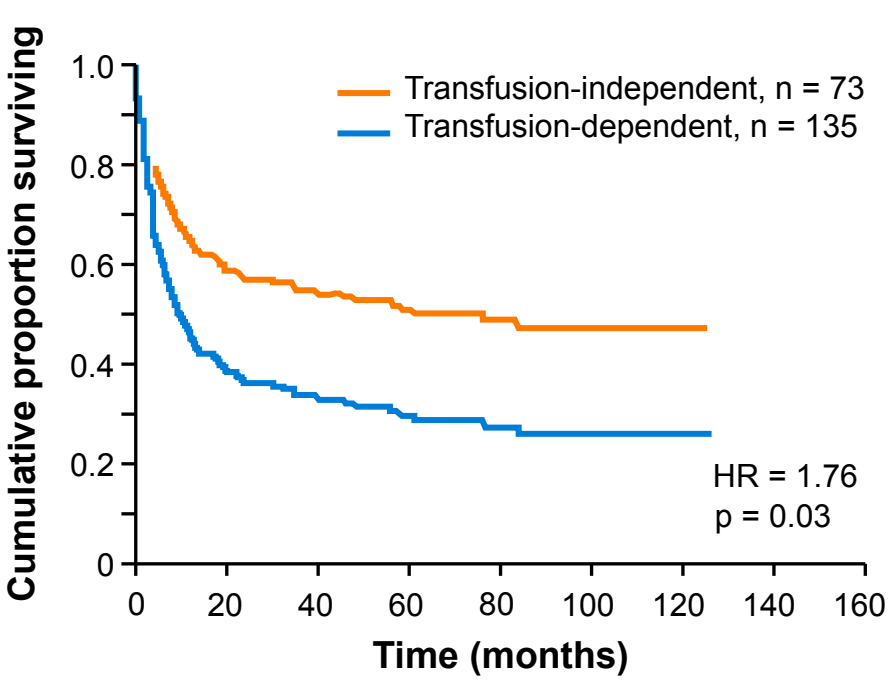


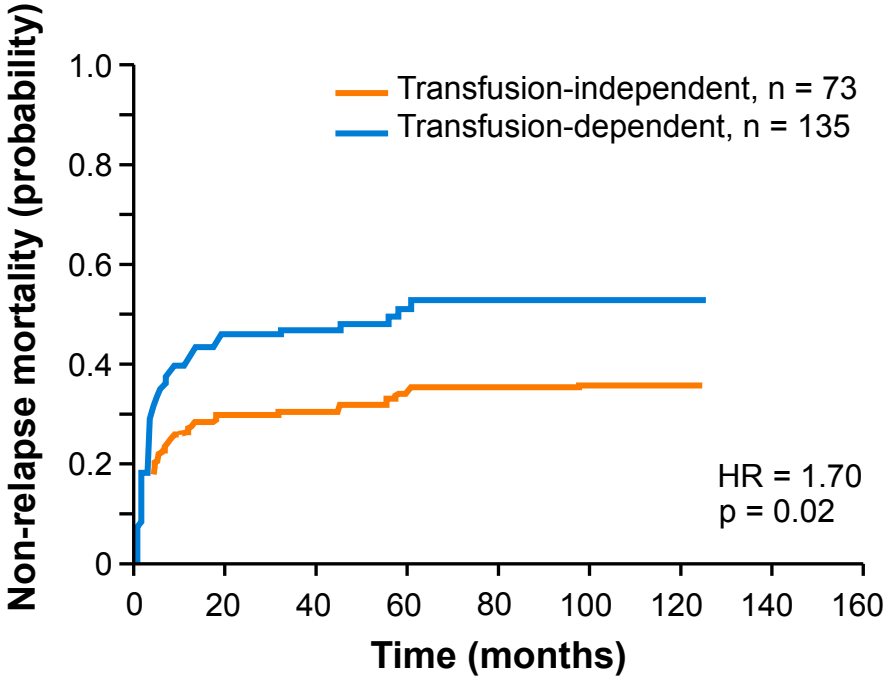






Impact of transfusion dependence on overall survival and non-relapse mortality in myeloablative SCT*





Lower overall survival in transfusion-dependent patients

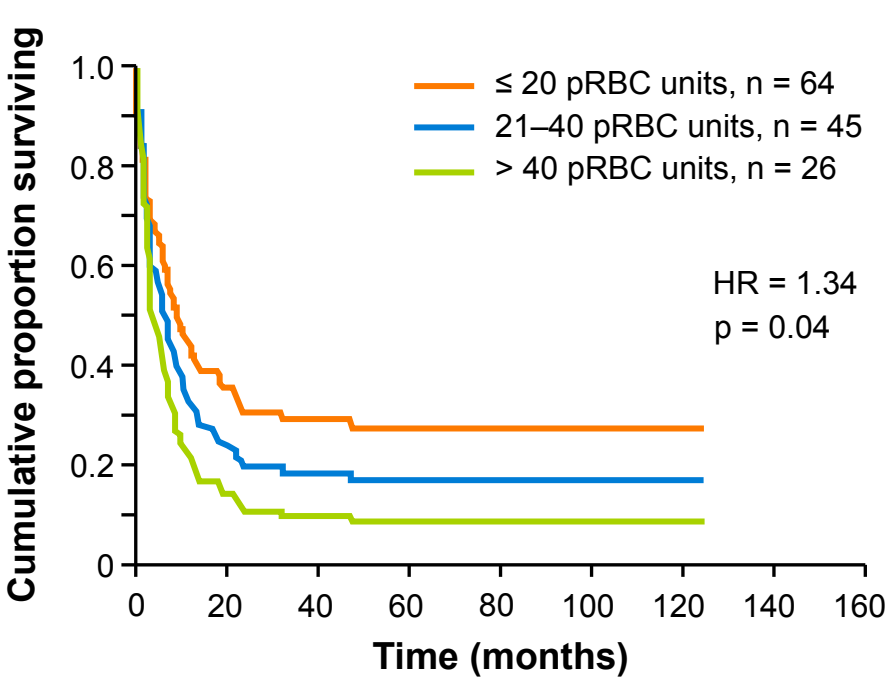
Higher non-relapse mortality in transfusion-dependent patients

*Multivariate analysis adjusted for other prognostic factors

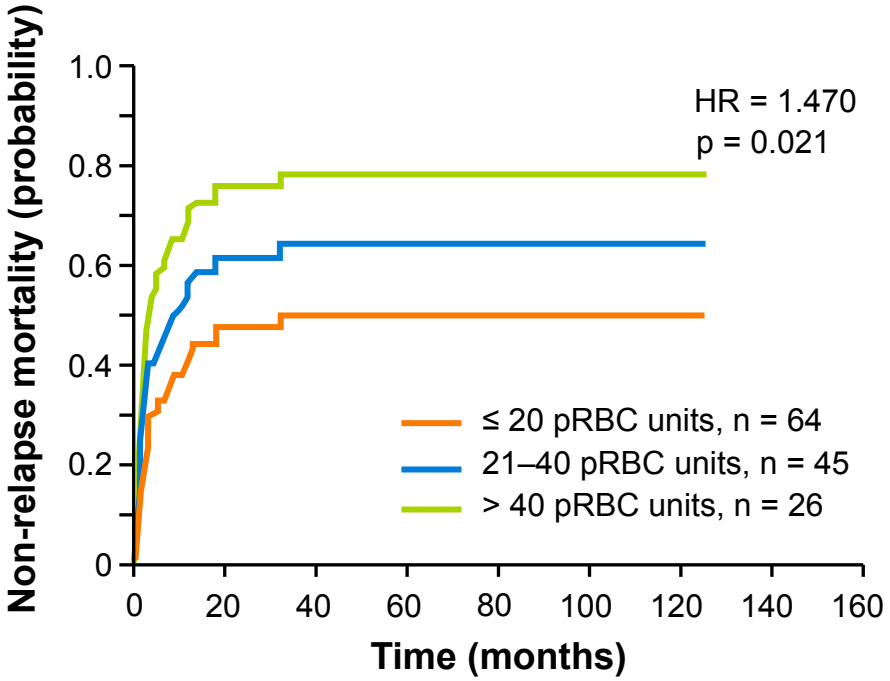
HR = hazard ratio;
SCT = stem cell transplantation.

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



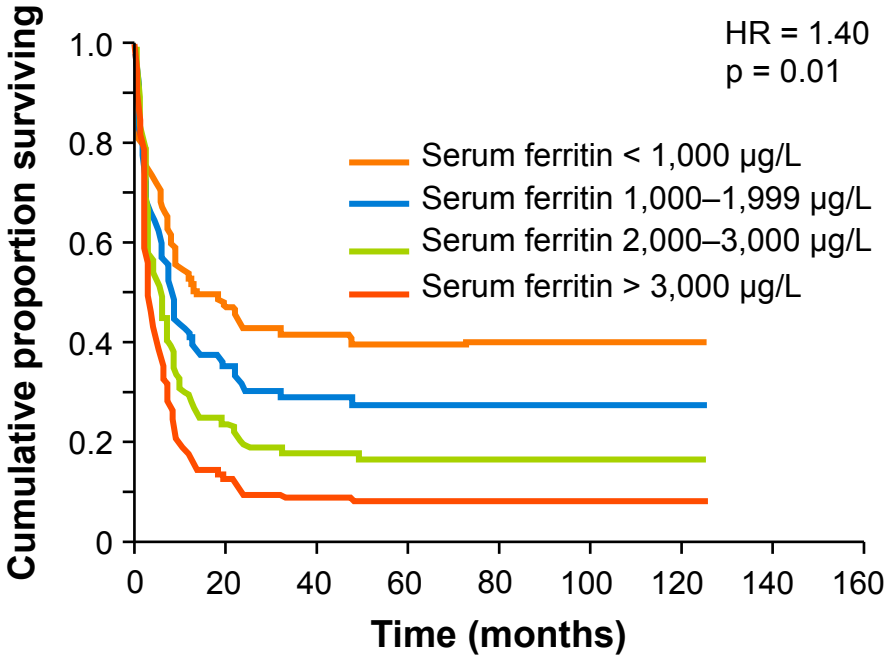
Non-relapse mortality by transfusion burden prior to SCT

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

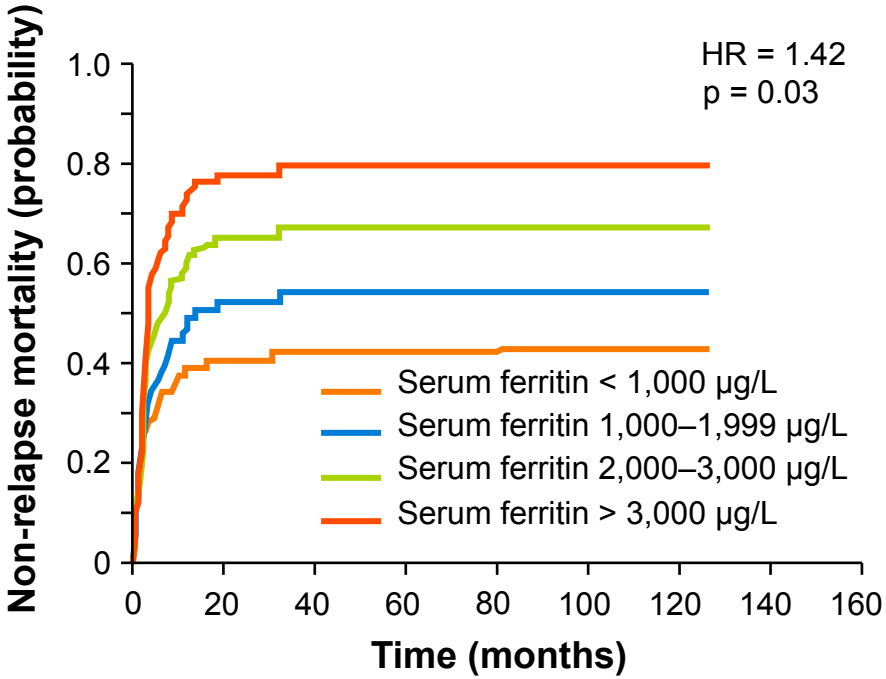
pRBC = packed red blood cells.

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



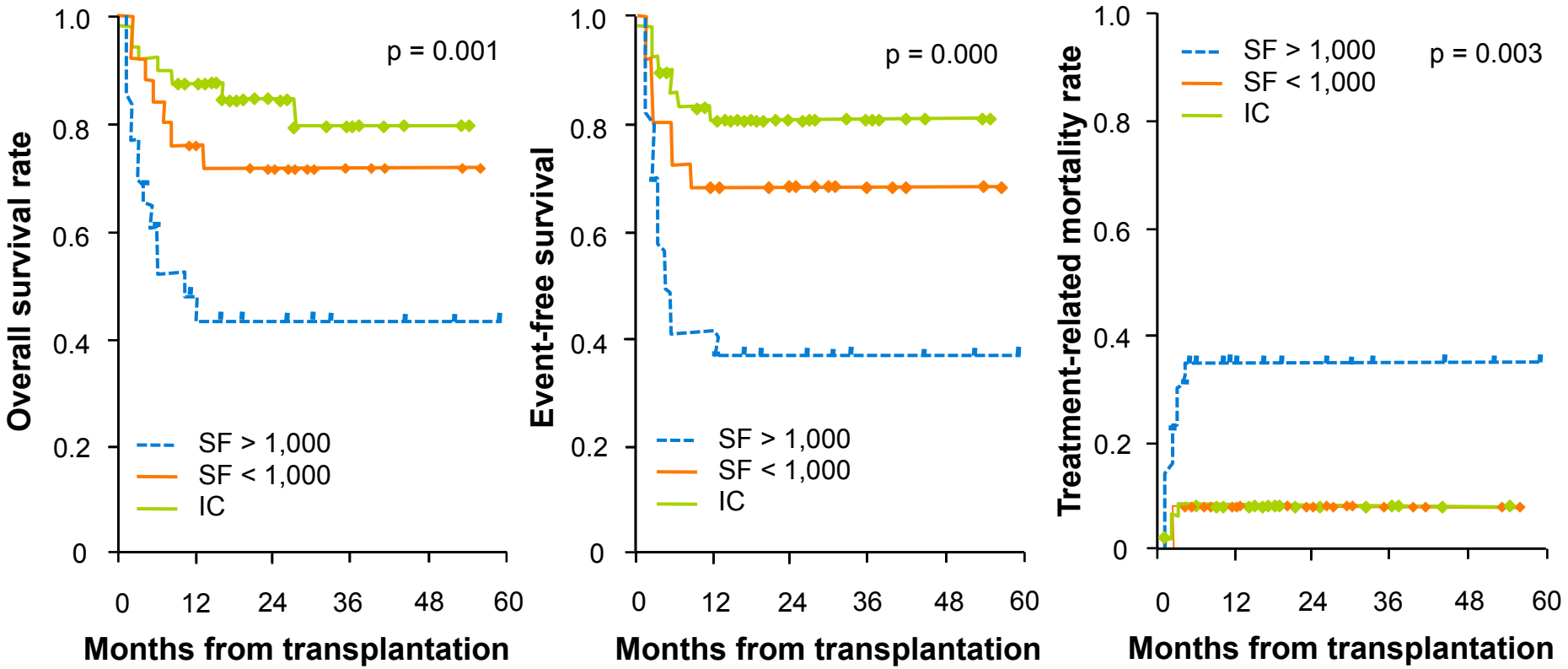
Non-relapse mortality by serum ferritin level prior to SCT

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

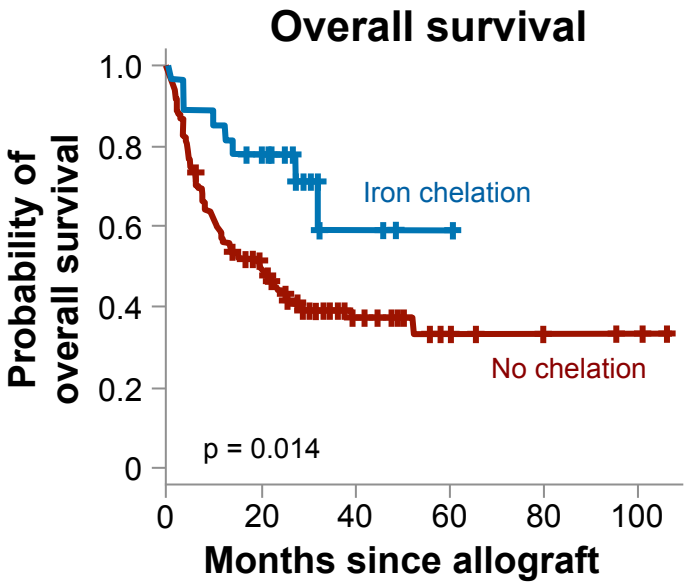
(retrospective study, 101 pediatric pts)



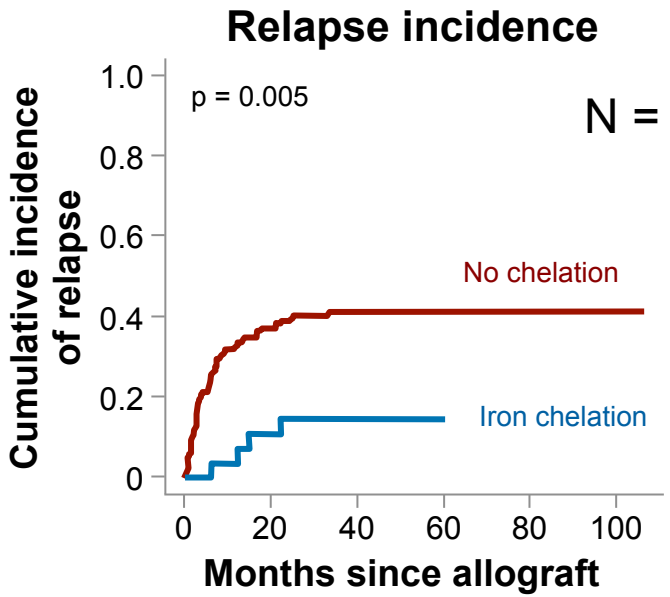
IC = patients with serum ferritin decreased to < 1,000 µg/L with ICT before HSCT;
ICT = iron chelation therapy;
SF > 1,000 = patients with serum ferritin ≥ 1,000 µg/L at the time of HSCT;
SF < 1,000 = patients with serum ferritin < 1,000 µg/L at the time of HSCT, without ICT.

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.

TERAPIA CHELANTE NELLE MDS: RIDUZIONE DEL FABBISOGNO TRASFUSIONALE *(Jensen, Br J Haematol, 1996)*

- 11 paz. con MDS trattati con DFO (standard in 4 paz., bolo i.c. in 7 paz) (+ vit C) (fino a 60 mesi)
- 7/11 paz (64%): ↓ del fabbisogno trasfusionale > 50%, 5/11 : miglioramento trilineare
- 7 paz: aumento delle piastrine e dei PMN
- 5/11 (46%): trasfusione-indipendenti,
- efficacia clinica (↓ ferro epatico con RMN) associata ad aumento del recettore della transferrina e dell'attività eritropoietica (b.ossea)
- **max risposta dopo almeno 18 mesi**, correlata all'efficacia della ferro-chelazione

Nei pazienti affetti da MDS deferasirox può migliorare l'emopoiesi: prime evidenze aneddotiche

Pubblicazione	n	Rischio IPSS	Risposta GR*	Risposta neutrofili*	Risposta PLT*
Breccia et al., 2010[1]	1	Basso	Maggiore	NR	NA
Capalbo et al., 2009[2]	1	Basso	Maggiore	NA	NA
Messa et al., 2008[3]	3	Intermedio 1 Intermedio 1 Alto	Minore Maggiore Maggiore	NA NA Maggiore	NA NA NR
Okabe et al., 2009[4]	1	NR	Maggiore	Maggiore	NR
Oliva et al., 2010[5]	1	Basso	Maggiore	NA	NA

***Le risposte di globuli rossi, piastrine e neutrofili sono valutate in base ai criteri IWG 2000.**

1. Breccia M, et al. Acta Haematol. 2010;124:46-8; 2. Capalbo S, et al. Acta Haematol. 2009;121:19-20.
3. Messa E, et al. Acta Haematol. 2008;120:70-4; 3. Okabe H, et al. Rinsho Ketsueki. 2009;50:1626-9.
5. Oliva EN, et al. Transfusion. 2010;50:1568-70; Tabella adattata da Guariglia R, et al. Leuk Res. 2011;35:566-70.

Pubblicazione	n	Rischio IPSS	Risposta GR*	Risposta neutrofili*	Risposta PLT*
Guariglia et al., 2011[1]	1	Intermedio 1	Maggiore	Maggiore	NA
List et al., 2009[2]	6	Basso/Int-1	2 maggiori 1 minore†	1 maggiore 1 maggiore‡	1 maggiore 1 maggiore‡
Badawi et al., 2010[3]	1	Intermedio 1	Maggiore§	NA	NA
Nishiuchi et al., 2010[4]	1	Intermedio 1	Maggiore‖	Maggiore‖	NA
Molteni et al., 2010[5]	6	NR	5 minori	1 maggiore	NA

*** Le risposte di globuli rossi, piastrine e neutrofili sono valutate in base ai criteri IWG 2000.**
† Il paziente ha ricevuto anche darbopoietina.
‡ Il paziente ha ricevuto anche G-CSF e decitabina.
§ La durata della risposta era 38 mesi; è stata osservata infiltrazione leucemica cutanea.
‖ La durata della risposta è stata > 12 mesi.

Tabella adattata da 1. Guariglia R, et al. Leuk Res. 2011;35:566-70.
2. List AF, et al. Blood. 2009;114:[abstract 3829]; 3. Badawi MA, et al. Adv Hematol. 2010;2010:164045.
4. Nishiuchi T, et al. Int J Hematol. 2010;91:333-5; 5. Molteni A, et al. Haematologica. 2010;95 Suppl 2:[abstract 1410].

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 asses 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

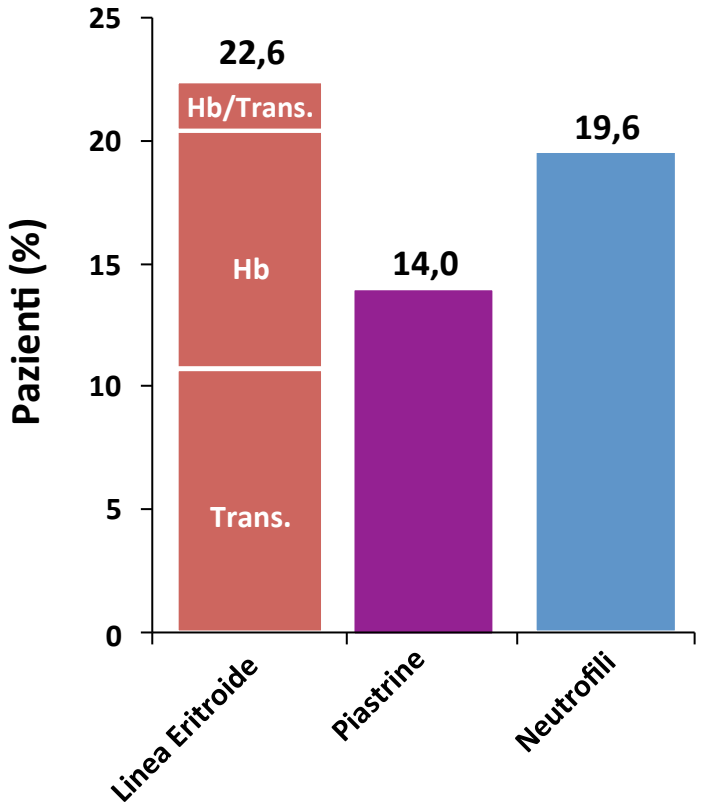
Hematologic responses to deferasirox therapy in transfusion-dependent patients with myelodysplastic syndromes

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]

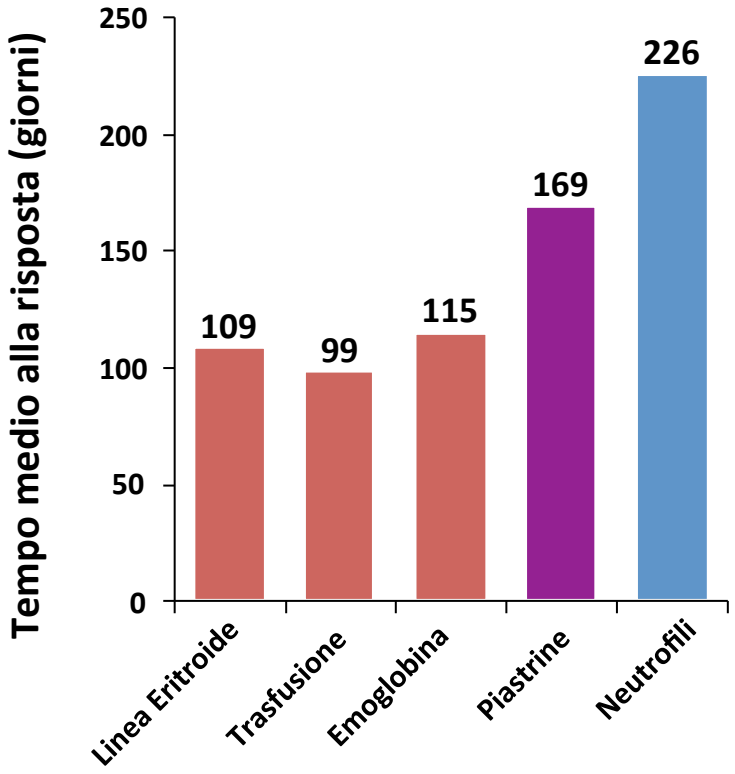
[1]Heinrich-Heine-Universität, Düsseldorf, Germany; [2]Policlinico S. Orsola-Malpighi, Bologna, Italy; [3]IRCCS Policlinico S. Matteo, Pavia, Italy; [4]Service d'hématologie Clinique, Hôpital Avicenne/Université Paris, Bobigny, France; [5]Medizinische Hochschule Hannover, Hannover, Germany; [6]CHU Brabois, 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



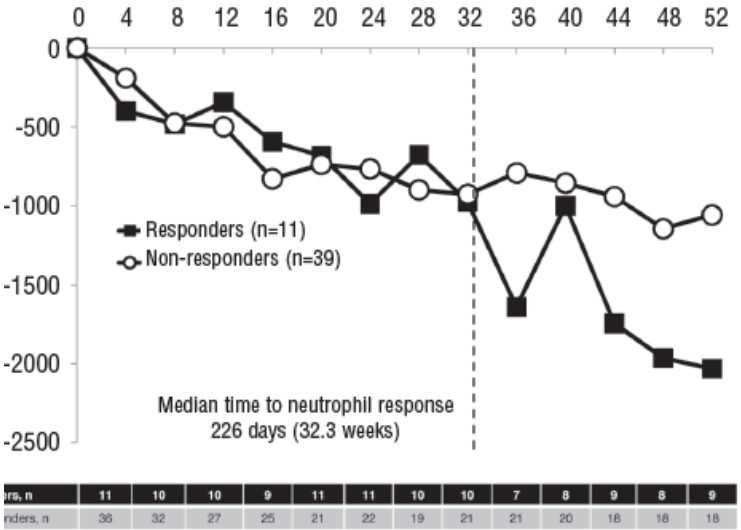
Tempo alla risposta ematologica



Gattermann N, et al. Haematologica 2012

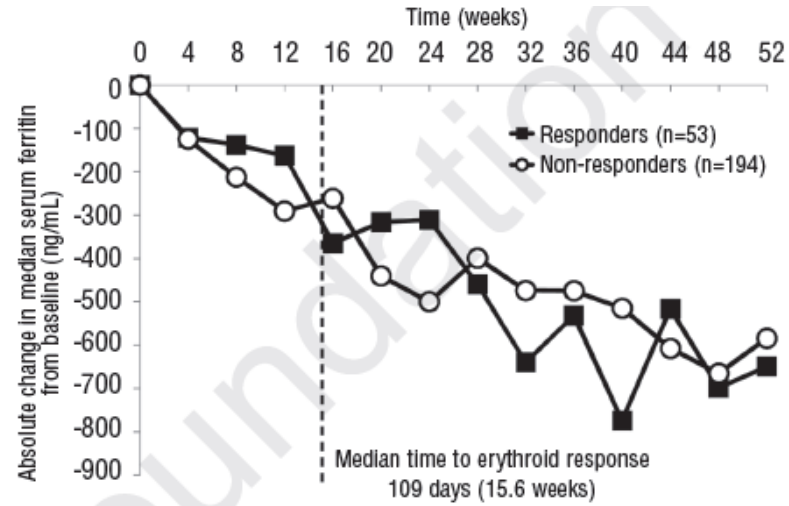
Ferritina Serica

Risposta Neutrofila



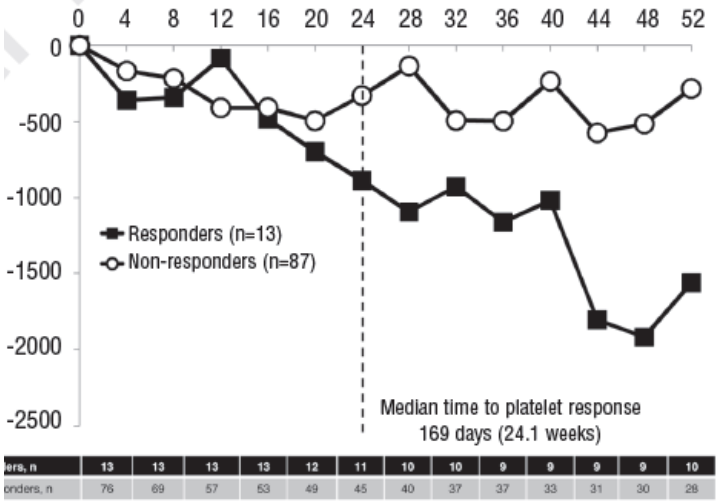
ers, n	11	10	10	9	11	11	10	10	7	8	9	8	9
nders, n	36	32	27	25	21	22	19	21	21	20	18	18	18

Risposta Eritroide



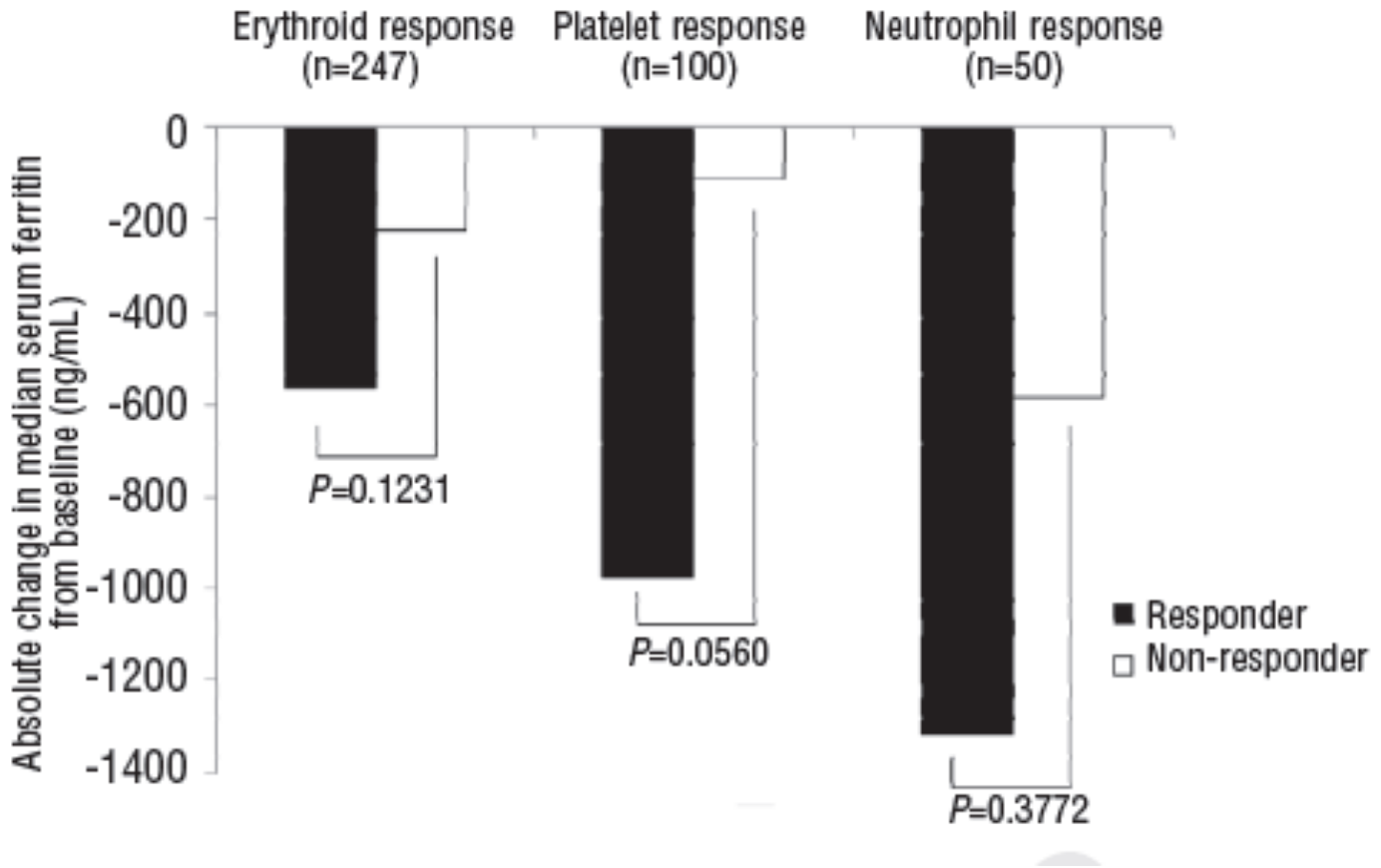
Responders, n	50	51	50	48	46	44	47	40	42	39	40	40	40
Non-responders, n	173	160	138	135	130	126	111	106	103	101	97	92	92

Risposta Piastrinica



ers, 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

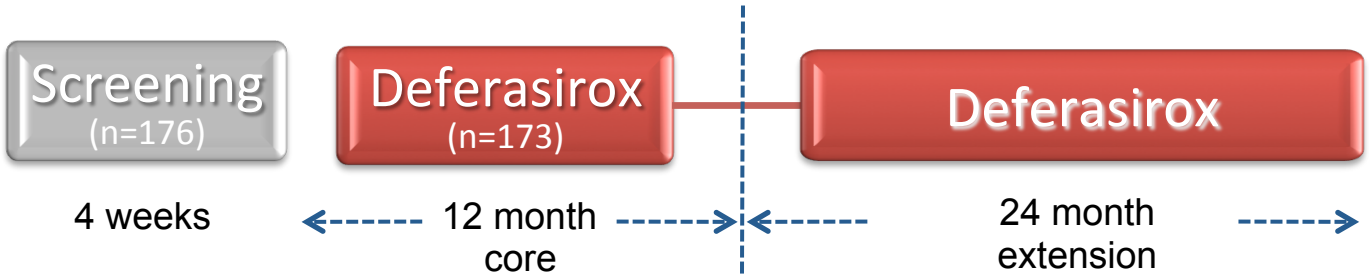
JOURNAL OF CLINICAL ONCOLOGY

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

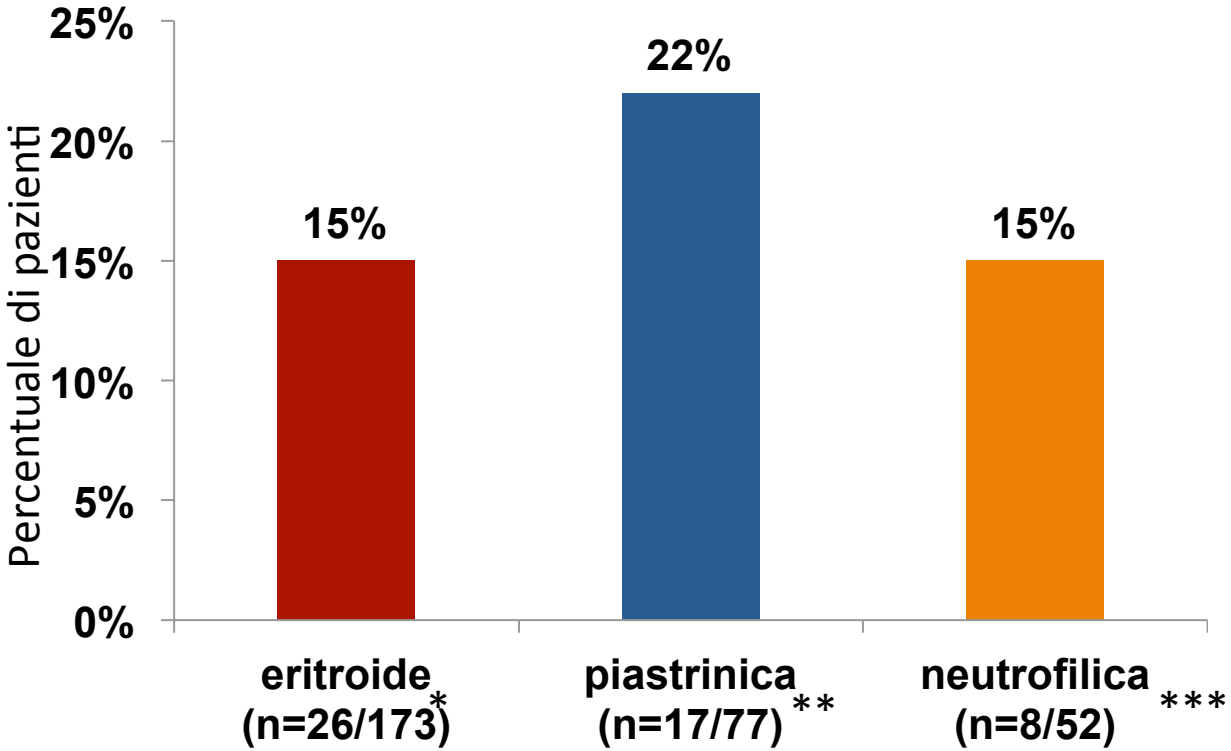
- Studio prospettico, multicentrico, di 3-aa, per stabilire sicurezza ed efficacia del deferasirox in 173 pazienti, con MDS a rischio basso o intermedio-1 (72%)
- Criteri di inclusione: almeno 20 unita' RBC, ferritina serica > 1,000 ng/mL.
- Accettabile creatinina aumentata fino a 2 volte il valore normale



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

Variazioni assolute della ferritinemia maggiori nei pazienti con risposta ematologica

Table 3. Change in Serum Ferritin From Baseline to End of Study in Patients With and Without Hematologic Response

Serum Ferritin Level	Patients Without Hematologic Improvement (n = 123)	Patients With Hematologic Improvement (n = 41)
Baseline serum ferritin, μg/L		
Median	2,751	3,045
Range	863-9,238	1,160-36,280
Change in serum ferritin from baseline to end of study, μg/L		
Median	−228	−693
Range	−4,227 to 5,317	−30,313 to 5,948

- Ferritinemia mediana ridotta in entrambi i gruppi, ma variazioni maggiori nel gruppo dei pazienti che ottenevano anche risposta ematologica
- Riduzione del LPI medio sia nei pazienti con HI, che in quelli che non ottenevano HI (media 0.47 mol/L v 0.32mol/L, rispettivamente).
- Vi era un trend per un miglioramento della sopravvivenza nei pazienti responsivi.

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

Hematological Response with Deferasirox: Retrospective Italian Study
Hematological Response (RBC)

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

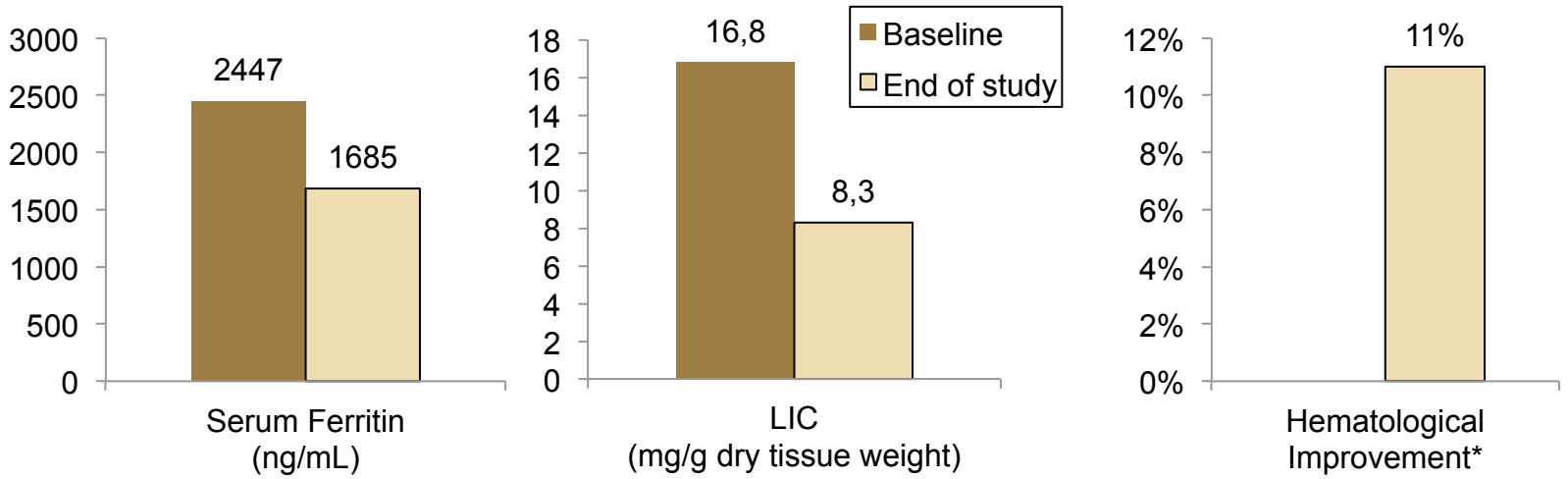
3 patients achieving complete erythroid response (2 with DFO and 1 with DFX) were receiving concomitant Epo from 15, 17 and 53 months with stable transfusion requirement at the time of ICT

IWG response criteria: Cheson et al. Blood 2006

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

1-year, Open-label, Single Arm, German Multi-center Trial: Hematological improvement in 11% Patients

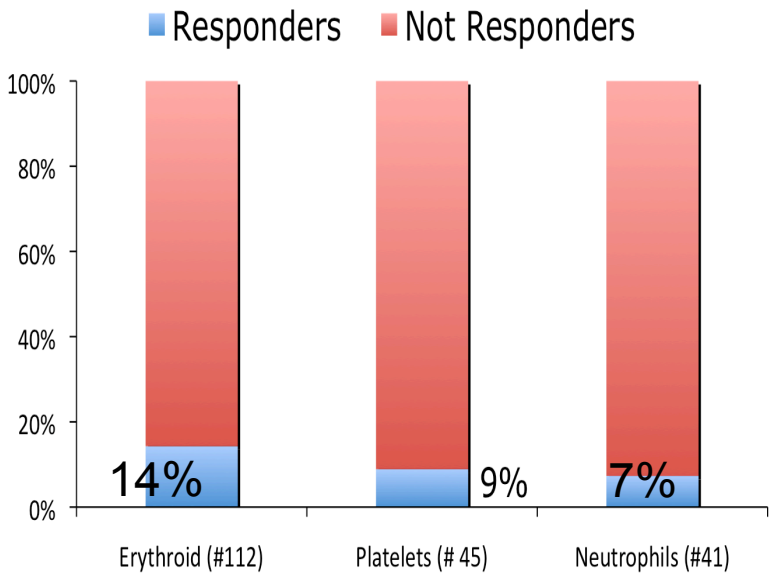
- Multi-center trial evaluating the efficacy and safety of deferasirox (DFX) in low and intermediate-1 risk MDS patients with transfusion-dependent IOL.
- Mean daily dose of DFX was 19 mg/kg/day.
- The intention to treat population consisted of 50 MDS patients (28 male; 22 female) with a median age of 69 years who were treated with DFX for a median duration of 354 days.



*Hematologic improvement according to IWG criteria (2006)

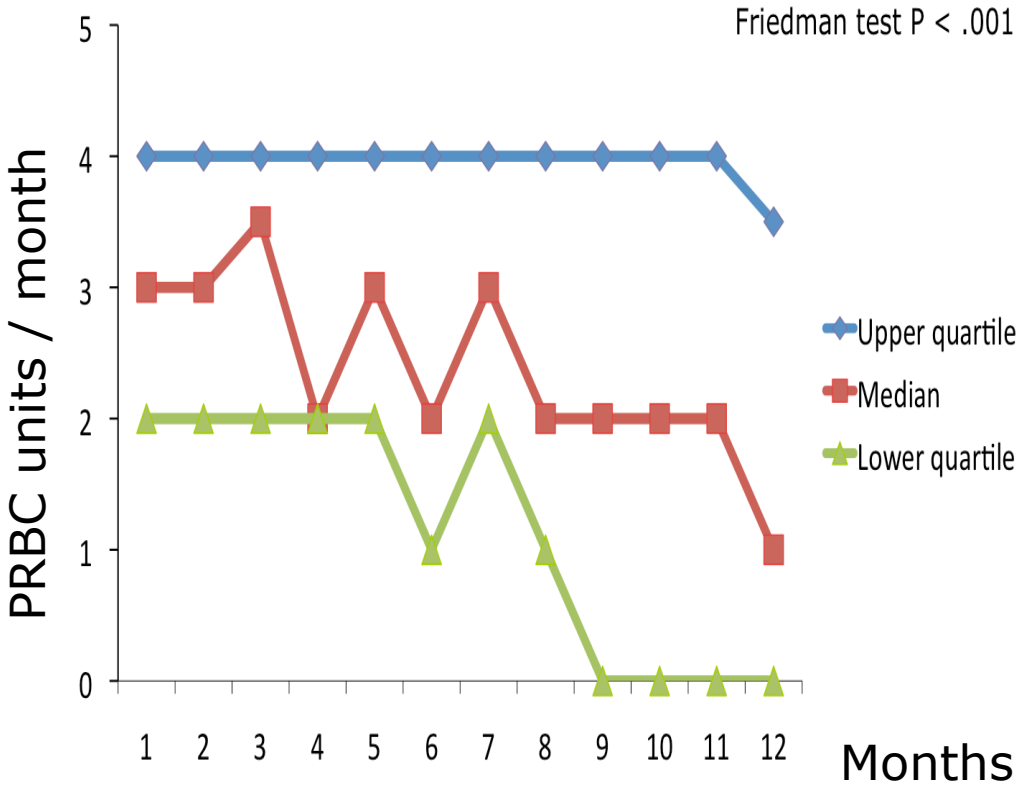
Nolte et al., *Ann Hematol*. 2013 Jan;92(2):191-8.

Risposta Ematologica



PRBC Units

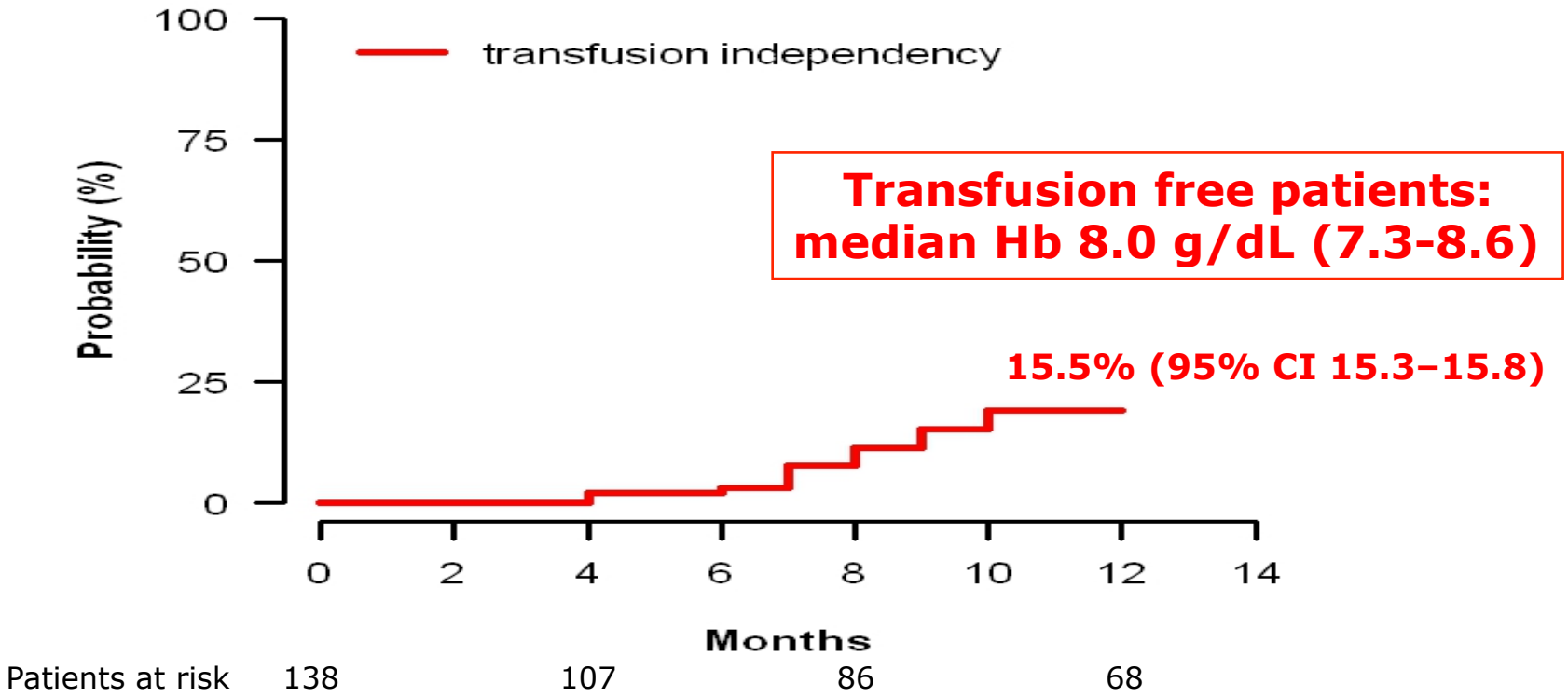
In 68 pts dopo 1 anno di trattamento



- 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

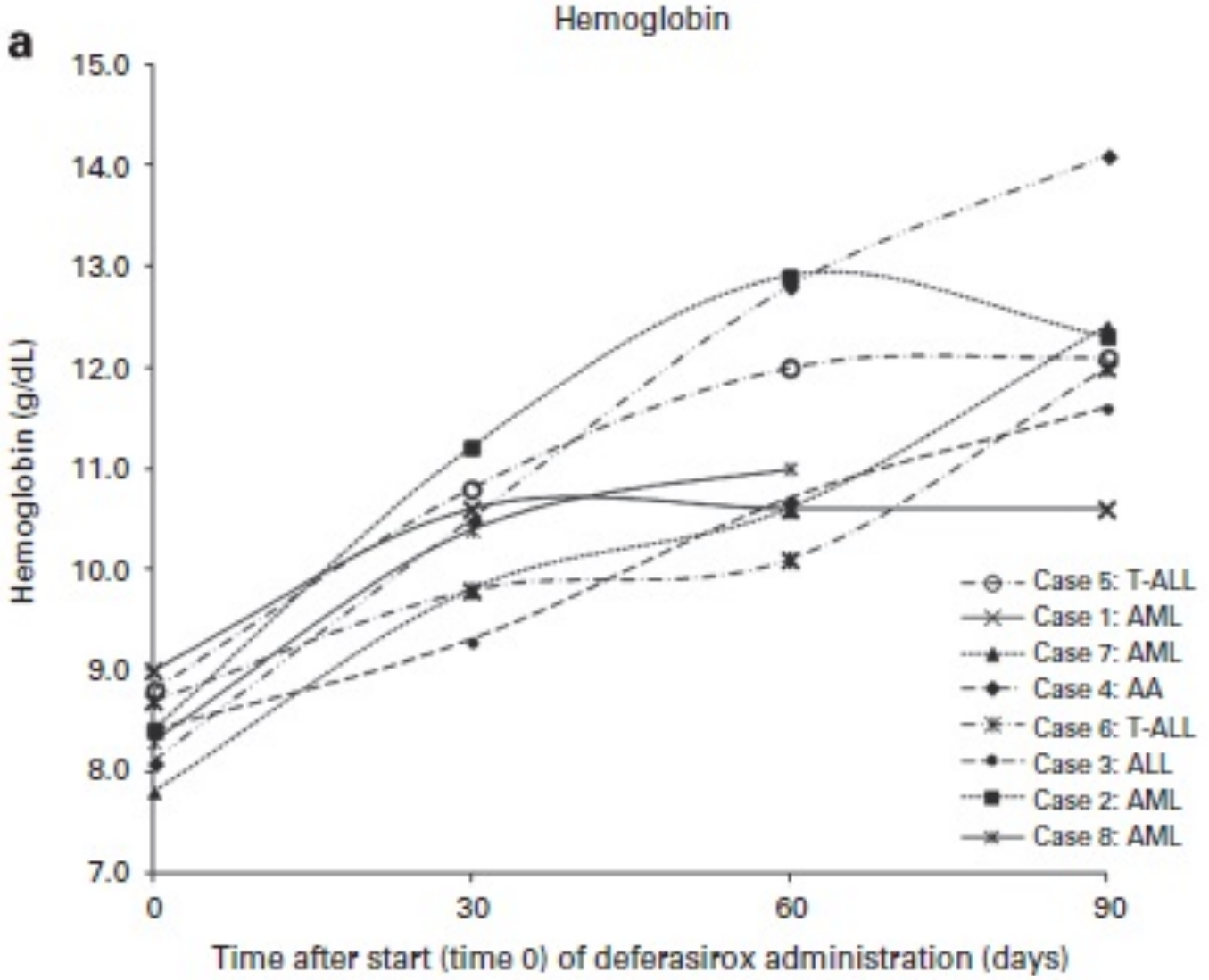
Angelucci E et al. Eur J Haematol, 2014.

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

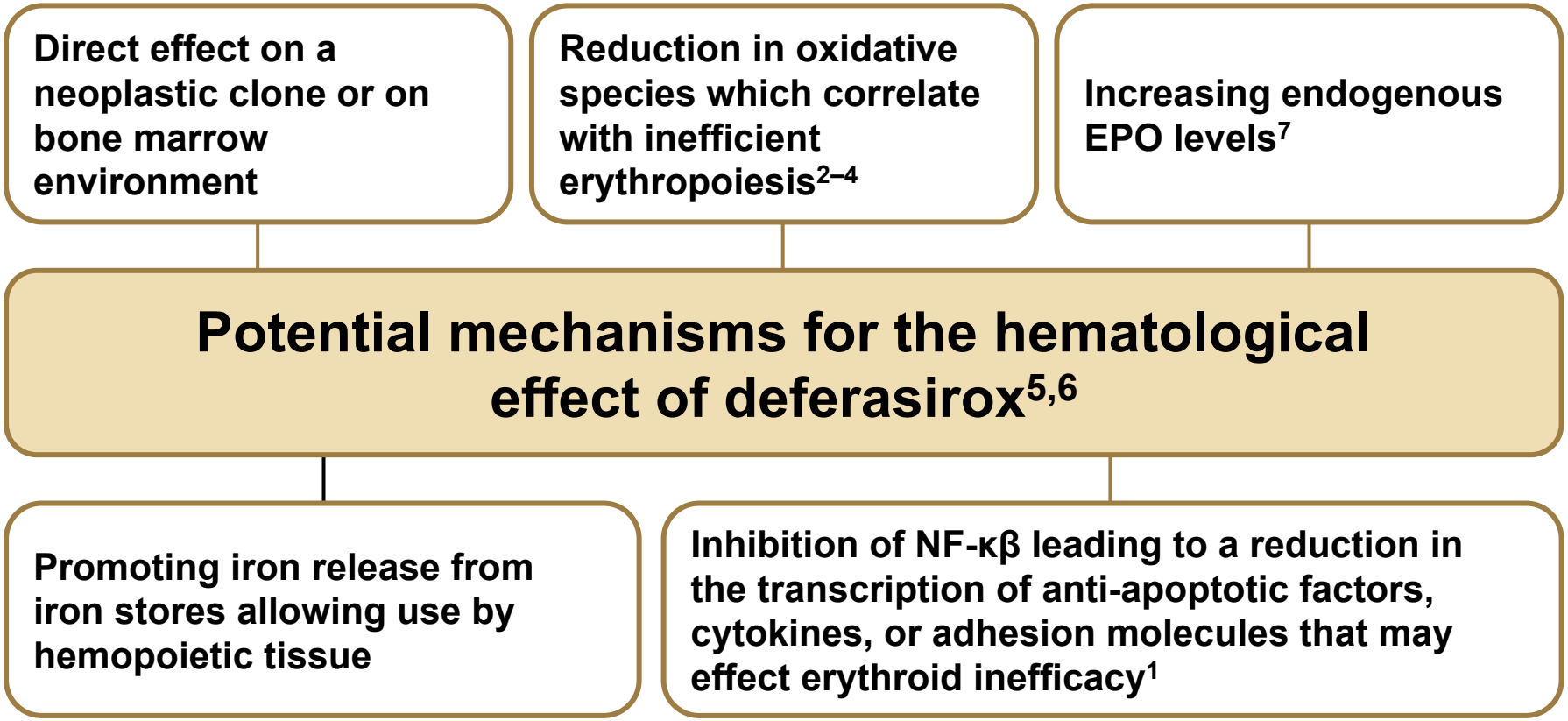
Abbreviations: AA = aplastic anemia; AML = acute myeloid leukemia; ALL = acute lymphoblastic leukemia; ATG = anti human thymocyte immunoglobulin (rabbit); BU = Busulphan; Cy = Cyclophosphamide; DFX = deferasirox; HSCT = hematopoietic stem cell transplantation; MUD = matched unrelated donor; TBI = total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

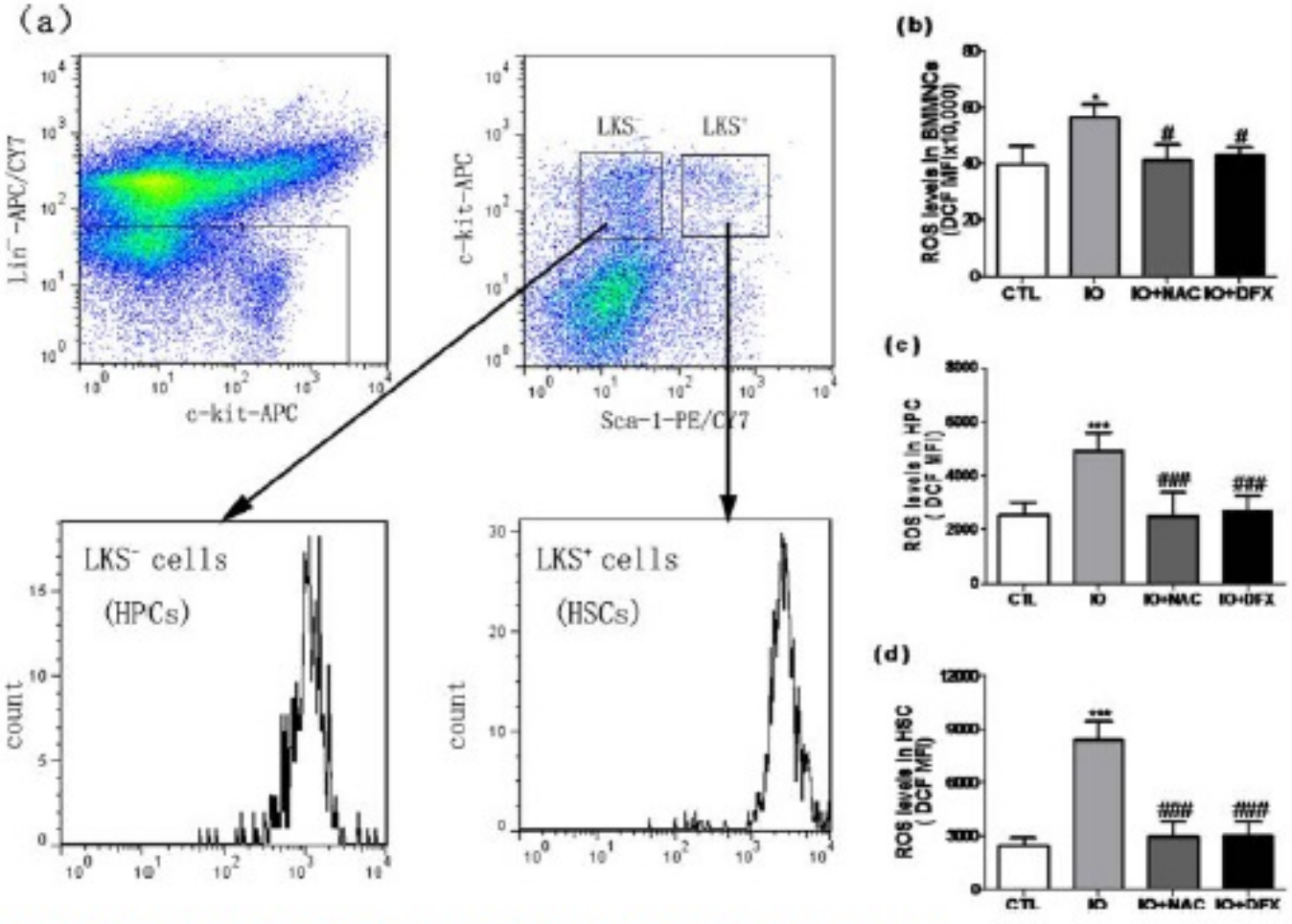
Bowen D, Wang L, Frew M, Kerr R, Groves M (2003)
Antioxidant enzyme expression in myelodysplastic and acute myeloid leukemia bone marrow: Further evidence of a pathogenetic role for oxidative stress?
Haematologica 88:1070-1072

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

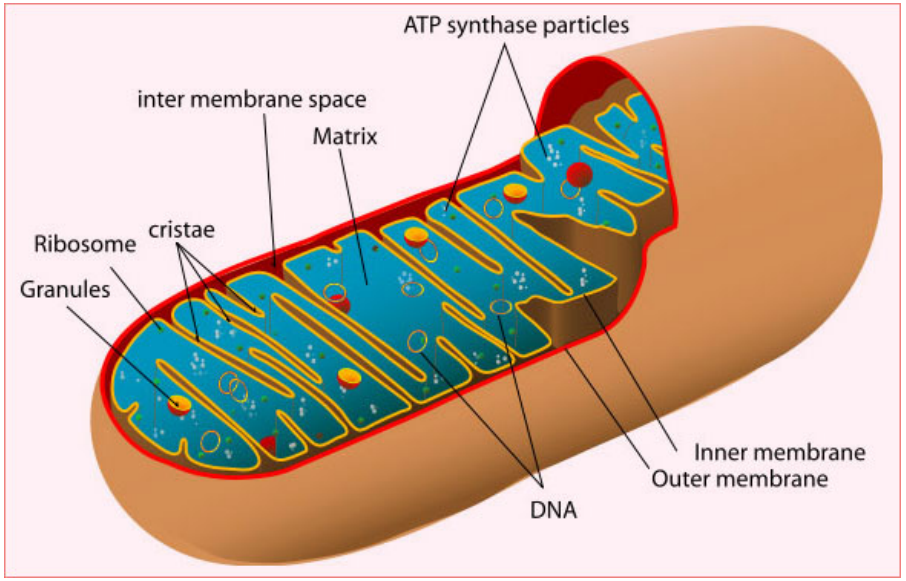
- RBCs, retics, and developing erythroid precursors take up iron through a Tf-independent pathway.
- This pathway is operative under pathological iron-overload situation in the presence of non-Tf iron in the serum.
- The incoming non-Tf iron does not participate in haeme synthesis and Hb production,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

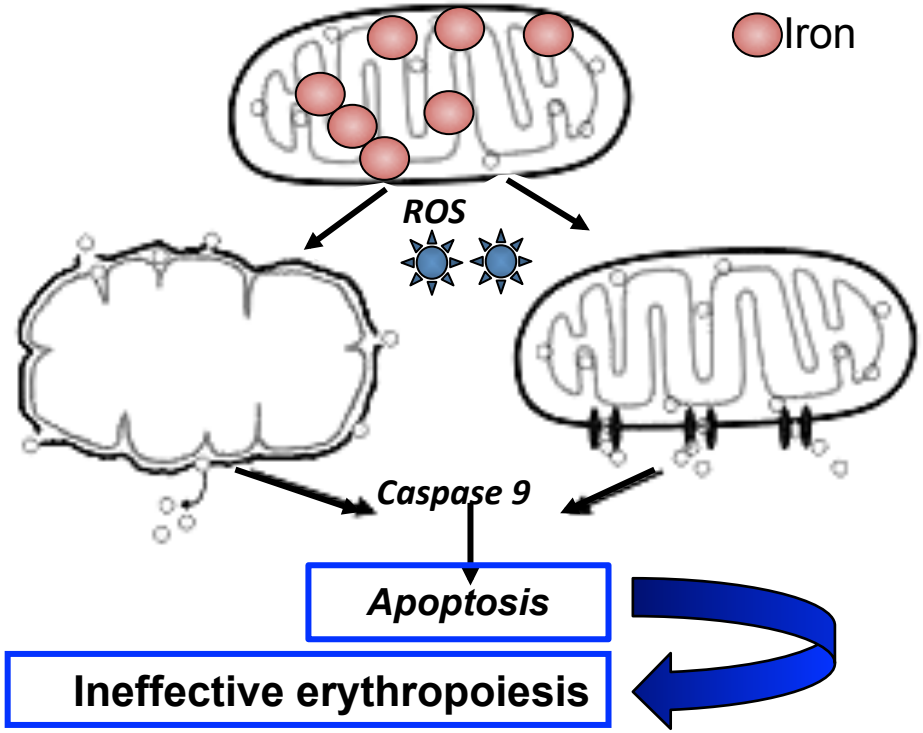
ROS Promote Apoptosis through Activation of the Caspase Cascade

Iron is also a potentially toxic metal

Labile iron can catalyze the production of toxic radicals:

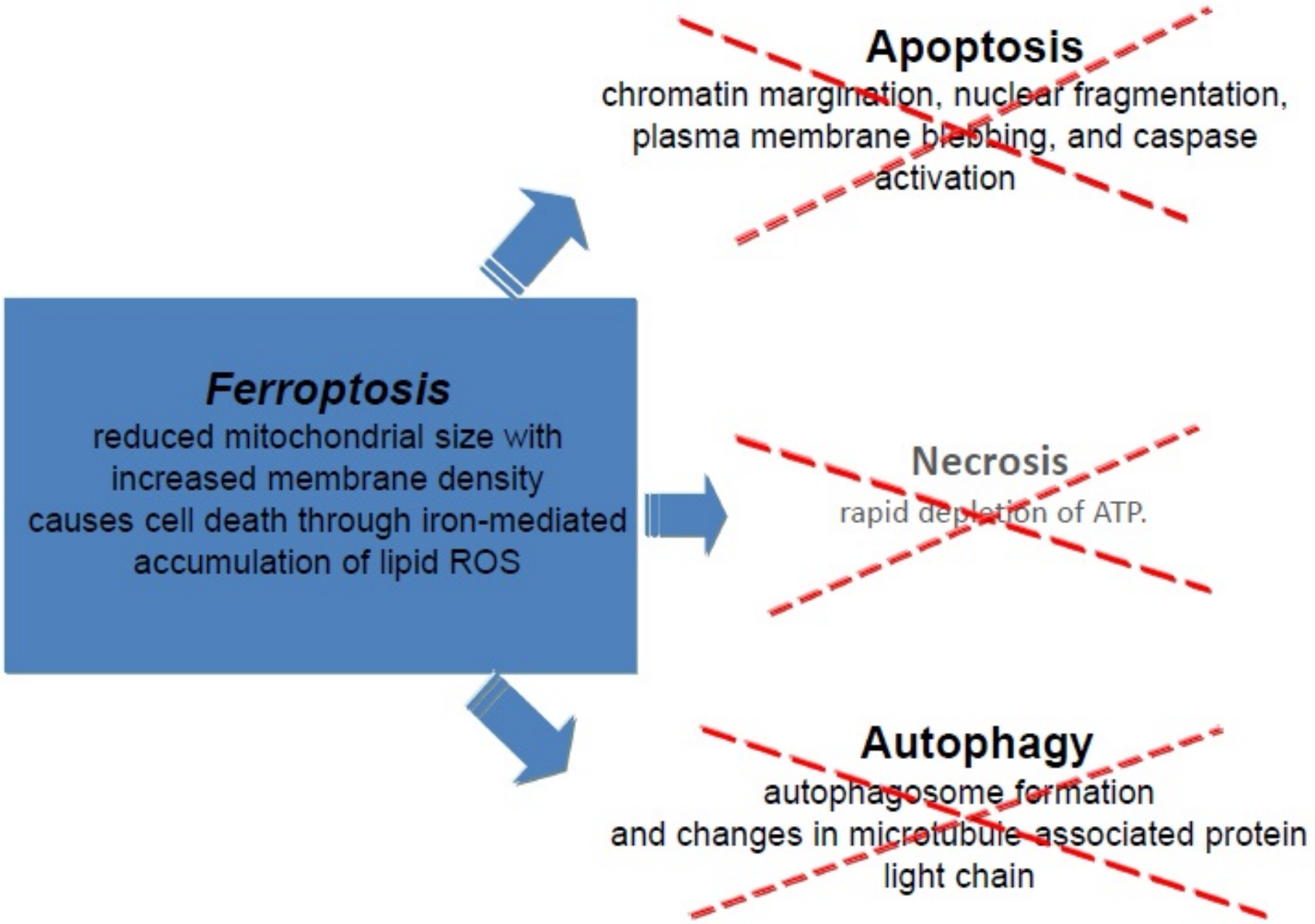
$$O_2^{\bullet -} + H_2O_2 \xrightarrow{Fe(II)} O_2 + OH^- + OH^{\bullet}$$ that can damage the cells



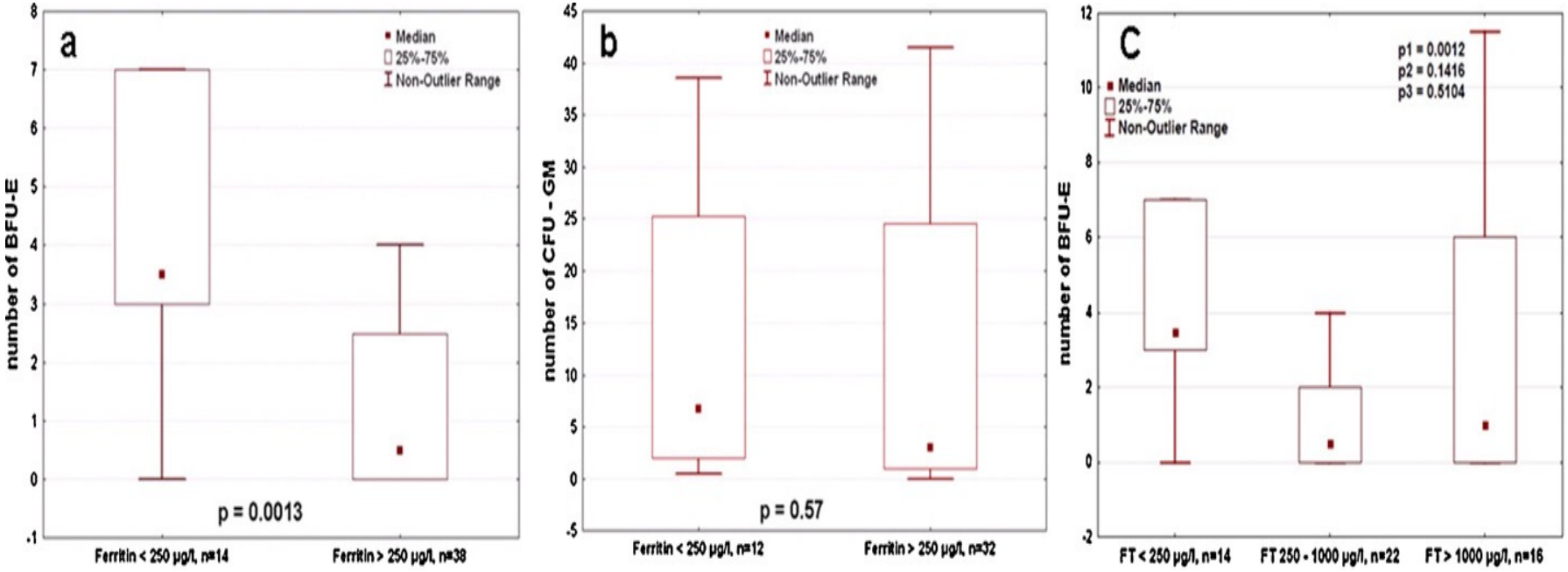


Zuo Y, *et al. Cell Res*. 2009;19:449-57.

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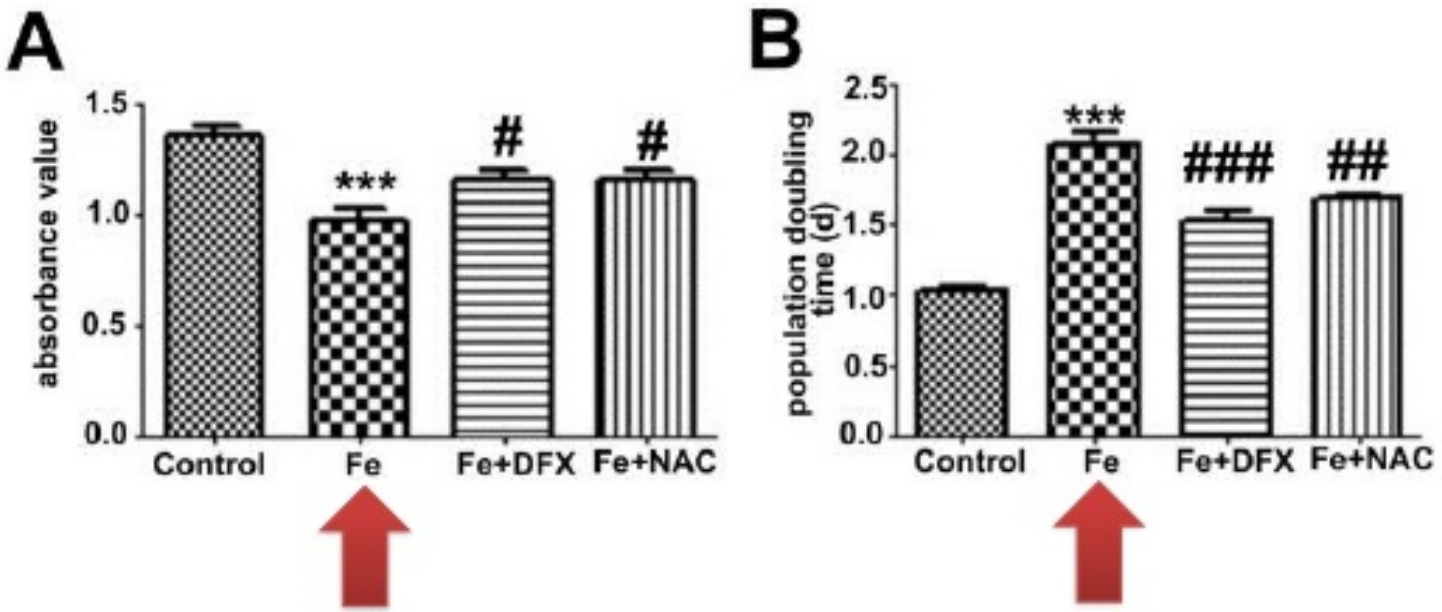
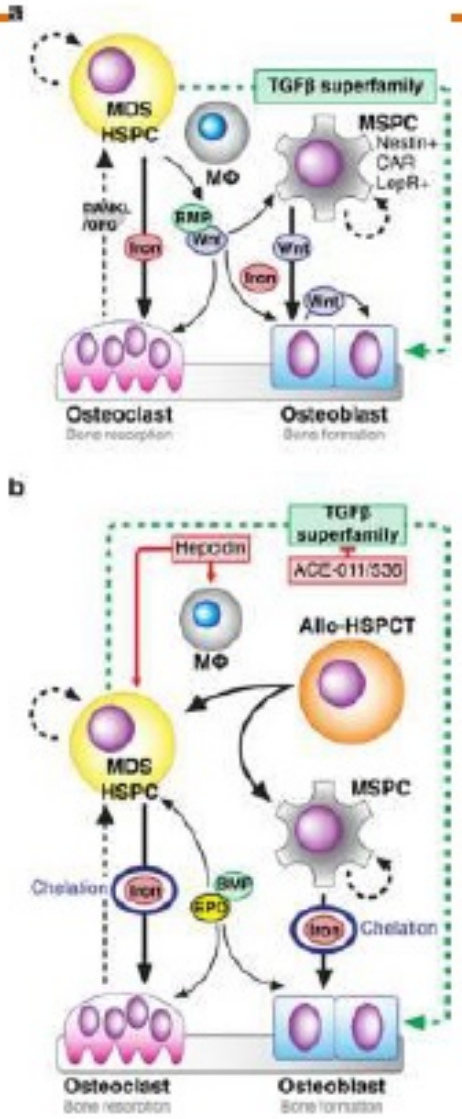
Yuchen Zhang et al.PLoS One. 2015; 10(3): e0120219
Effects of Iron Overload on the Bone Marrow Microenvironment in Mice

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**

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bjh research paper

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

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Summary

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

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

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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.