IRON OVERLOAD IN MDS

LET'S IRON THINGS OUT

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McGill

CCMDS|CCSMD

DISCLOSURES

- Roche: advisory board, honoraria
- Celgene: advisory board, honoraria, speaker's fee
- Novartis: advisory board, honoraria

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1. ANEMIA IN MDS
2. TRANSFUSIONAL IRON OVERLOAD
3. IRON CHELATION
4. GUIDELINES

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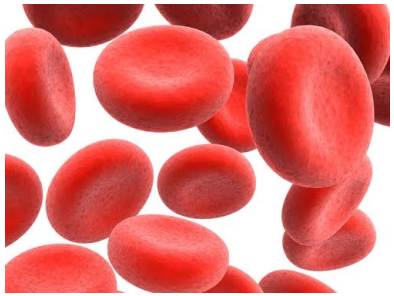
MDS

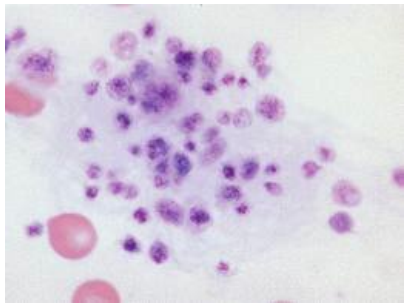
red blood cells



ANEMIA

Hemoglobin <120mg/dl F
<140mg/dl M

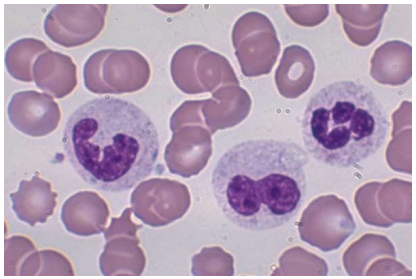
platelets



THROMBOCYTOPENIA

Platelets <150,000x10^6/L

neutrophils

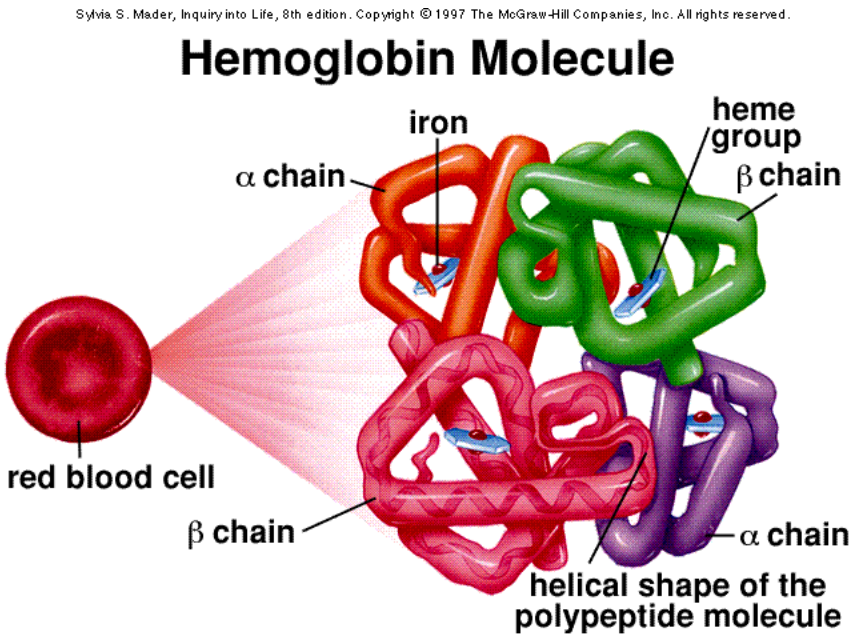


NEUTROPENIA

Neutrophils <1.8x10^9/L

HEMOGLOBIN

- large protein molecule in rbc
- several hundred per cell
- carries oxygen through circulation to the tissues
- 4 iron atoms per hgb



ANEMIA

- Hgb: <120g/dl F <140g/dl M
- ~80% MDS pts are anemic at diagnosis
- ~50% have Hgb <100g/dl
- symptoms: fatigue, exercise intolerance, weakness, shortness of breath on exertion/at rest, palpitations, headache, dizziness, angina, roaring in ears
- symptoms can appear at different levels of hgb depending on the pt. and their other conditions

TREATMENT OF SYMPTOMATIC ANEMIA IN MDS

- ESA: erythropoietin (epo) stimulating agents
  - erythropoietin (Eprex), darbopoietin (Aranesp)
  - used alone or in combination with GCSF (Neupogen)
  - IPSS low or int-1 patients
  - especially for pts with low natural epo levels and lower rbc transfusion requirements
  - Some studies show improved QOL
  - No survival benefit
  - 30-40% of patients respond, <2 years

TREATMENT OF SYMPTOMATIC ANEMIA IN MDS

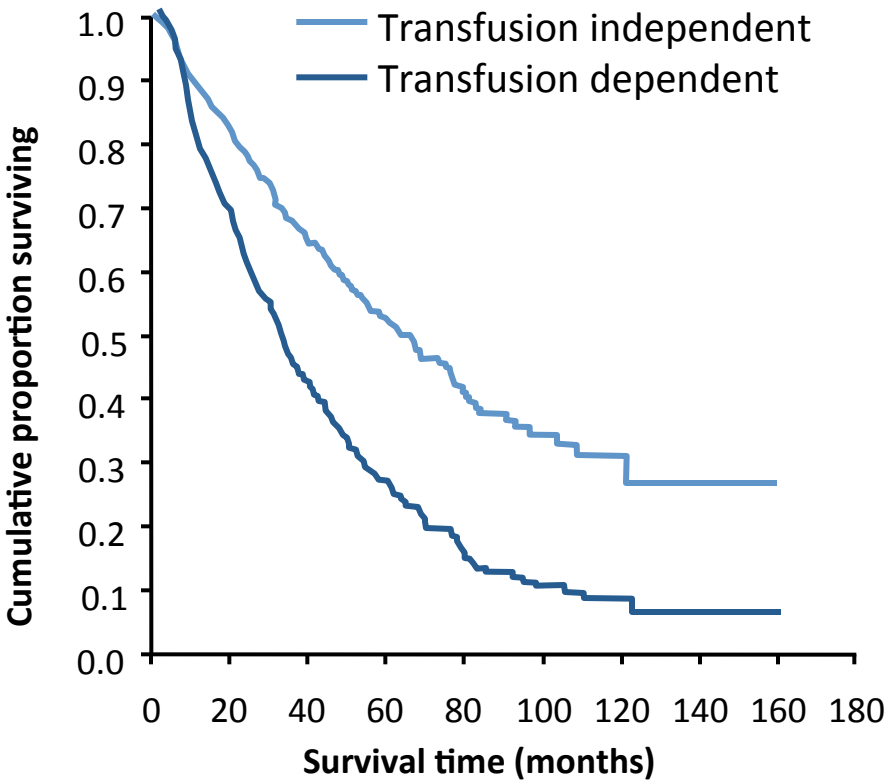
- TRANSFUSION OF PRBC
  - Main treatment option
  - Hgb < 80mg/dl without symptoms, higher if symptoms

1 Donation = 3 products

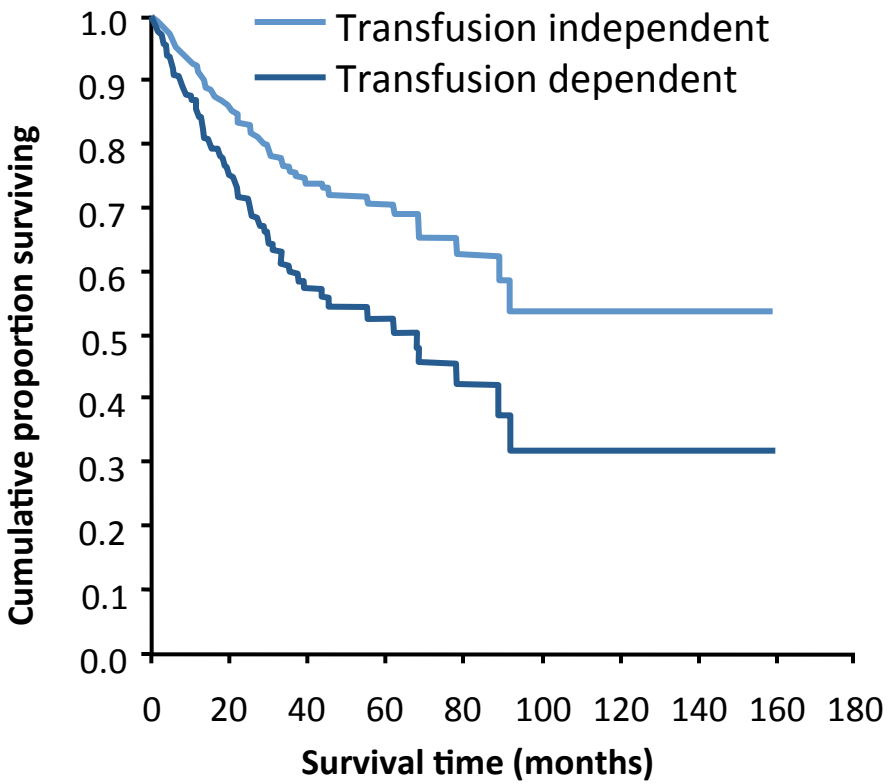
Red Blood Cells | Plasma | Platelets

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

Overall survival
(HR = 1.91; p < 0.001)



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

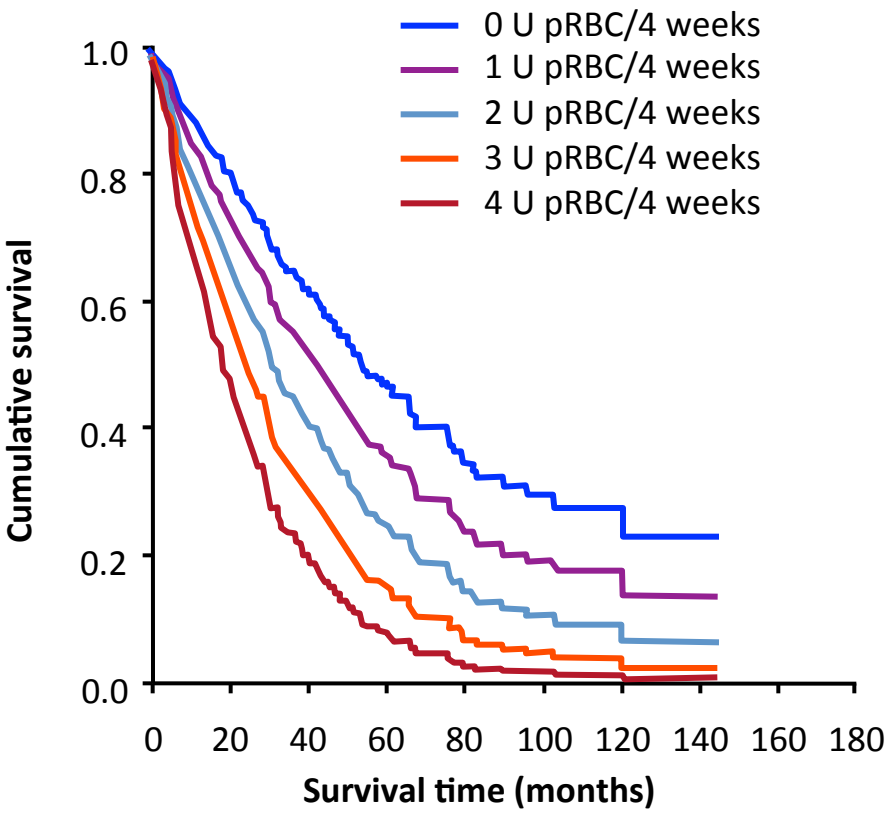


HR = hazard ratio.

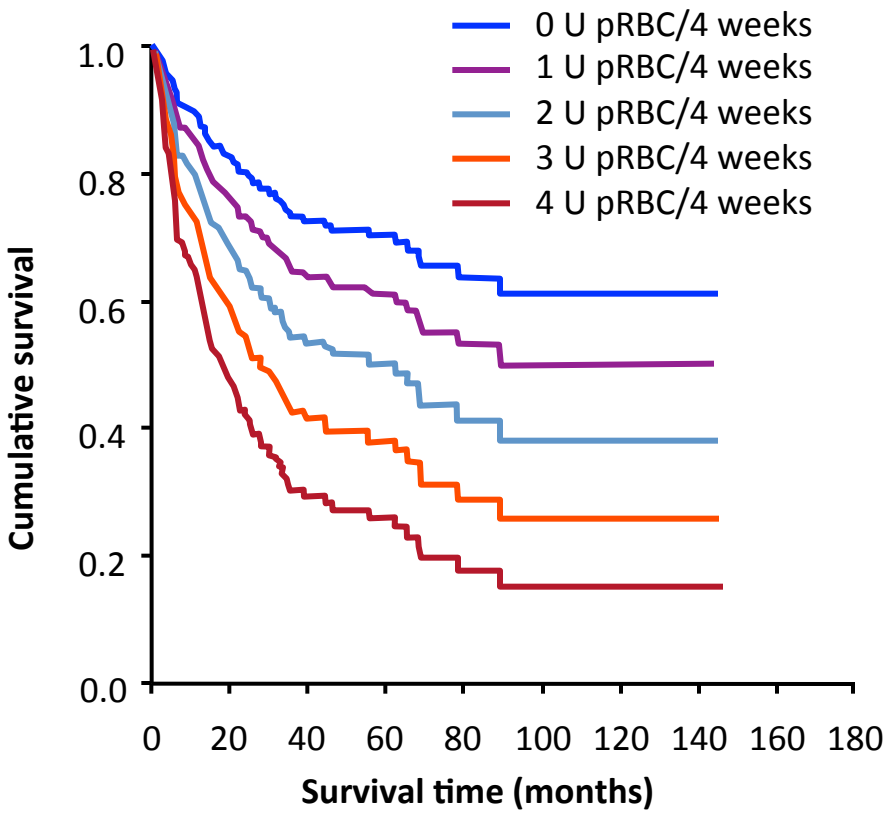
Malcovati L, et al. J Clin Oncol. 2005;23:7594-603.

Survival of MDS patients by severity of RBC transfusion requirement

Overall survival
(HR = 1.36; p < 0.001)



Leukaemia-free survival
(HR = 1.40; p < 0.001)



pRBC = packed red blood cells.

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

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IRON OVERLOAD FROM TRANSFUSION THERAPY

The body has no mechanism to excrete excess iron

Moderate transfusion requirement:

- 2 units/month
- **~ 100 units/4 years**

High transfusion requirement:

- 4 units/month
- **~ 100 units/2 years**

- **100 units: ≥ 20 g iron**

'Pure' red cells: 1.16 mg iron/mL

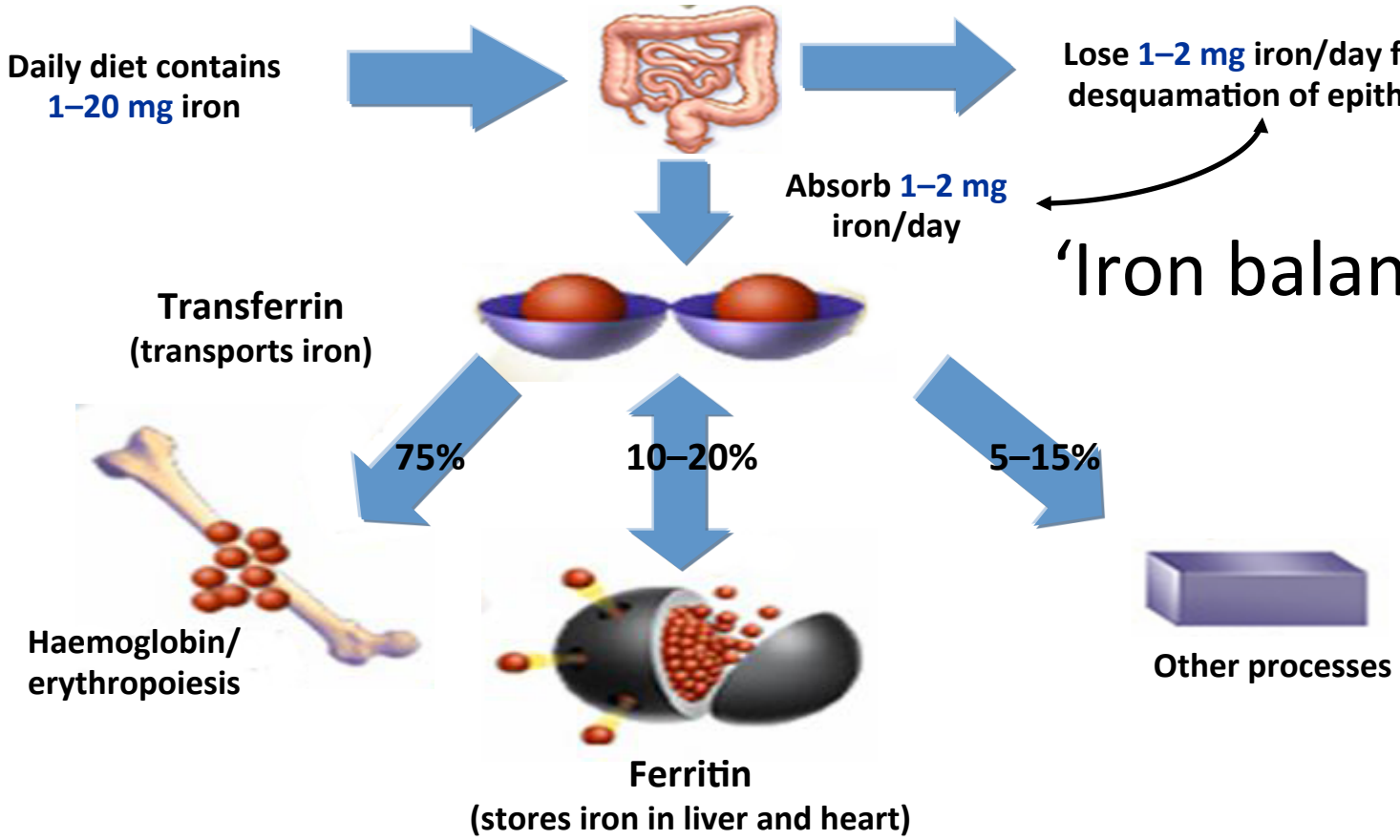
DISTRIBUTION AND STORAGE OF BODY IRON

Stimulation of intestinal iron uptake by ineffective erythropoiesis in MDS

High GDF15 - Down-regulation of hepcidin

Out

In body



The human body has many mechanisms to absorb, transfer, and store iron, *but none to excrete it*

IRON HOMEOSTASIS

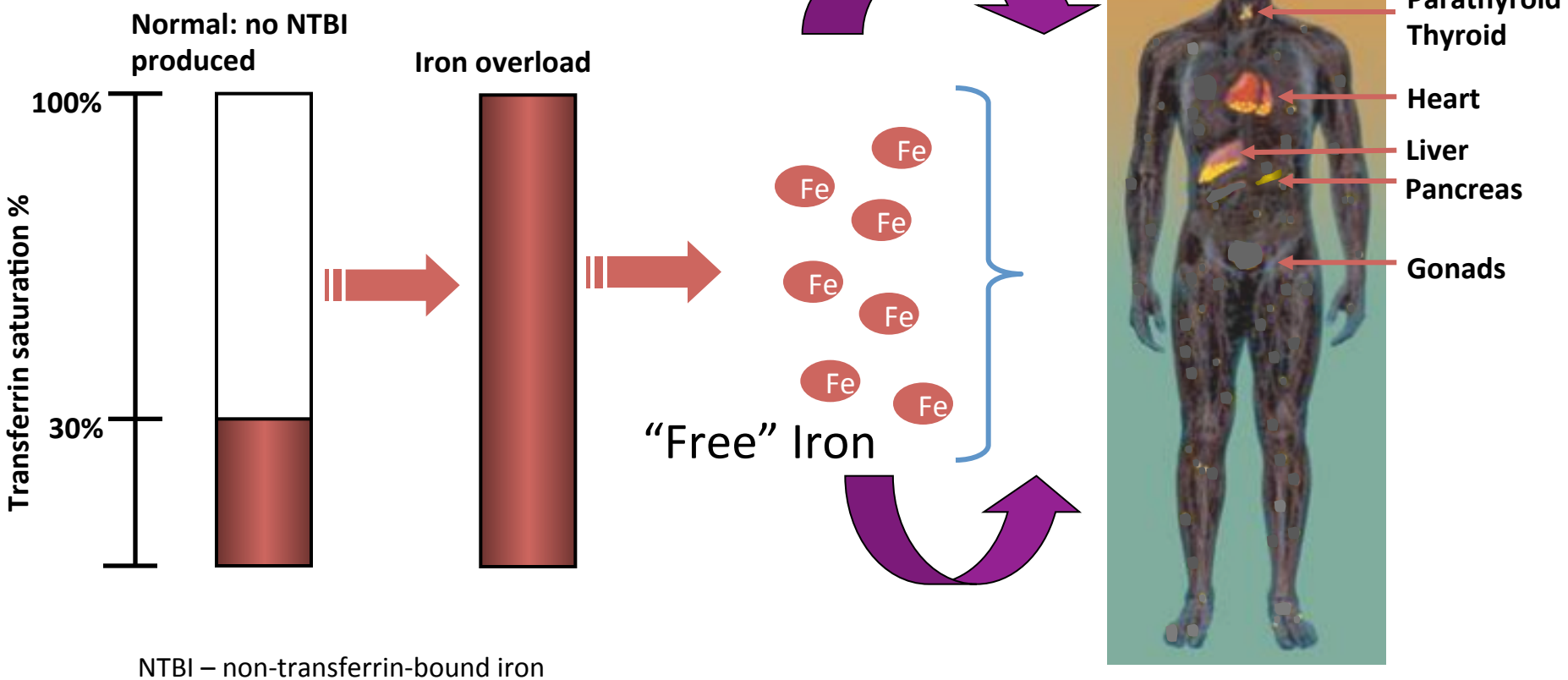
- Normal daily iron flux is 1-2mg
- Normal body iron load is 2.5-3g
- MDS pts hyperabsorb iron from gut
- Each unit of PRBC contains 200-250mg of iron
- Tissue damage occurs when body iron is 7-15g
- This corresponds to transfusion of 20 units of RBC

Free Iron:
The Essence of Iron Overload

Saturation of transferrin due to
- **Frequent blood transfusions, and**
- **Ineffective erythropoiesis leading to increased iron absorption**

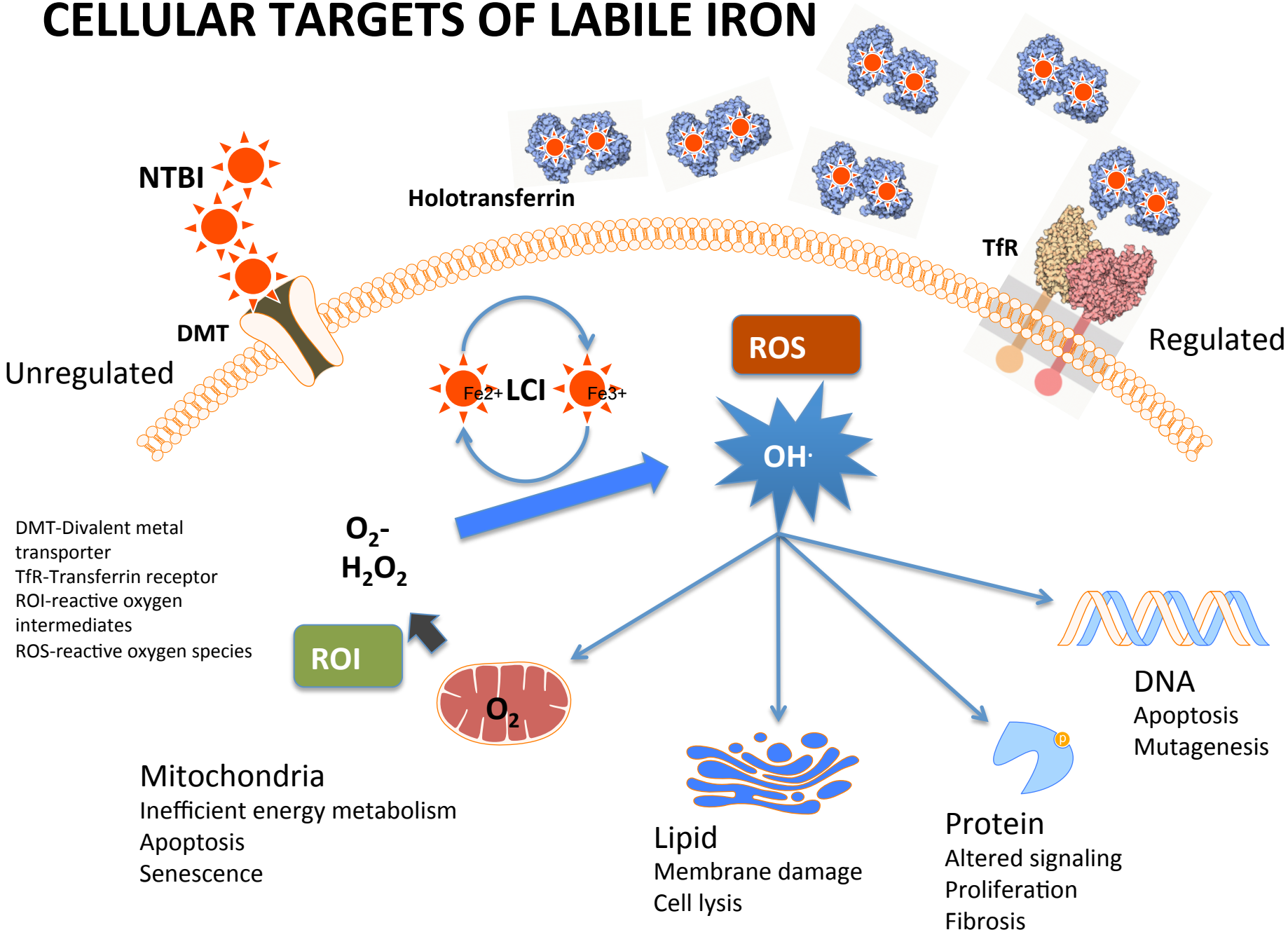
Subsequent formation of NTBI in plasma

Uncontrolled iron loading of organs

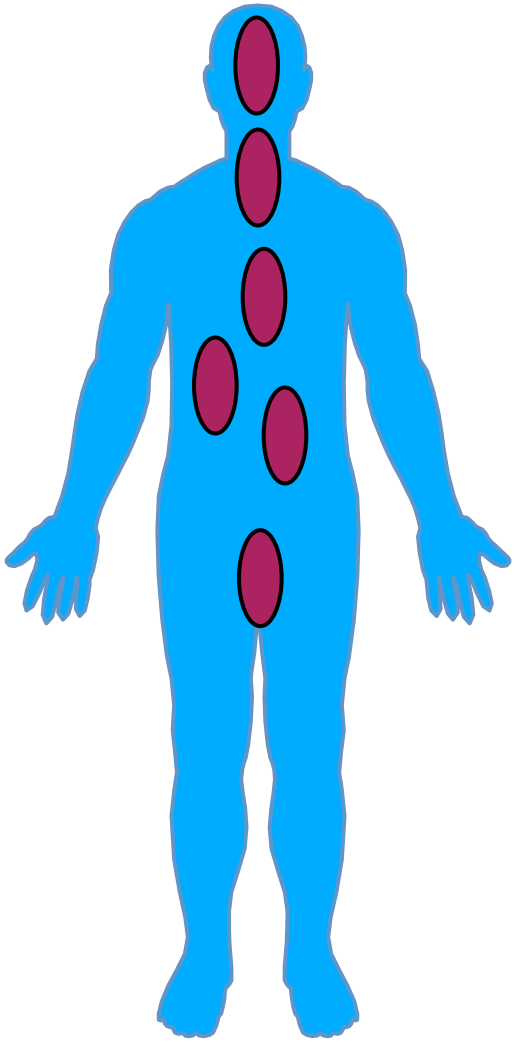


NTBI – non-transferrin-bound iron

CELLULAR TARGETS OF LABILE IRON

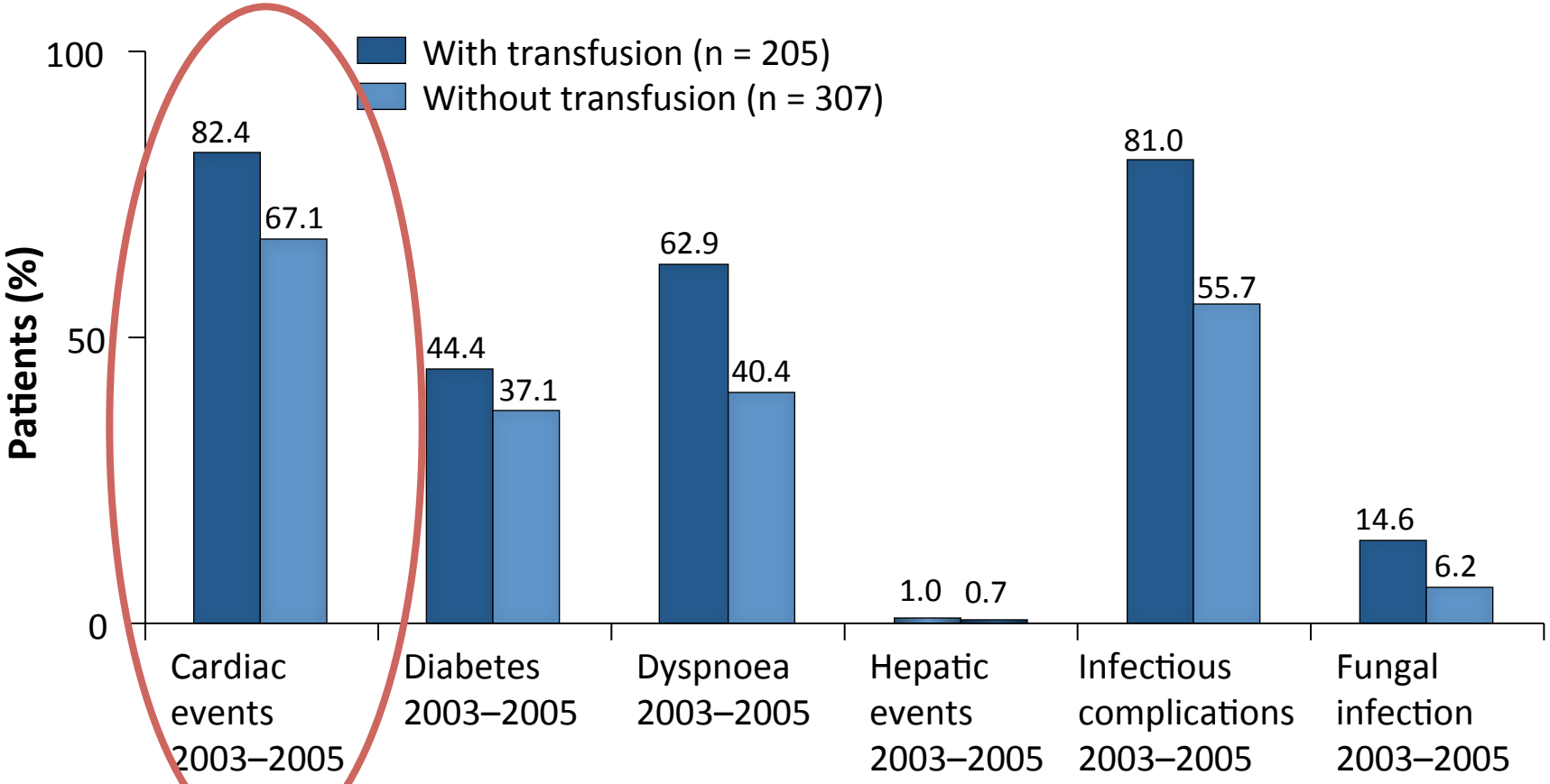


CLINICAL SEQUELAE OF IRON OVERLOAD



Pituitary	→	impaired growth
Heart	→	cardiomyopathy, cardiac failure, cardiac arrythmias
Liver	→	hepatic cirrhosis
Pancreas	→	diabetes mellitus
Gonads	→	hypogonadism, infertility
Bone marrow hematopoietic cells	→	cytopenias
Other	→	arthropathy, skin pigmentation, ?mutagenesis

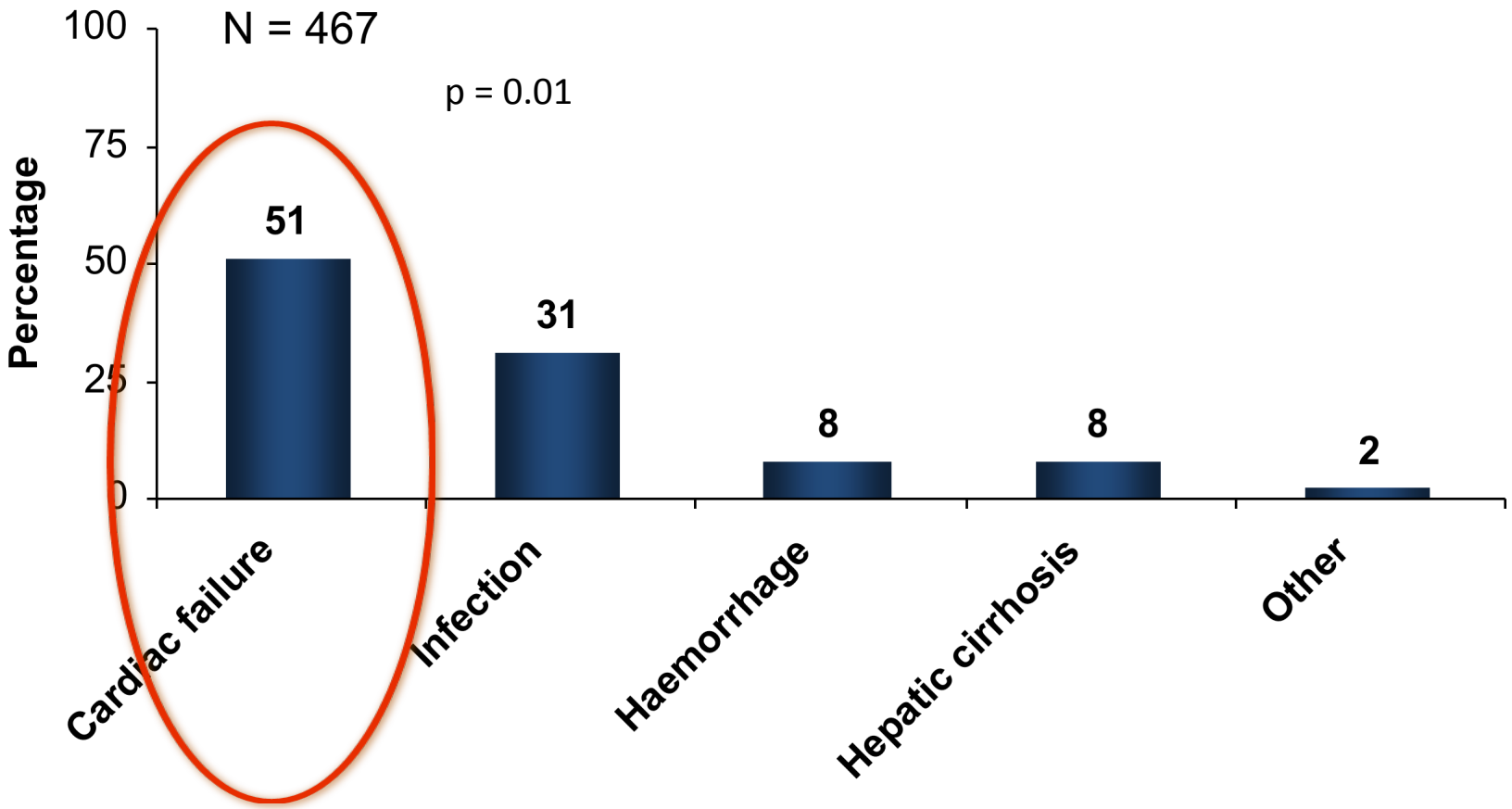
Prevalence of comorbidities in transfusion-dependent MDS



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

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

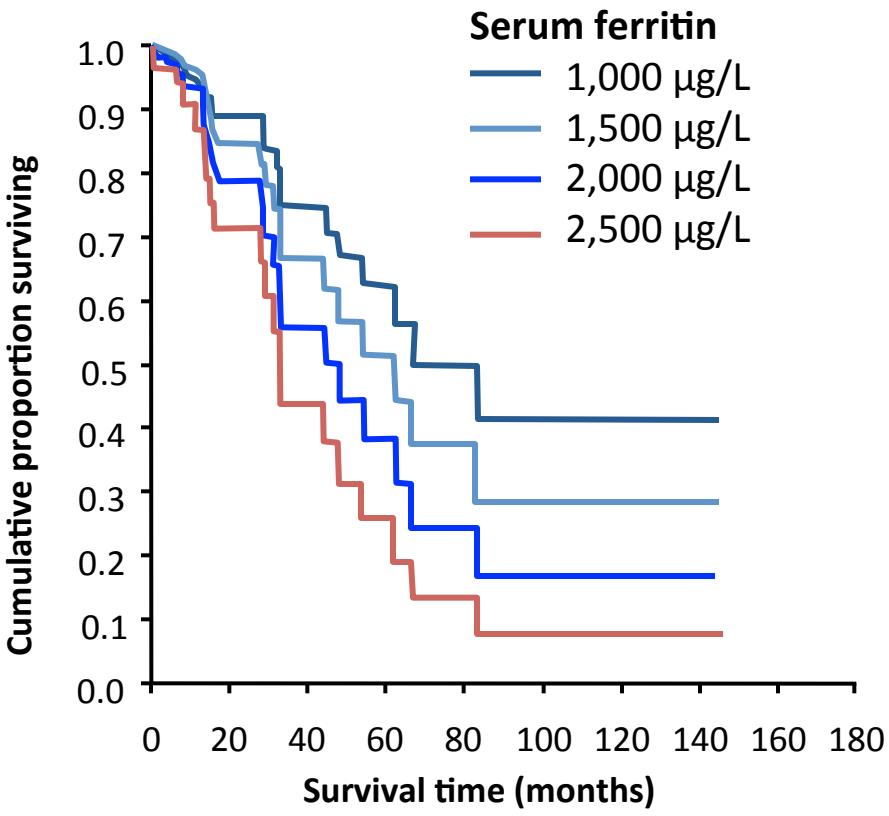
Probability of non-leukaemic death in transfusion dependent MDS patients



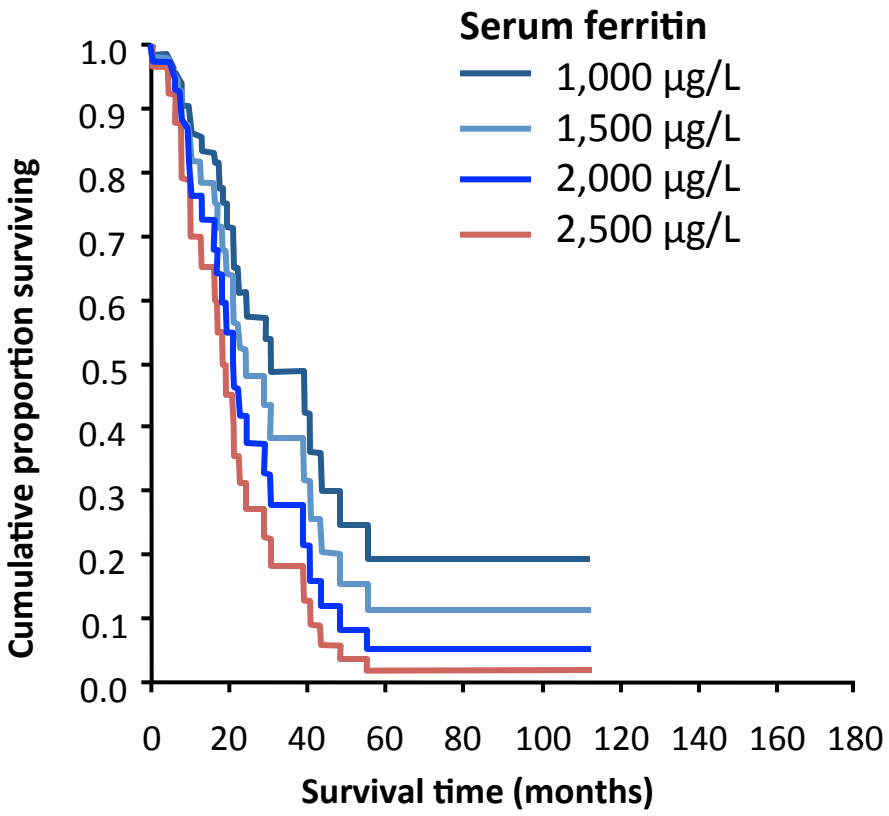
Malcovati L, et al. J Clin Oncol. 2005;23:7594-603

Overall survival of transfusion-dependent MDS patients by serum ferritin level

RA/RARS/5q−
(HR = 1.42; p < 0.001)



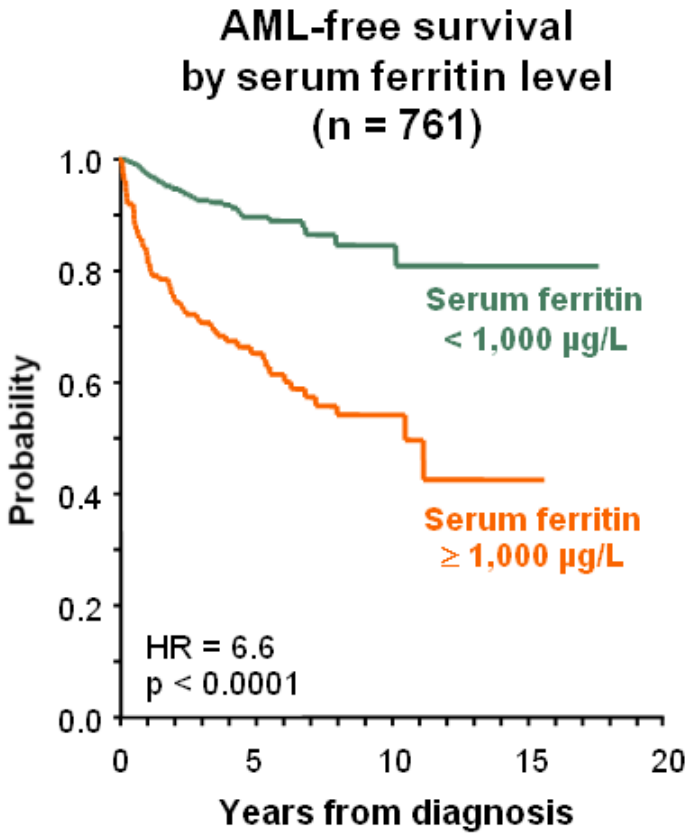
RCMD/RCMD-RS
(HR = 1.33; p = 0.07)



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.

Serum Ferritin & AML in MDS



Sanz G, et al. Blood. 2008;112:[abstract 640].

- Sanz (2008): better LFS in MDS patients with SF<1000

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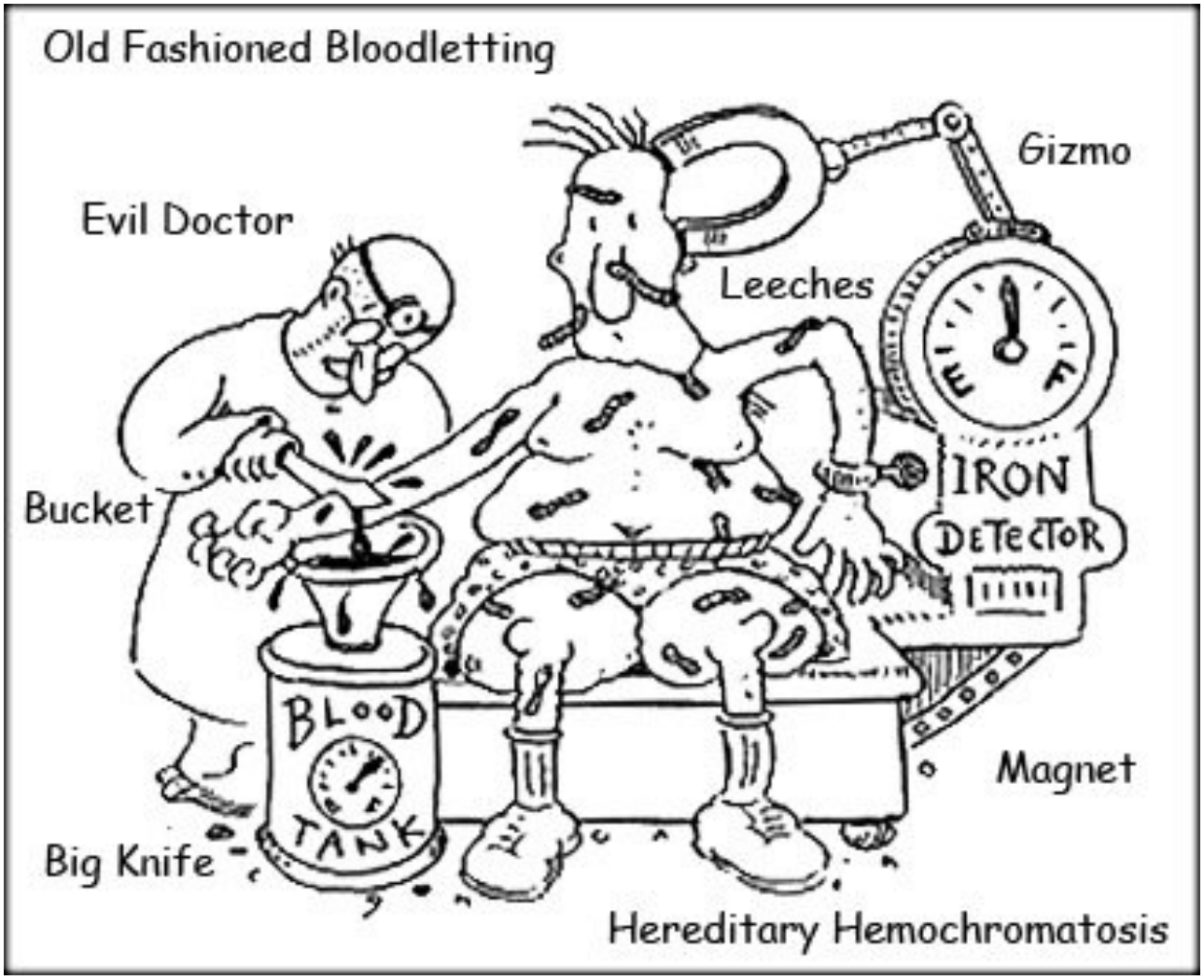
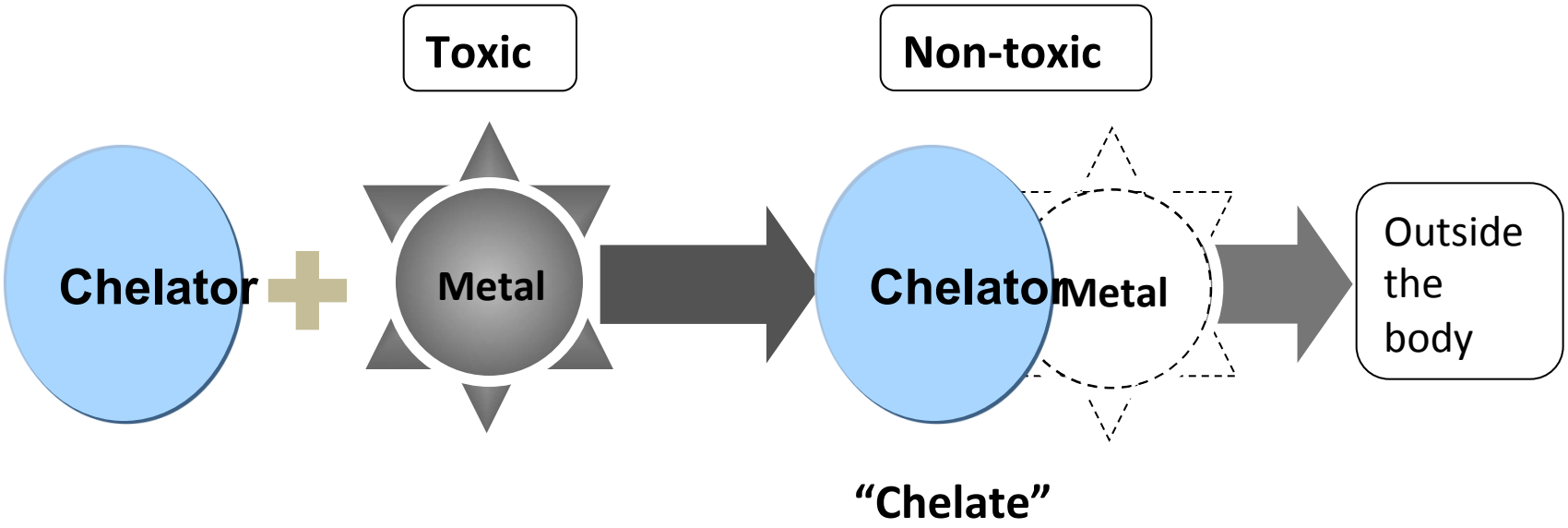
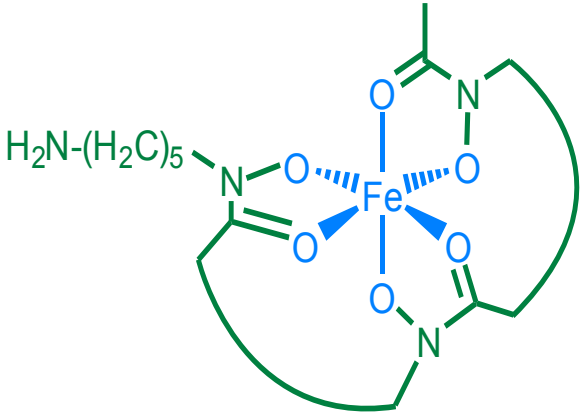

Old Fashioned Bloodletting
Gizmo
Evil Doctor
Leeches
IRON
DETECTOR
Bucket
BLOOD
TANK
Magnet
Big Knife
Hereditary Hemochromatosis

IRON CHELATION THERAPY



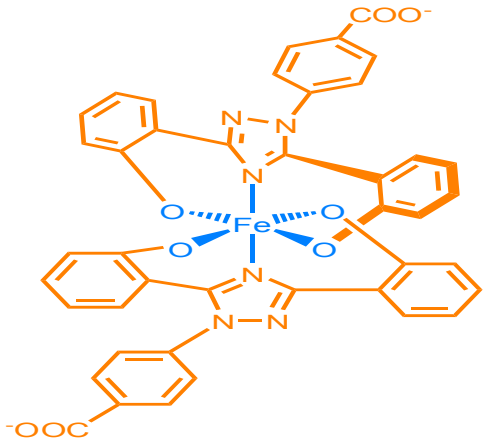
IRON CHELATORS

Deferoxamine **Hexadentate**
(1:1); high MW



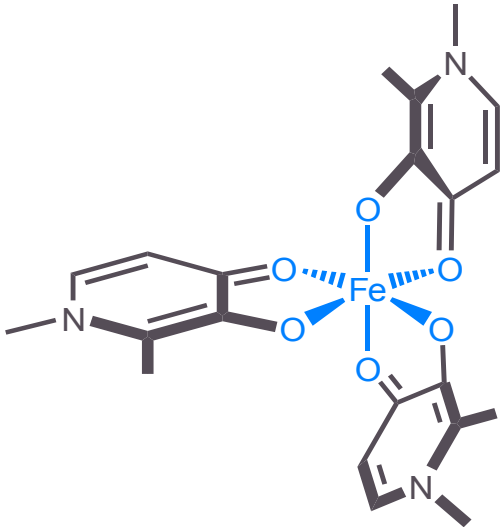
Continuous sq infusion
≥12h/d ≥5d/wk

Deferasirox
Tridentate (2:1); low MW



Oral

Deferiprone **Bidentate**
(3:1); low MW



Oral
NOT available in NA

IRON CHELATORS

- DEFEROXAMINE (DFO,Desferal):
  - Each molecule binds 1 Fe atom
  - Bound iron is excreted in the urine and bile
  - Pts wear pumps which infuse DFO subcutaneously or IV 8-12 hours daily, occasionally 24hrs
  - Risk of visual and auditory toxicity, diarrhea, nausea, vomiting, abdominal pain

IRON CHELATORS

- DEFERASIROX (Exjade):
  - Oral iron chelator; 2 molecules per Fe atom
  - Ongoing studies comparing to DFO
  - Dose 20mg/kg – 40mg/kg per day
  - Tablets dissolved in apple or orange juice or water
  - Dosing based on treatment goals and ongoing rate of transfusion
  - Adjust dose every 3 months based on serum ferritin levels (surrogate for LIC, iron stores)

EPIC STUDY

Evaluation of **P**atient's **I**ron **C**helation with deferasirox

- Evaluates iron chelation efficacy and safety in transfusion dependent pts.
- 341 MDS patients
- Serum ferritin >1000ng/ml or <1000 with >20 transfusions **and** MRI confirming LIC
- Followed for 1 year
- Deferasirox dose adjusted according to serial ferritin levels

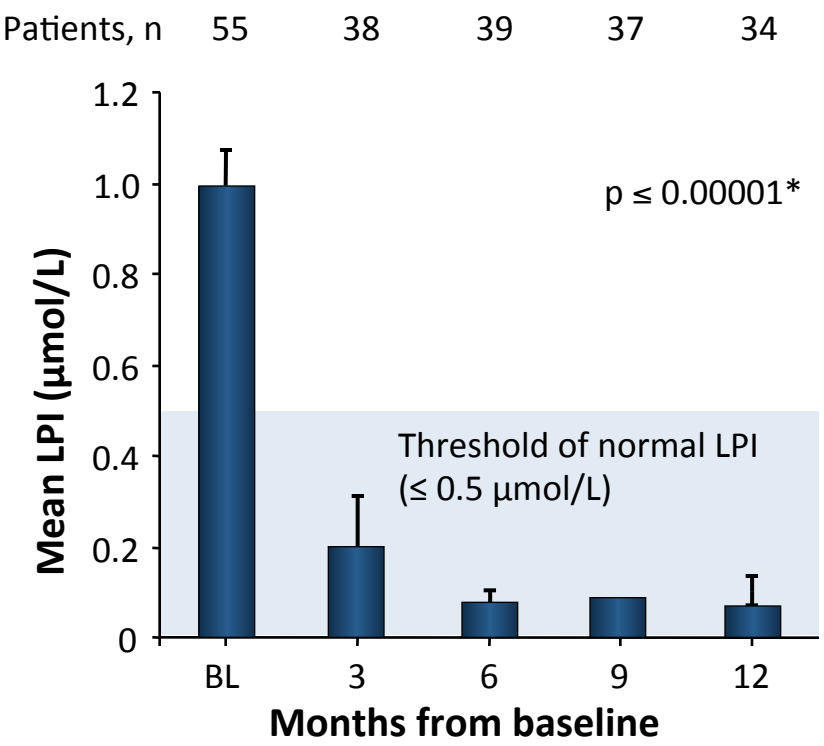
EPIC STUDY: RESULTS

- Significant decreases in serum ferritin
- Ferritin decrease correlated with ↓ALT
- Sustained ↓ LPI (labile plasma iron)

- 48% discontinuation rate
- 25% had >33% rise in serum creatinine
- Creatinine resolved with lower dosing/holding

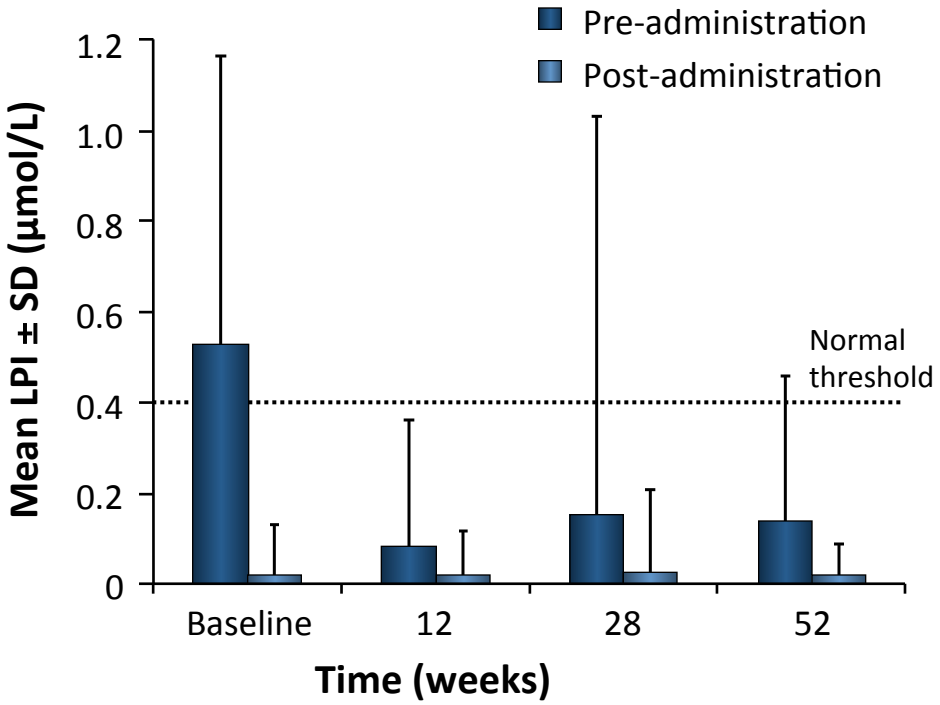
Effect of deferasirox on LPI in MDS

US03 study[1]



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

EPIC study – MDS cohort[2]



Deferasirox normalizes LPI in patients with MDS

*Comparison of baseline LPI vs each treatment time point

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

EPIC STUDY: DEFERASIROX SIDE EFFECTS

Adverse event*	Number (%)
Diarrhea	111 (32.6)
Nausea	45 (13.2)
Vomiting	26 (7.6)
Abdominal pain	26 (7.6)
Upper abdominal pain	25 (7.3)
Rash	23 (6.7)
Constipation	21 (6.2)
Total number	341

*Drug-related as assessed by the investigator.

Gattermann N, et al. Leuk Res. 2010;34:1143-50.

Hematologic responses in MDS patients treated with deferasirox: **EPIC**

Aim: to evaluate hematologic responses in a large cohort of transfusion-dependent patients with MDS following 1 year of deferasirox treatment

341 MDS patients with iron overload enrolled in 1-year EPIC study
Deferasirox initiated at 20 mg/kg/day; adjusted up to 40 mg/kg/day

Pre-treatment hemoglobin levels < 11 g/dL or red blood cell transfusion requirements
> 4 units/8 weeks and not receiving erythropoietin

Pre-treatment platelet counts of < 100 x 10^9/L or platelet-transfusion dependence

Pre-treatment absolute neutrophil counts of < 1.0 x 10^9/L and not receiving granulocyte-colony stimulating factor

Erythroid response analysis (n=279)

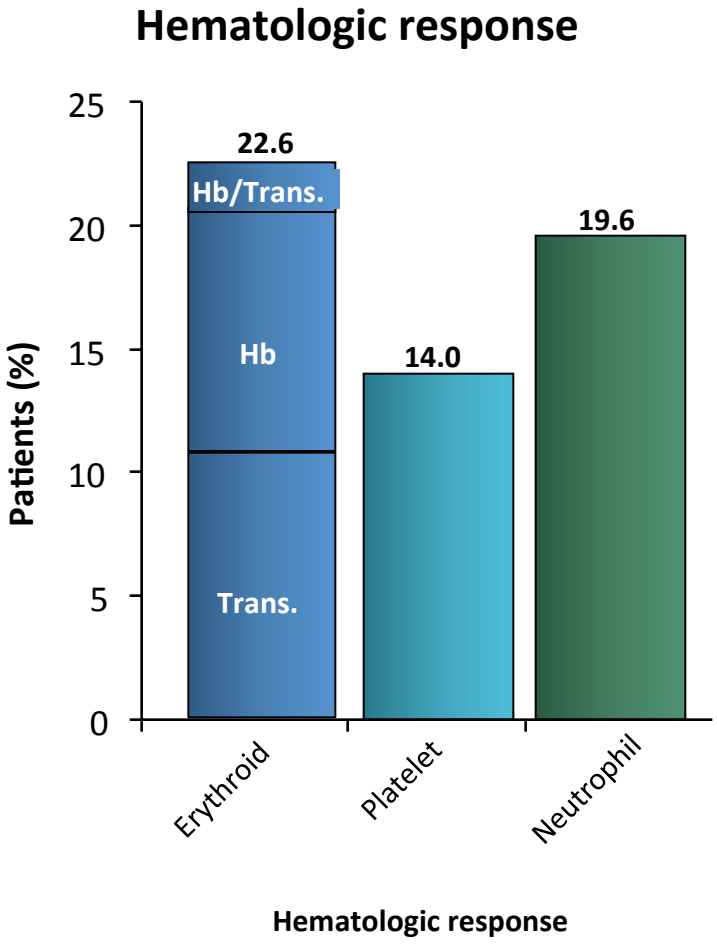
Platelet response analysis (n=121)

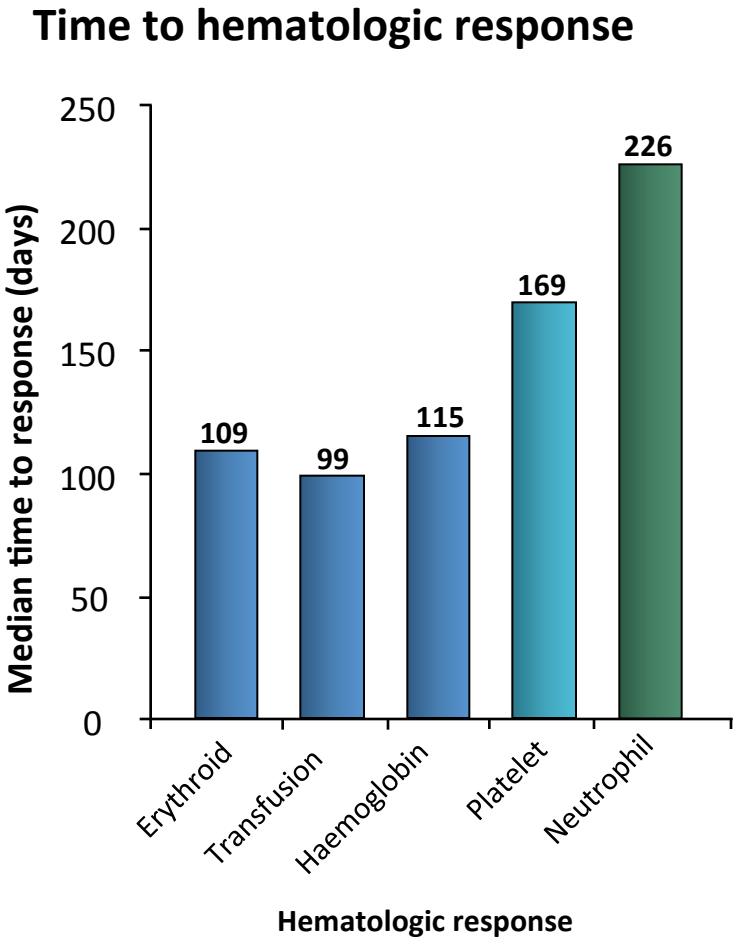
Neutrophil response analysis (n=56)

All responses to last ≥8 weeks

Gattermann N *et al*. Presented at ASH 2010 [*Blood* 2010;116(21):abst 2912]

Results: hematologic responses

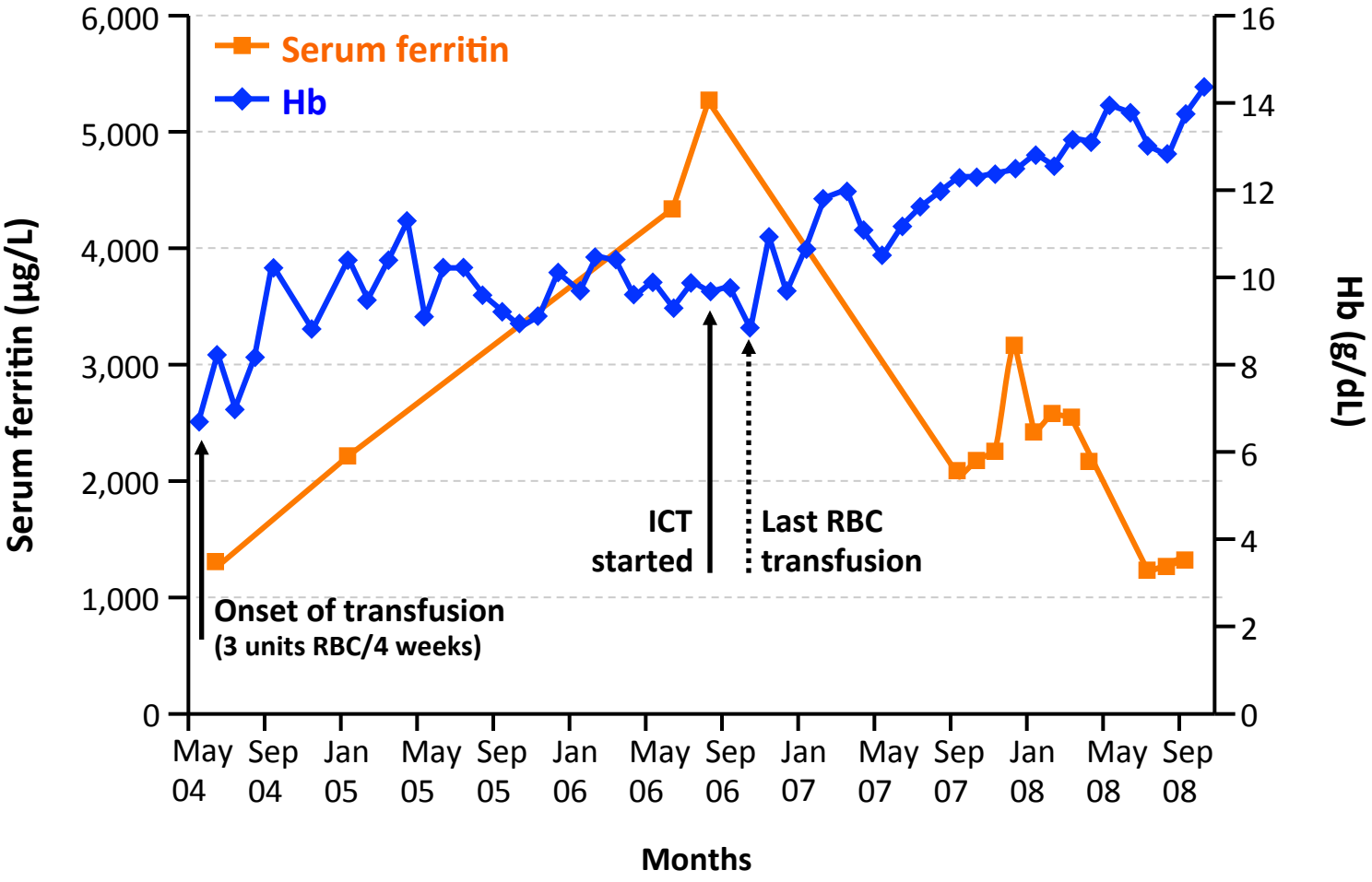




Trans. = Transfusion

Gattermann N *et al*. Presented at ASH 2010 [*Blood* 2010;116(21):abst 2912]

Bone marrow complications in MDS: improvement in cytopenias with chelation



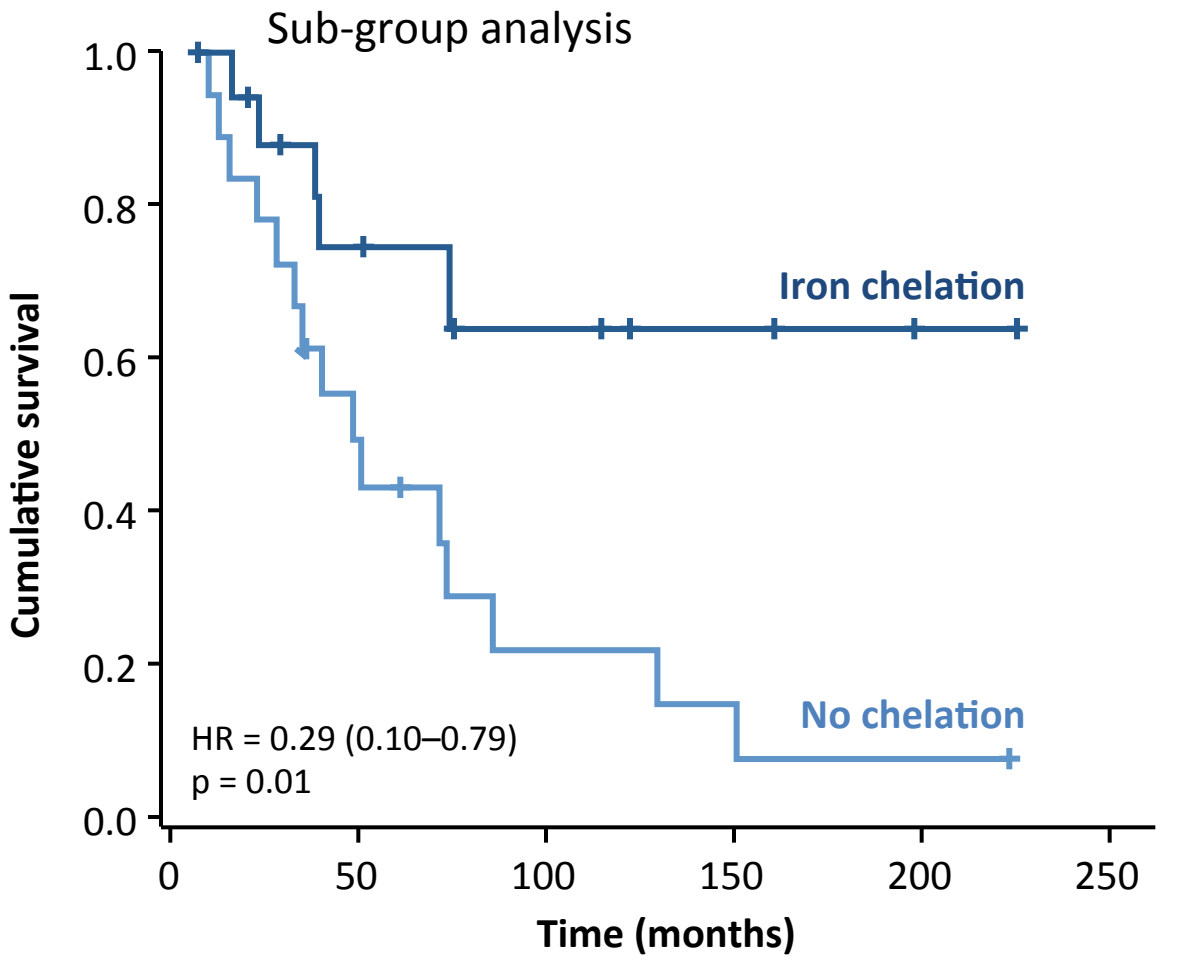
ICT = iron chelation therapy.

Badawi MA, et al. Adv Hematol. 2010;2010:164045.

EPIC STUDY: IMPACT

- Deferasirox reduces iron burden
- Deferasirox may improve blood counts
- Not designed to prove this leads to decreased cardiac, hepatic, endocrine complications
- Not designed to show improved overall survival

Vancouver: effect of iron chelation therapy on survival in lower-risk MDS patients



Leitch HA, et al. Clin Leuk. 2008;2:205-11.

ICT at Moffitt

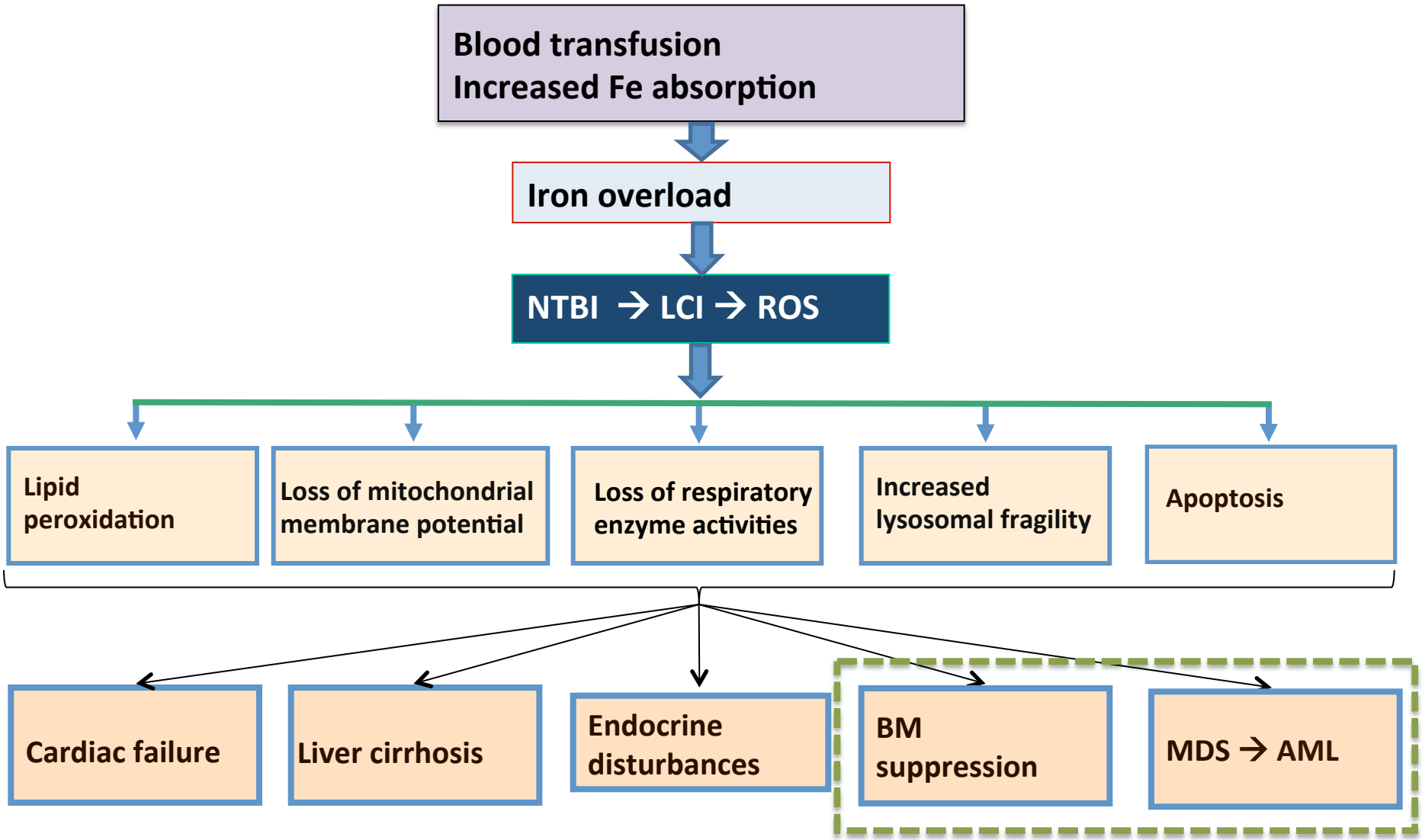
- 97 lower risk MDS patients with ferritin >1000 were identified. Retrospective chart review.
- 35/45 pts. received deferasirox.

	OS (mo)	p	HR	95%CI	p	AML (%)	P
ICT (n=45)	59	**0.01**	0.52	0.31-0.87	**0.01**	15.6	NS
No ICT (n=52)	33.7					21.2	

- Conclusion: iron chelation therapy in lower IPSS risk MDS patients with ferritin >1000 was associated with improved overall survival. Trend to lower AML transformation.

Komrokji et al Blood 2011 118 abstract 1776

SUMMARY: IRON TOXICITY



Summary: Clinical effects of iron chelation therapy in *lower-risk* MDS

- Prospective data from large clinical trials show that chelation
  - reduces serum ferritin levels
  - reduces labile plasma iron
  - reduces liver iron concentration
  - improves liver abnormalities
  - improves cytopenias in a substantial minority of patients
- Within the limitations of non-controlled analyses, the data in lower-risk MDS suggest that chelation may be associated with improved survival, and improved leukemia free survival
- Whether the apparent survival impact was a result of reducing iron or from confounding factors or bias should be settled by prospective, controlled trials

FERROSCEPTICISM
Relevance of iron overload on MDS

It takes months to years to offload significant amounts of organ & total body iron so how can chelation result in clinical benefits within months?[1]

Given advanced age of MDS patients, will patients survive long enough to develop iron overload tissue damage or benefit from chelation therapy?

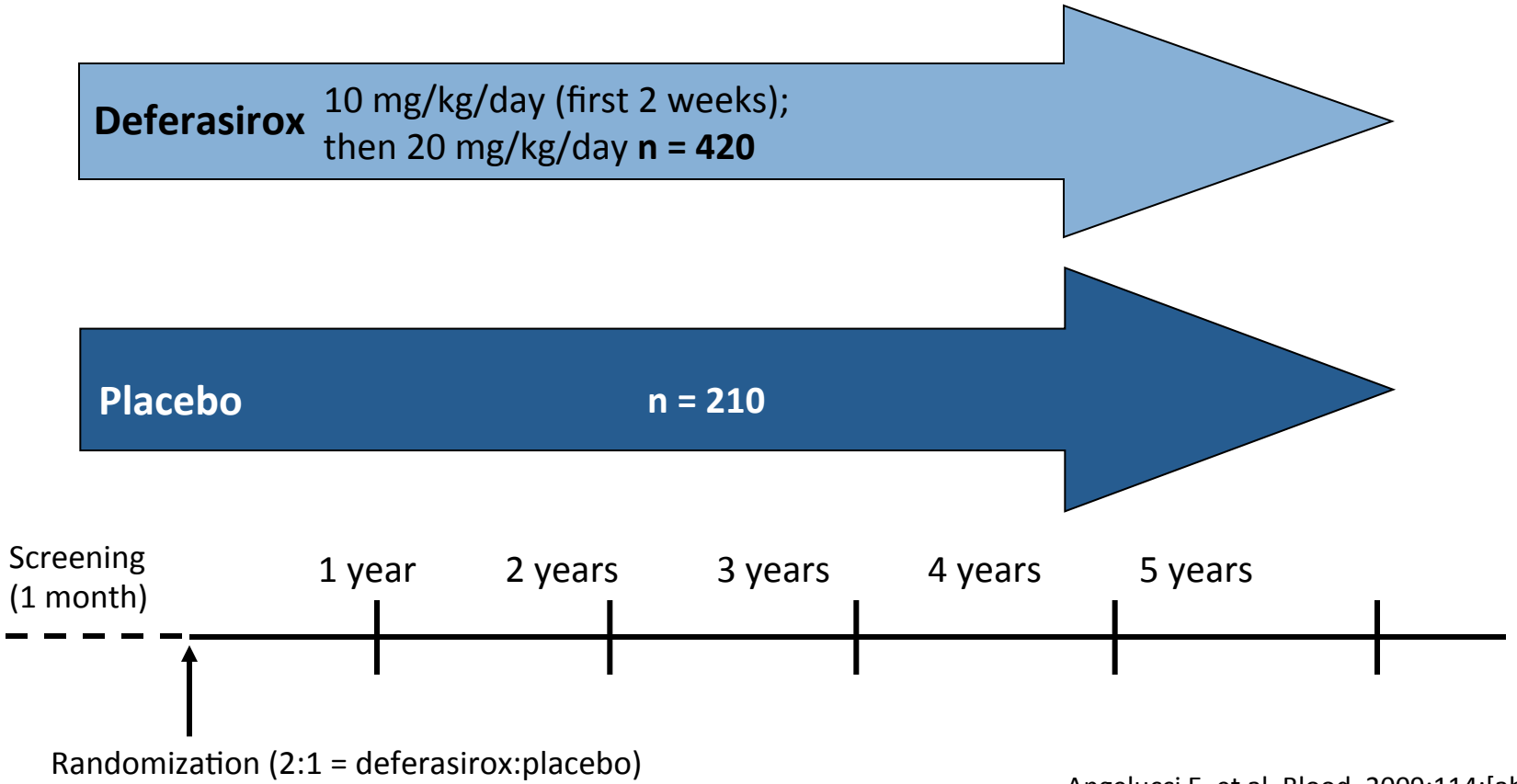
"Neither Serum Ferritin Nor Number of Red Blood Cell Transfusions Affect Overall Survival in Refractory Anemia with Ringed Sideroblasts"[2]

Can iron chelation modify clinical outcome?
Lack of prospective, randomized data

[1]Steensma DP. Curr Hematol Malig Rep 2011;6:136-44
[2]Chee C.E. Am J Hematol 2008;83:611-3

TELESTO study of DFX in MDS

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



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

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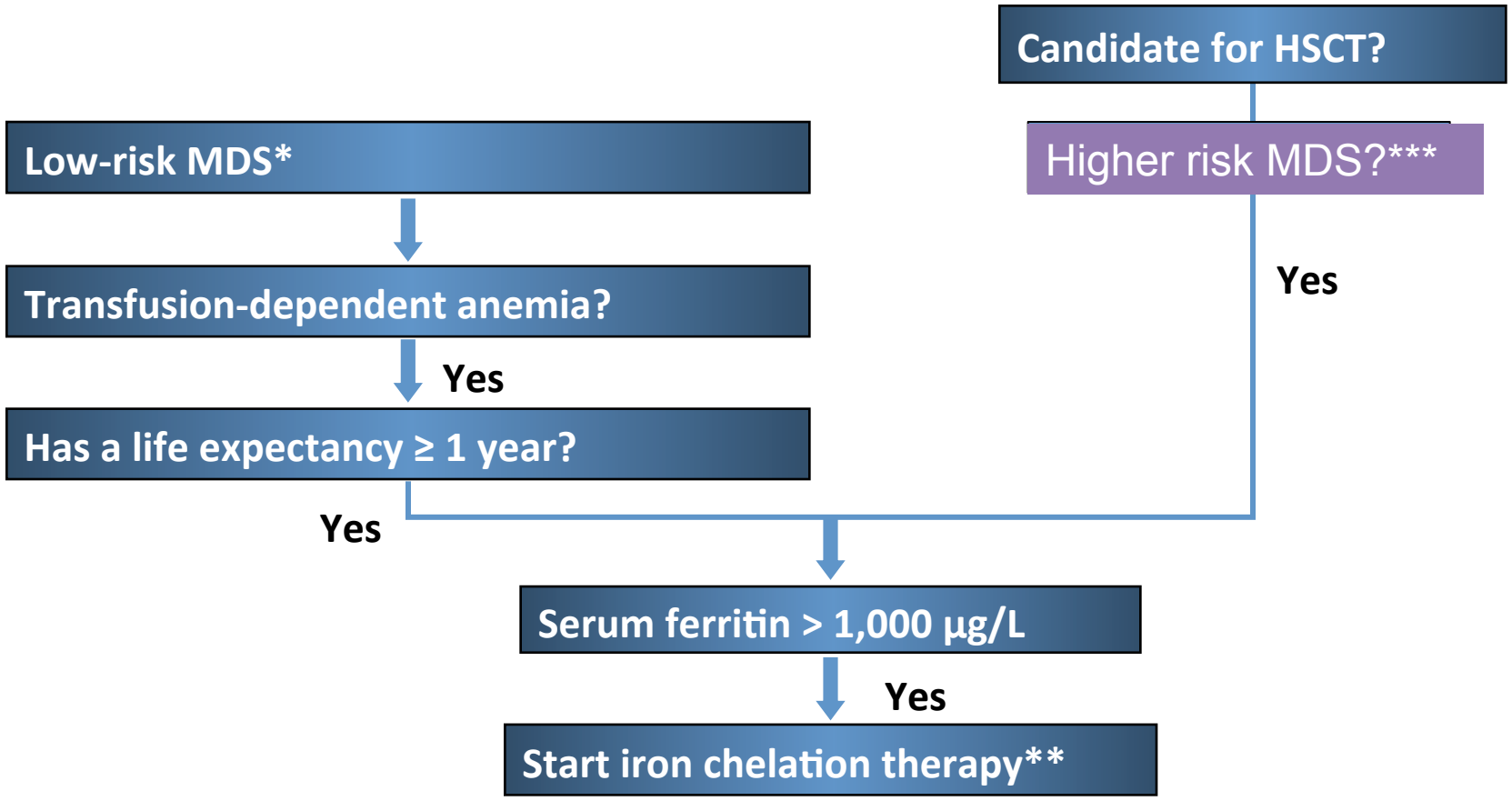
GUIDELINES FOR CHELATION IN MDS



*Includes IPSS Low and Int-1.
**Duration: as needed to maintain serum ferritin < 1,000 µg/L.
***Eligible for disease modifying therapy

Bennett JM, et al. Am J Hematol. 2008;83:858-61.
Gattermann N. Int J Hematol. 2008;88:24-9.
.*** Santini V, et al. Leuk Res. 2010;34:1576-88.
***Pullarkat V. Blood. 2009;114:5251-5.

GUIDELINES FOR DEFERASIROX

- Starting dose: 20mg/kg/day if <4 units/month, 30mg/kg/day if >4units
- Increase up to 40mg/kg
- Tablets dissolved in apple or orange juice or water (do not chew or swallow whole)
- Adjustments according to serum ferritin every 3 months
- Monitor serum creatinine: avoid in pts with creatinine clearance <40ml/min
- Manage volume status – diarrhea, nausea & vomiting
- Anecdotal reports suggest reduction of the frequency and severity of GI disturbances with BID dosing

Management of deferasirox GI side effects

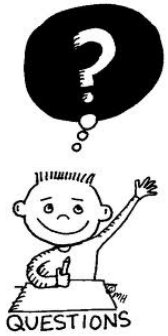
Diarrhea	Abdominal pain	Nausea and vomiting
• Hydration • Loperamide • Lactaid if indicated • Dose at night • Use water to disperse tablets • Reduce dose or interrupt treatment	• Switch to pre-prandial evening dosing • For upper abdominal pain, use anti-acids • Consider spasmolytic drugs • Reduce dose or interrupt treatment	• Use anti-emetics • Switch to pre-prandial dosing • Reduce dose or interrupt treatment

Nolte et al. Leuk Res.2011;35:1131-1135

WHAT SHOULD A PATIENT DO?

• Stay informed

Ask questions



- Connect with support services: Aplastic Anemia and Myelodysplasia of Canada, EPASS (Exjade Patient Assistance and Support Services)
- Transfusion dependent patients: inquire about serum ferritin levels
- Inquire about chelation
- While on chelation ask about serum ferritin, creatinine (kidneys), liver enzymes
- Follow your CBC
- Report side effects: guidelines exist for management
- Consider joining the **Canadian MDS Patient Registry**

THE NATIONAL MDS REGISTRY IS COLLECTING HEALTH INFORMATION FROM CANADIAN MDS PATIENTS TO BETTER UNDERSTAND THE DISEASE AND THOSE AFFECTED BY IT.

IF YOU ARE INTERESTED PLEASE ASK YOUR DOCTOR TO REFER YOU TO A PARTICIPATING HOSPITAL NEAR YOU.

Future directions

- Clarify the mechanism of cardiac complications in MDS with iron overload
- Clarify the extent and impact of endocrine complications with iron overload
- Which MDS subtypes benefit most from iron reduction?
- Chelation for higher risk MDS?
- Chelation at a lower ferritin threshold/iron burden?
- Reduce IOL with medications other than chelators
- Examine results of oxidative stress (8-OH-dG, MDA, depletion of GSH, NAC) & clinical endpoints

Future directions

- Clarify the mechanism of cardiac complications in MDS with iron overload
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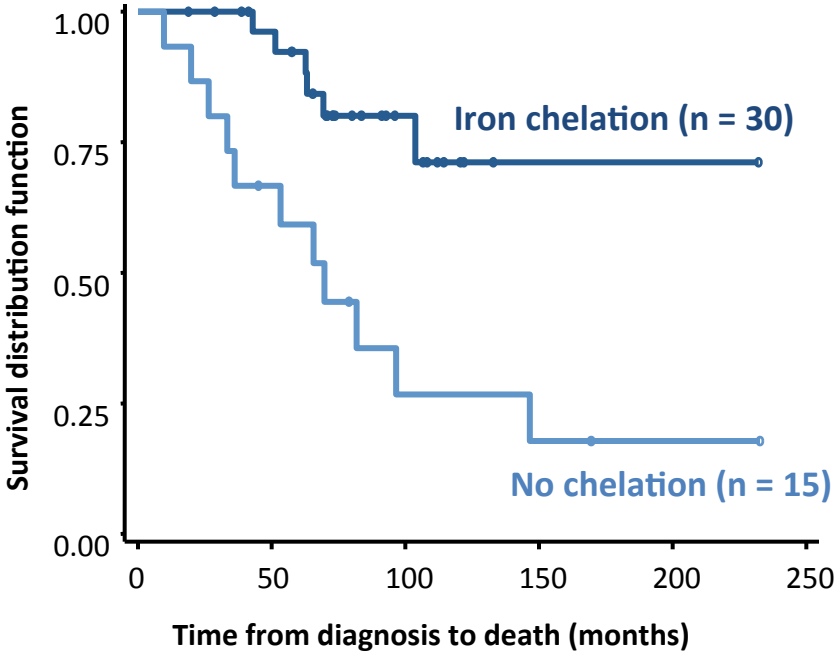
GFM: effect of iron chelation therapy on survival in lower-risk MDS patients

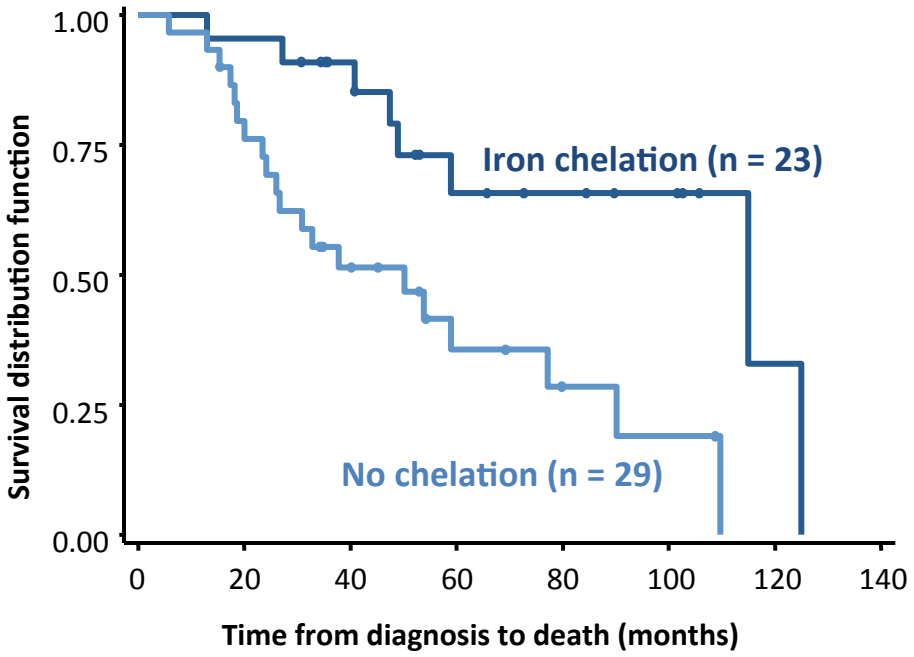
IPSS = Low

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



IPSS = Int-1

Median: 115 vs 50 months ($p < 0.003$)



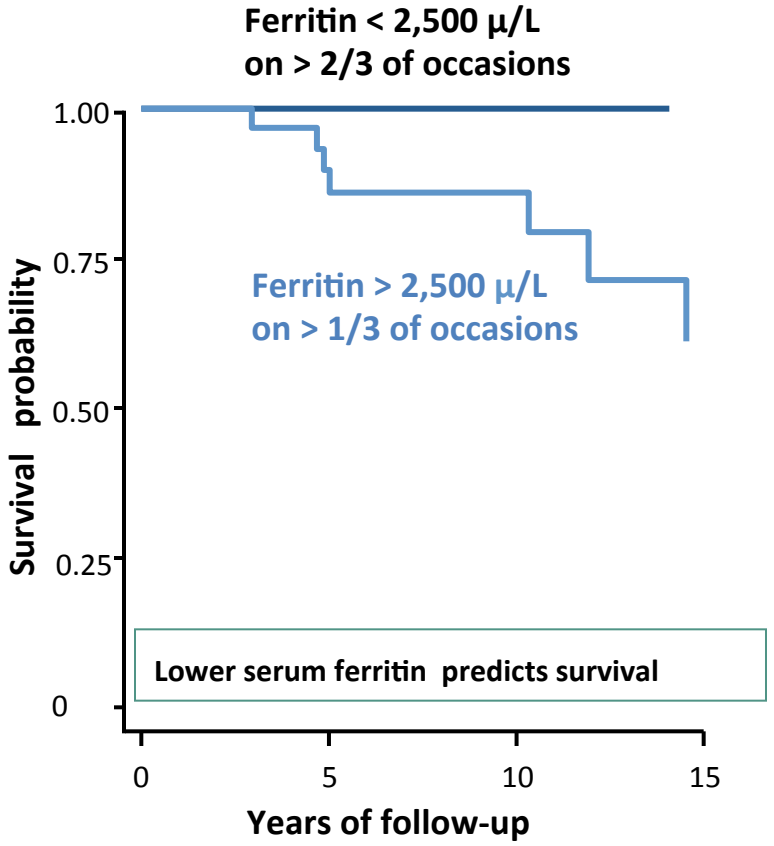
Results were the same regardless of sex and age.

GFM = Groupe Francophone des Myélodysplasies.

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

Serum ferritin – value of monitoring

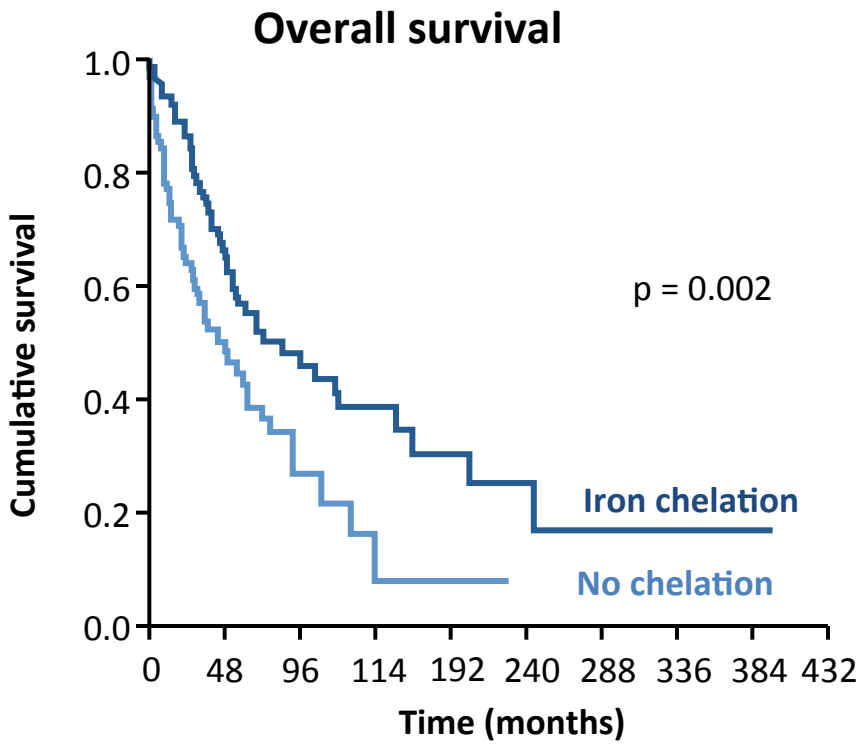
- Ferritin is a surrogate marker of LIC & iron-loading trends
- Target for iron control & good prognosis
  - long term <2,500 µg/L correlates with cardiac DFS[1–4]
- To avoid overchelation[5]



1. Gabutti V, Piga A. Acta Haematol. 1996;95:26-36.
2. Telfer PT, et al. Br J Haematol. 2000;110:971-7.
3. Davis BA, et al. Blood. 2004;104:263-9.
4. Borgna-Pignatti C, et al. Haematologica. 2004;89:1187-93.
5. Oliviera NF, Brittenham GM. Blood. 1997;89:739-61.

LIC = liver iron concentration;
UCLH = University College London Hospital.

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



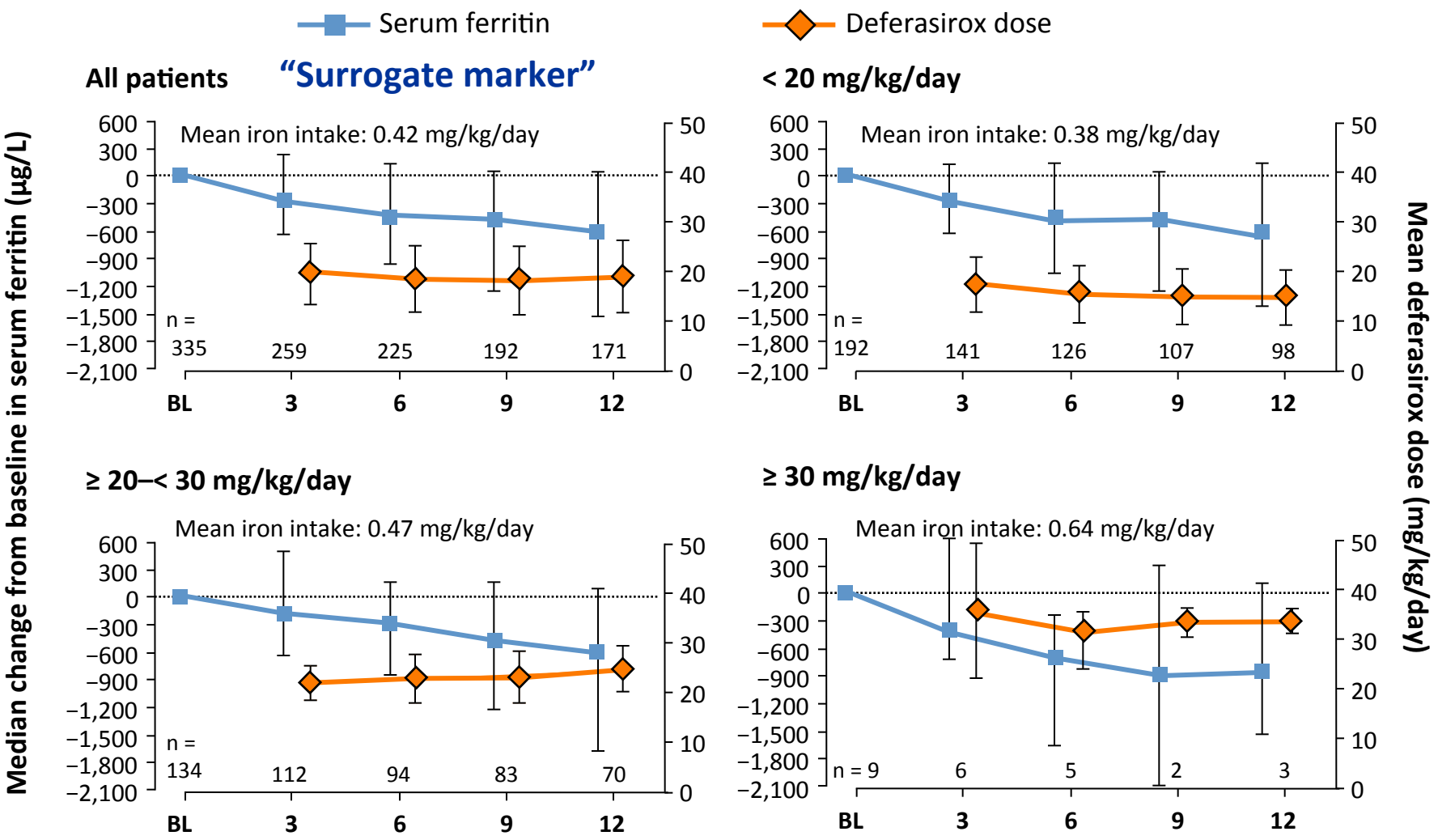
Median cumulative survival
Chelation: 75 months
No chelation: 49 months

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

Monitoring chelation!

- Clinical – as clinically indicated
  - GI symptoms, volume status
  - Rash
  - DFO – opthamology, audiology at least yearly
- Laboratory
  - Blood counts, **creatinine level**, hepatic profile - regularly
  - Measures of organ function – echocardiogram, glucose tolerance test, liver function tests – as clinically indicated

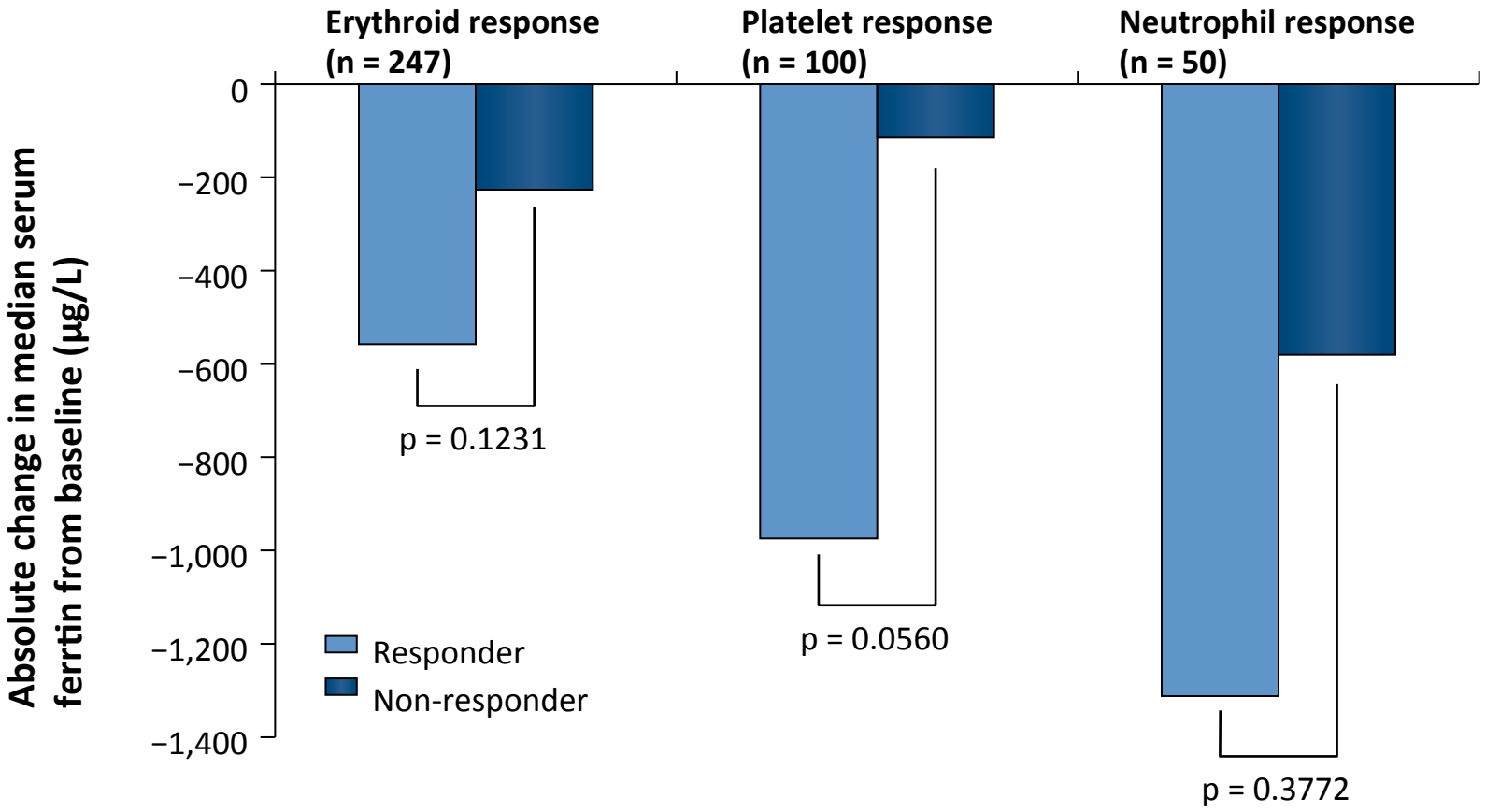
EPIC study: deferasirox dosing should be titrated to patient response and iron intake



BL = baseline.

Gattermann N, et al. Leuk Res. 2010;34:1143-50.

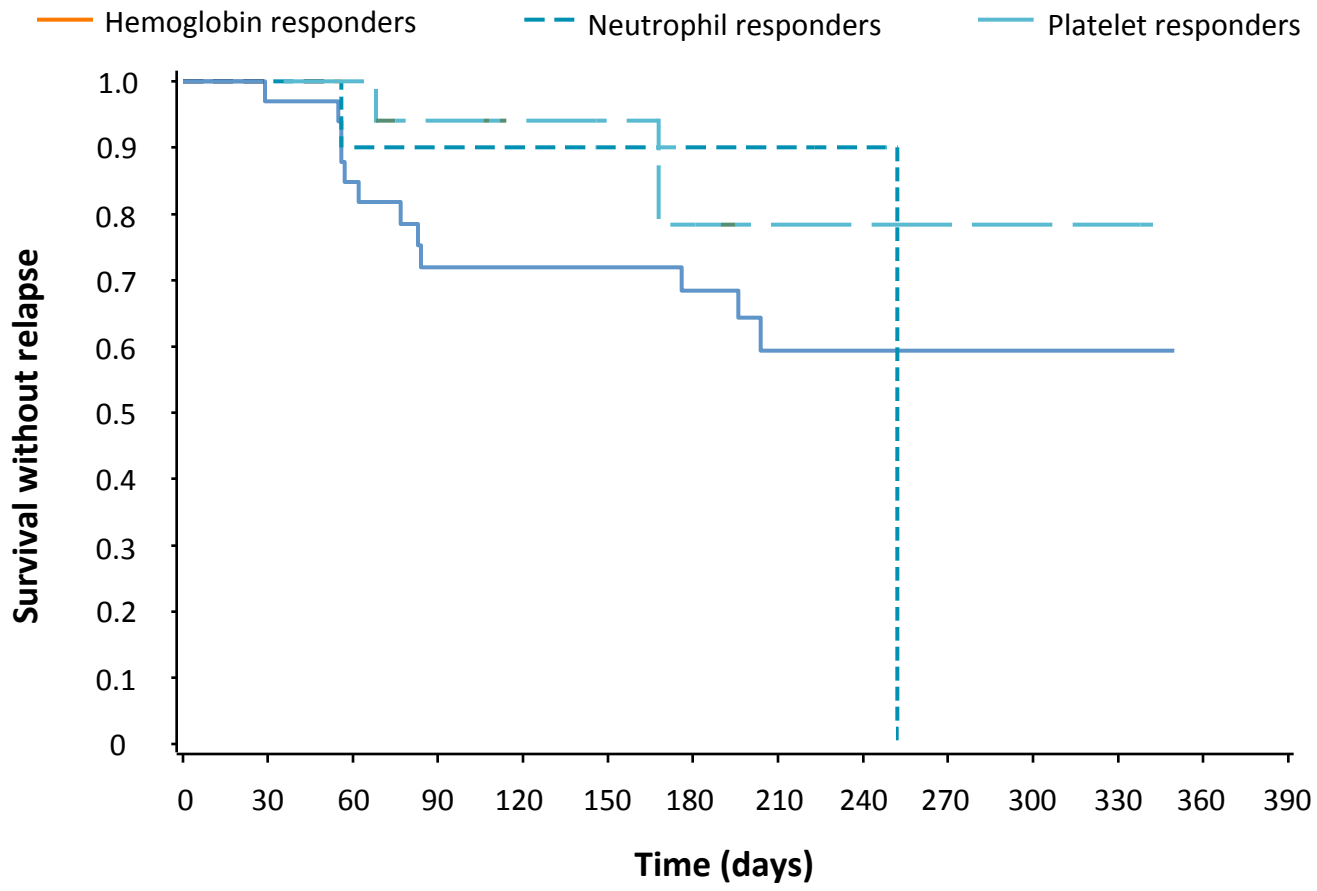
Results: change in serum ferritin



Baseline serum ferritin levels were comparable in responders and non-responders

Gattermann N, et al. Haematologica. 2012 Mar 14. [Epub ahead of print].

Results: survival without relapse



Relapse rates were highest for hemoglobin responders (36.4%), followed by neutrophil responders (18.2%), and were lowest in platelet responders (11.8%)

Gattermann N *et al*. Presented at ASH 2010 [*Blood* 2010;116(21):abst 2912]

Management of adverse events to deferasirox

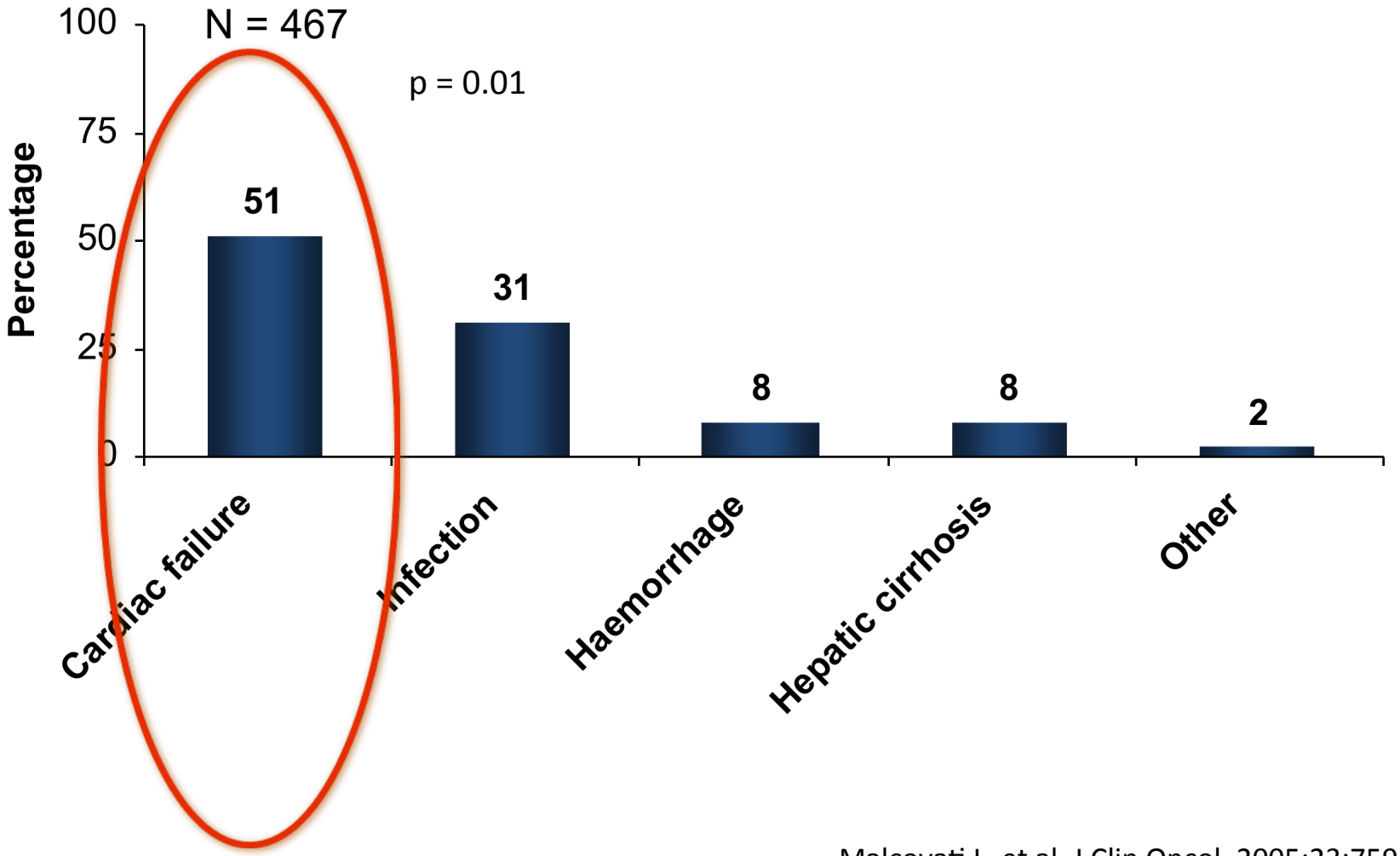
- Diarrhea, nausea & vomiting – there are published guidelines for management[1]
- All GI – if refractory to these maneuvers, may respond to dispersal with the 'shaker'

- Rash – most are mild

Successful Tolerance of Deferasirox Following Desensitization for Significant Skin Rash
Hatoon M Ezzat, R Robert Schellenberg, Heather A Leitch and Linda M Vickars

[1]Nolte F *et al. Leuk Res* 2011 [in press]

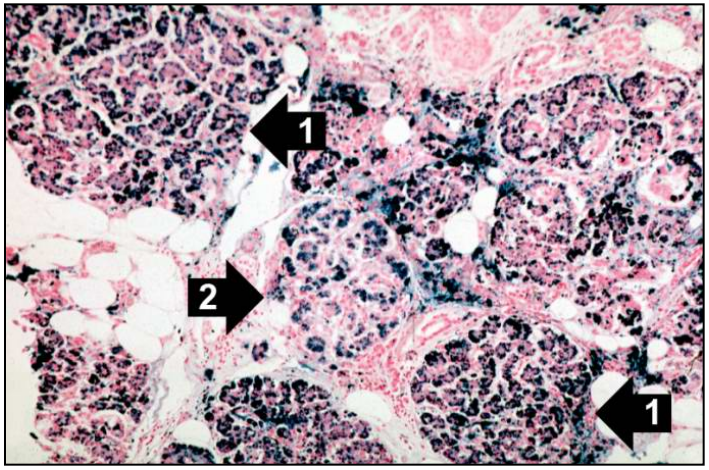
Probability of non-leukaemic death in transfusion dependent MDS patients



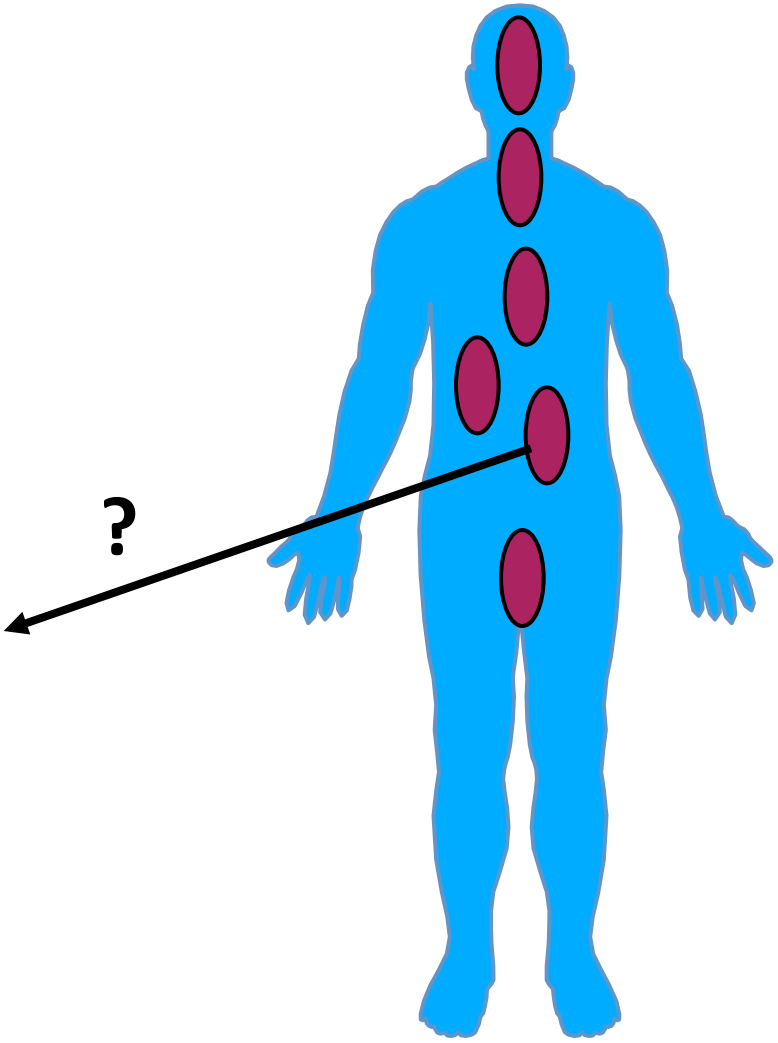
Malcovati L, et al. J Clin Oncol. 2005;23:7594-603

Endocrine complications of iron overload in MDS and effect of chelation

- Indirect data show
  - increase in diabetes and glucose intolerance in transfused patients
  - decrease in elevated blood glucose with chelation



Prussian blue stain



1. Delea TE, et al. Curr Med Res Opin. 2009;25:139-47.
2. Takatoku M, et al. Eur J Haematol. 2007;78:487-94.

Iron and Free Radicals

- Mitochodrial metabolism produces hydrogen peroxide (H_2O_2) as a byproduct

- H_2O_2 is not itself very toxic
  - Reactive oxygen intermediate (ROI)

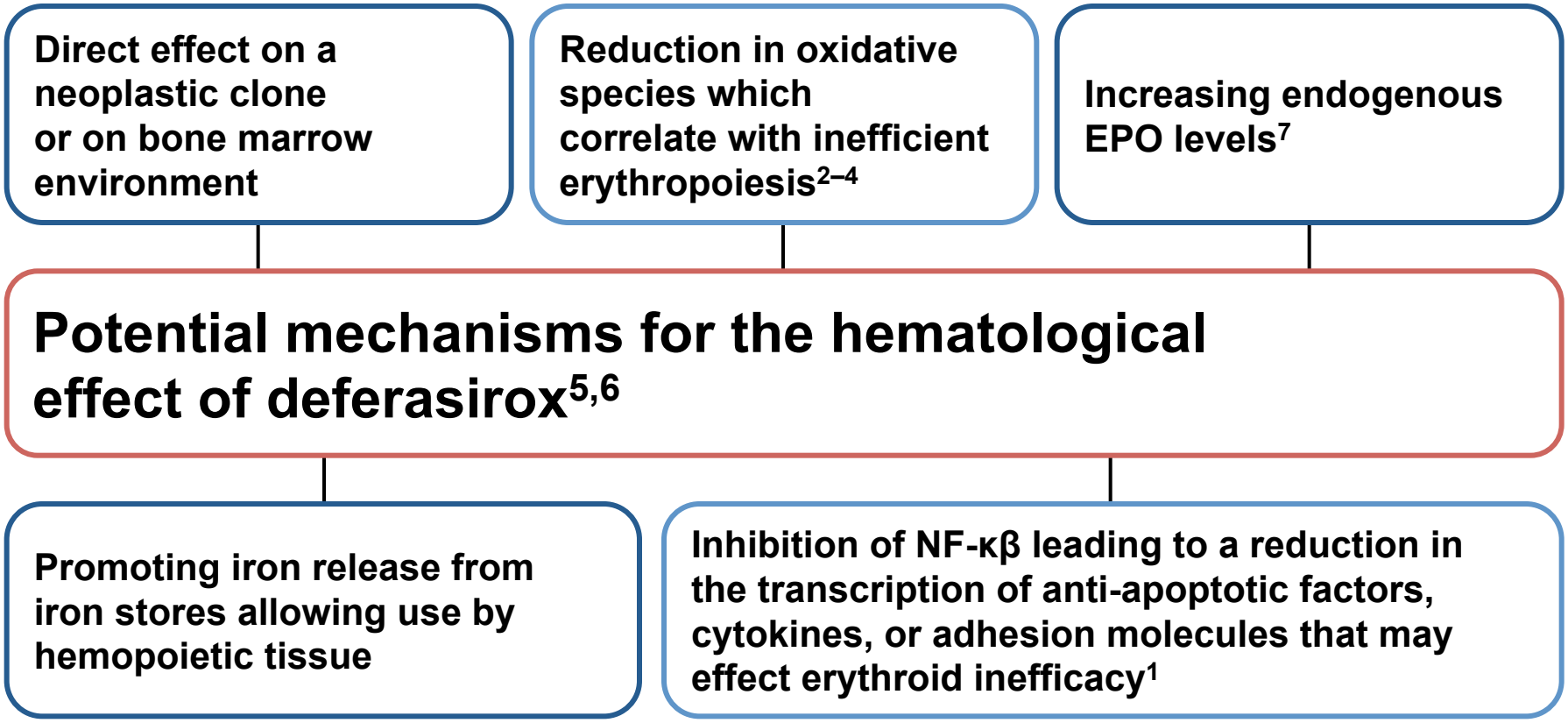
H_2O_2 Reactions

Fenton Reaction

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH\bullet + OH^-$$
$$Fe^{3+} + H_2O_2 \rightarrow Fe^{2+} + OOH\bullet + H^+$$

- Free iron reacts with H_2O_2 to form highly toxic radicals
  - Reactive oxygen species (ROS)

Potential Mechanisms for the Hematological 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.

Cardiac complications in MDS

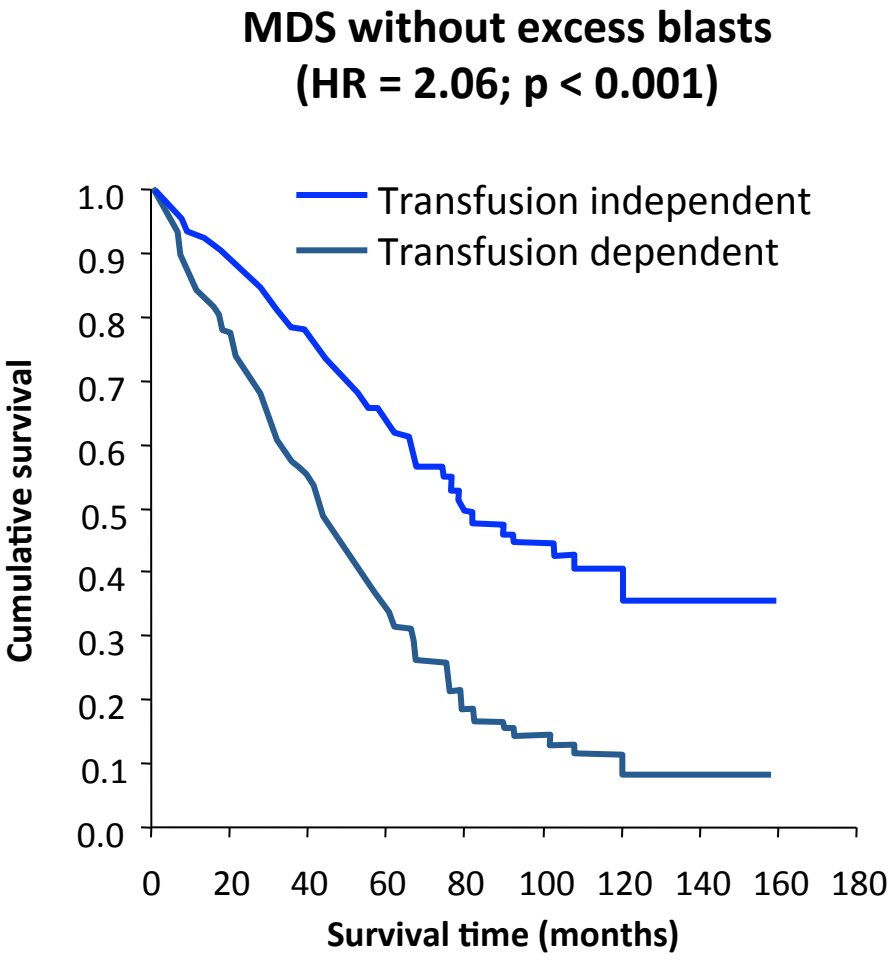
- Cardiac events are increased in MDS, especially in transfusion-dependent patients[1]
- Cardiac imaging[2]
  - 19% moderate IO (T2* ≤20ms)
  - 4% severe IO (T2* ≤ 10 ms)
- What is the mechanism of cardiac complications in MDS?

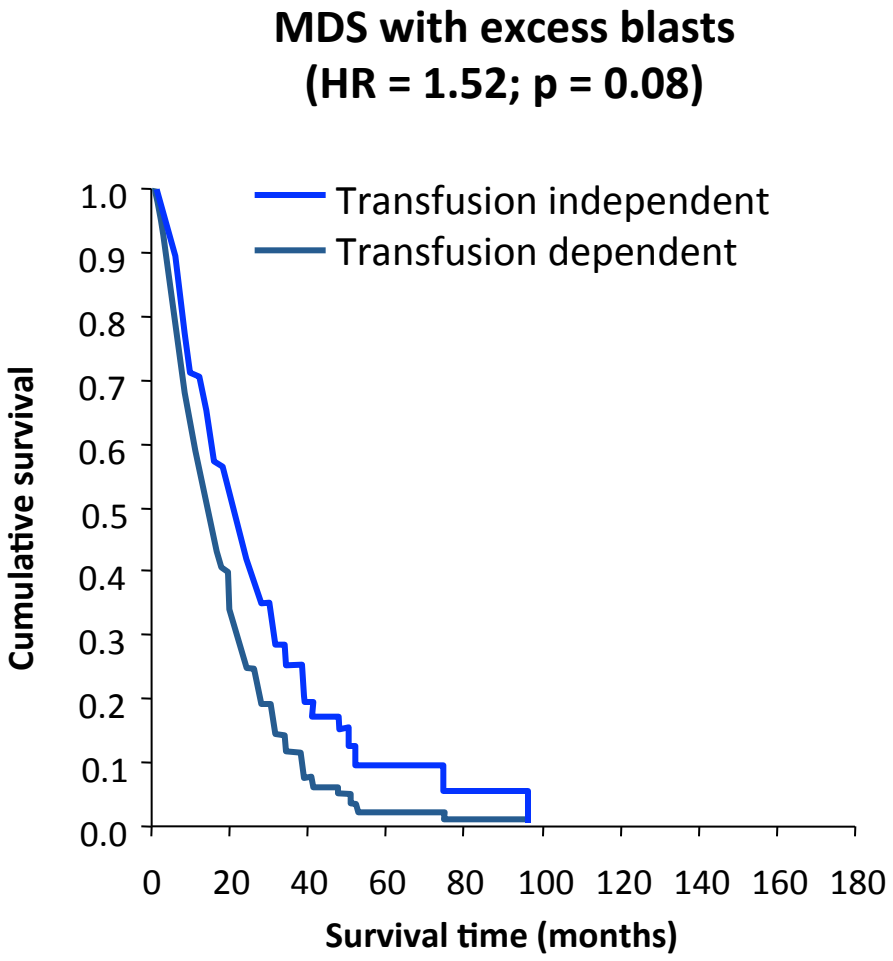
Preclinical: Uptake of LPI into cardiac cells leads to arrhythmia and CHF

CHF = congestive heart failure; IO = iron overload; LPI = labile plasma iron.

1. Goldberg SL, et al. J Clin Oncol. 2010;28:2847-52.
2. Pascal L, et al. Blood 2010;116:[abstract 2906].

Survival of MDS patients according to WHO subgroup and transfusion dependence

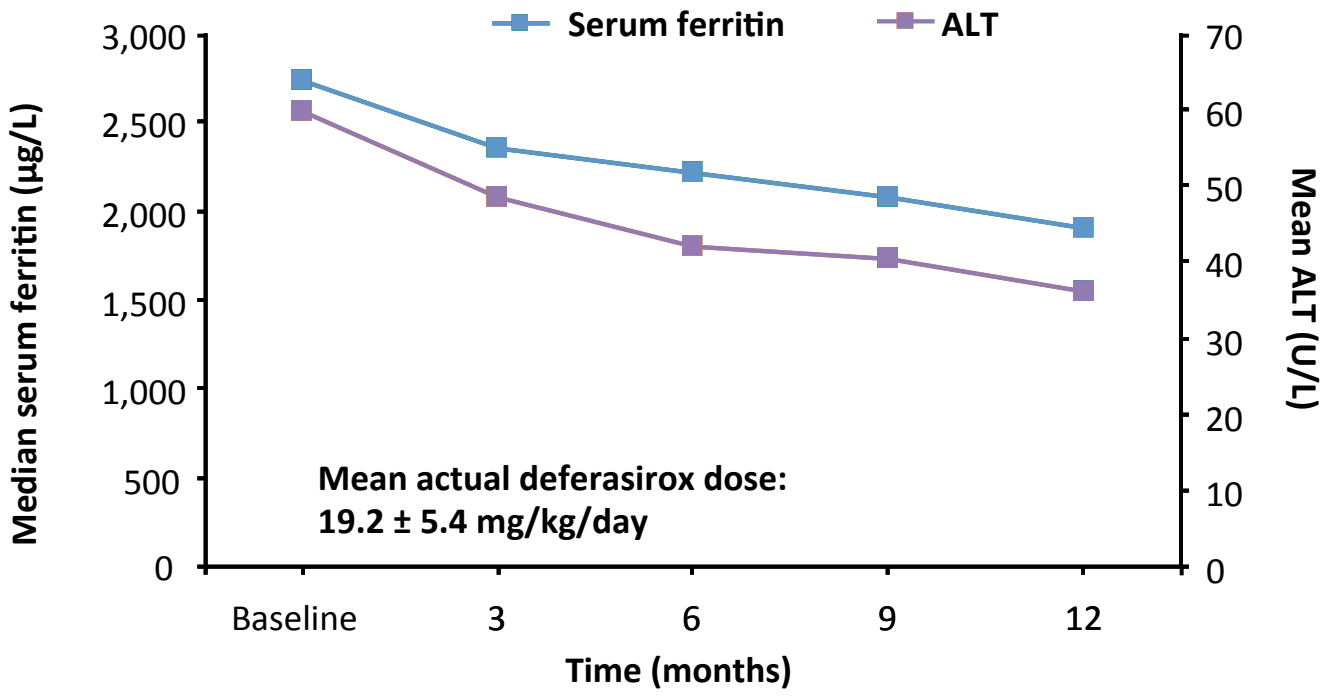




Based on Malcovati L, et al. J Clin Oncol. 2005;23:7594-603.

HEPATIC COMPLICATIONS
EPIC: reduction in serum ferritin is associated with improvement in ALT in MDS

- At 12 months, there were significant reductions in
  - median serum ferritin (−253 µg/L; p = 0.002)
  - mean ALT (−27.7 ± 37.4 U/L; p < 0.0001)



ALT = alanine transaminase; EPIC = European Prospective Investigation into Cancer and Nutrition.

Gattermann N, et al. Leuk Res. [Epub ahead of print 2010 May 5].

US03 trial: hematological response

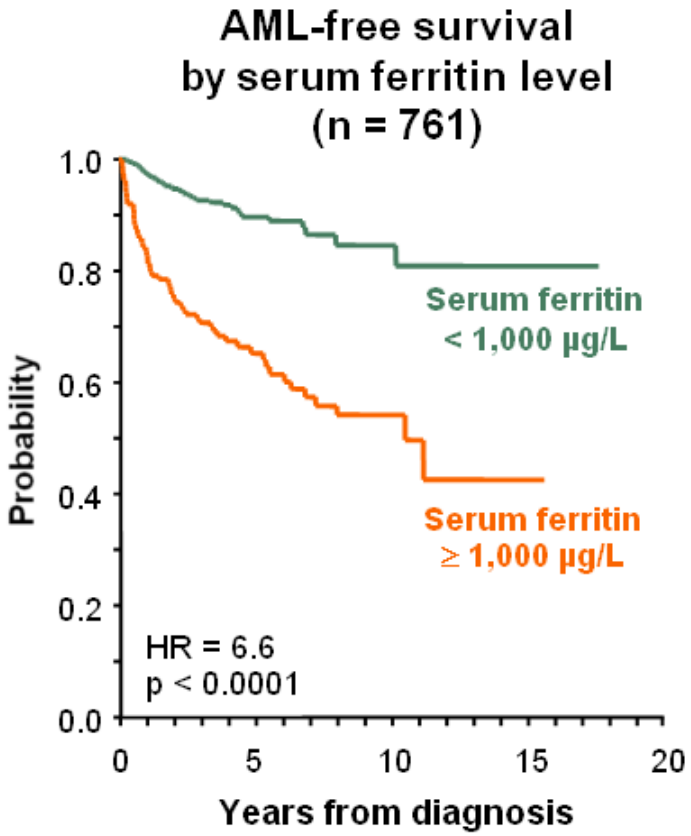
- Erythroid responses - 15% (26/173) of patients
- Platelet responses - 22% (17/77) of patients
- Neutrophil responses - 15% (8/52) of patients
- Multilineage responses were seen in
  - 4 neutrophil + erythroid
  - 5 platelet + erythroid
  - 3 neutrophil + platelet
  - 2 erythroid + neutrophil + platelet

List AF, et al. J Clin Oncol. [Epub ahead of print 2012 Apr 30].

Summary: transfusion dependence and iron overload in *lower risk* MDS

- Multiple sizeable studies show an association between transfusion dependence and iron overload & inferior overall survival with inferior leukemia-free survival in some

Fe and AML in MDS



Sanz G, et al. Blood. 2008;112:[abstract 640].

- Sanz (2008): better LFS in MDS patients with SF<1000
- Leitch (2007): better LFS in low/int-1 risk MDS patients who received ICT

Ferroscepticism

- DeLoughery TG. Iron: The fifth horseman of the apocalypse? Am J Hematol. 2009
- Steensma DP. Myelodysplasia paranoia: iron as the new radon. Leuk Res. 2009
- Tefferi A, Stone RM. Iron chelation therapy in myelodysplastic syndrome—Cui bono? Leukemia. 2009

Concerns about the relevance of iron overload in MDS:

- It takes months to years to offload significant amounts of organ & total body iron so how can chelation result in clinical benefits within months?[1]

- "Neither Serum Ferritin Nor Number of Red Blood Cell Transfusions Affect Overall Survival in Refractory Anemia with Ringed Sideroblasts"[2]

- Lack of prospective, randomized data

[1]Steensma DP. Curr Hematol Malig Rep 2011;6:136-44
[2]Chee C.E. Am J Hematol 2008;83:611-3

Summary: *higher-risk* MDS

- Studies suggest chelation in patients with higher-risk MDS could[1]
  - lower the risk of infection
  - delay leukemic transformation
  - improve the outcome of allogeneic SCT
- We should remain open to the potential mechanism of action of chelation in MDS on clinical endpoints

1. Pullarkat V. Blood. 2009;114:5251-5.

Iron Chelation in MDS: What is the Benefit?

- Lower incidence of cardiac events, diabetes, and hepatic impairment
- Fewer infectious complications
- Improved haemopoietic function
- Lower risk of leukaemic transformation
- Improved outcome of allogeneic SCT

Improved overall survival?