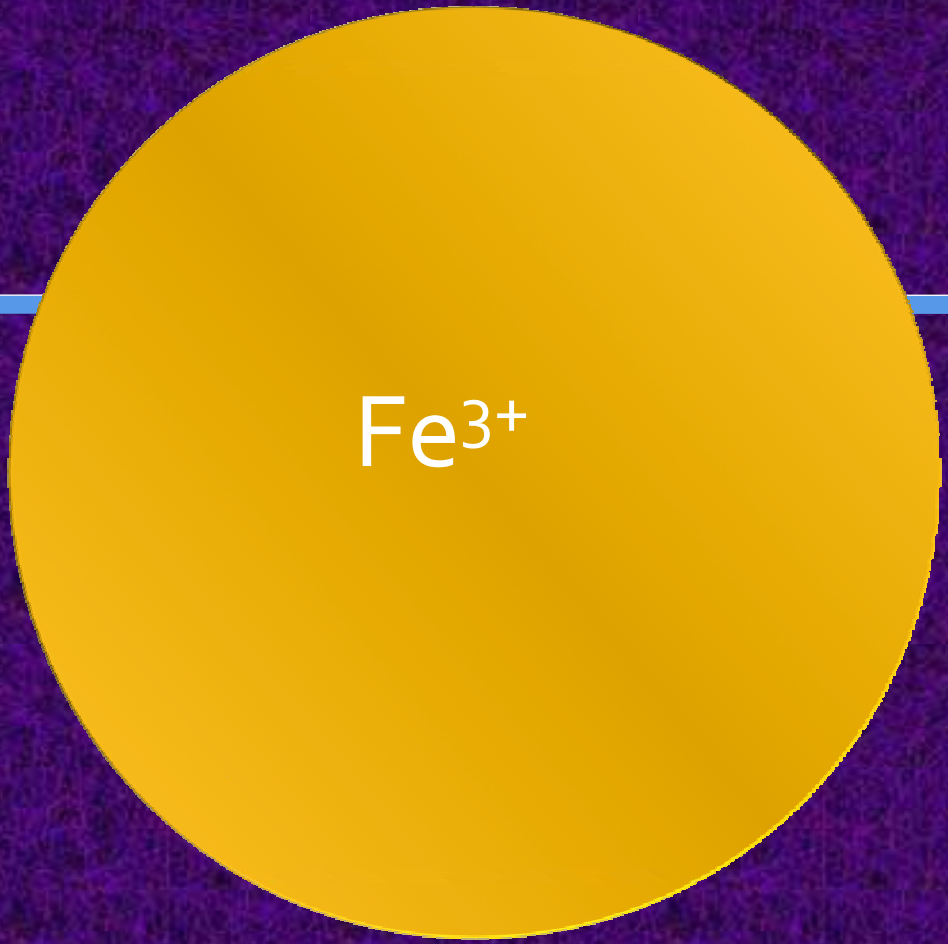


Should I Worry About Iron??

Rena Buckstein MD FRCPC
Co-Director MDS Research Program
Odette Cancer Center Toronto

Objectives

- Review iron balance in the human body
- Discuss how patients with MDS get iron overloaded
- What is the evidence that iron overload is bad in MDS?
- What is the evidence that iron chelation is good in MDS?
- What are available methods of iron chelation?
  - Do they work?
  - What are their side effects?
- Who should get chelated? When?

"Everything has its limit - *iron* ore cannot be educated into gold".

Mark Twain

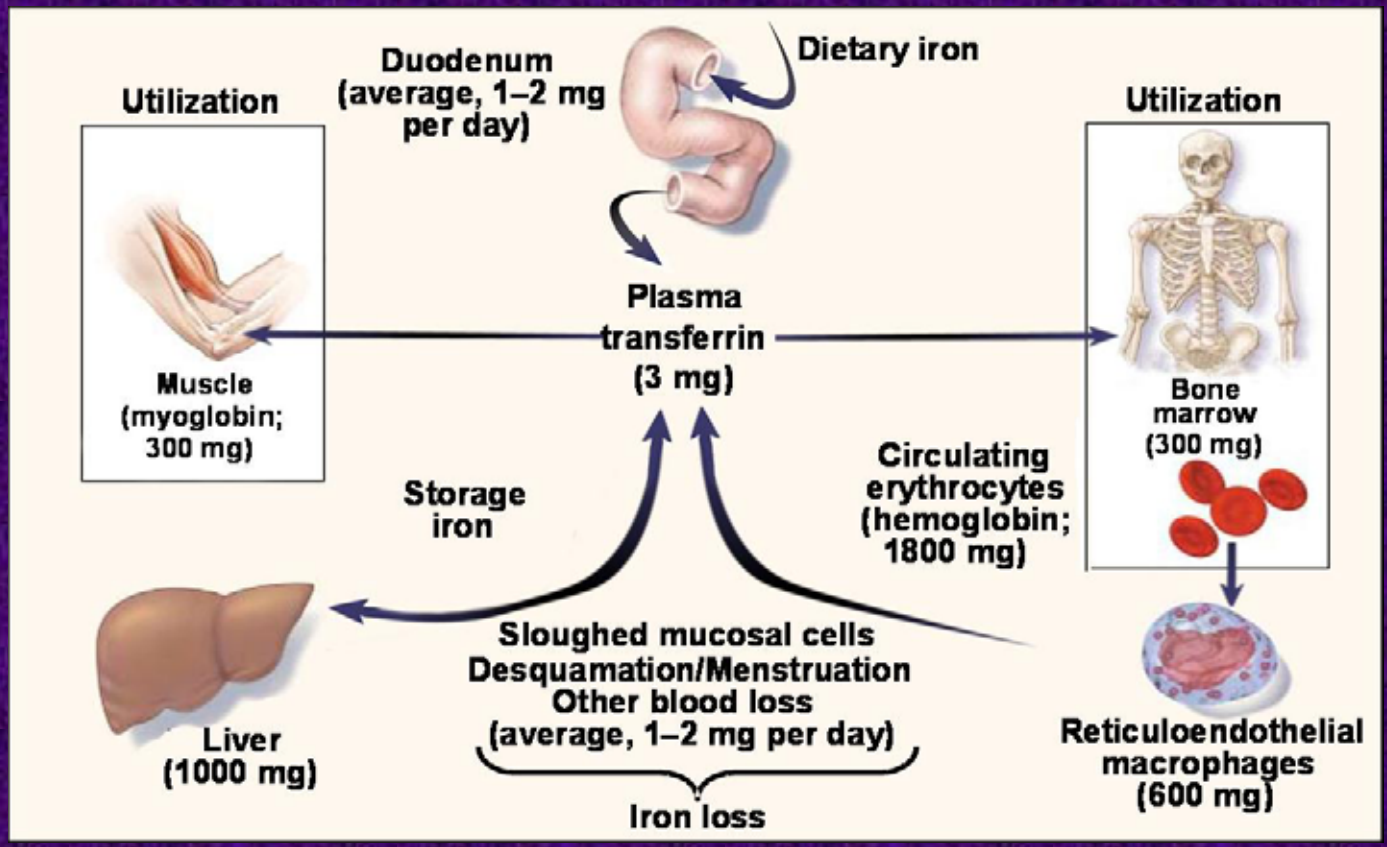
"The great questions of the day will not be settled by means of speeches and majority decisions but by *iron* and blood".

Otto von Bismarck

Iron is everywhere

- Found in many foods: heme and none heme
- Important Functions:
  - Create DNA
  - Produce energy in body cells
  - Carry oxygen in the blood

Body Iron Distribution and Storage



There is no physiologic mechanism to remove excess iron

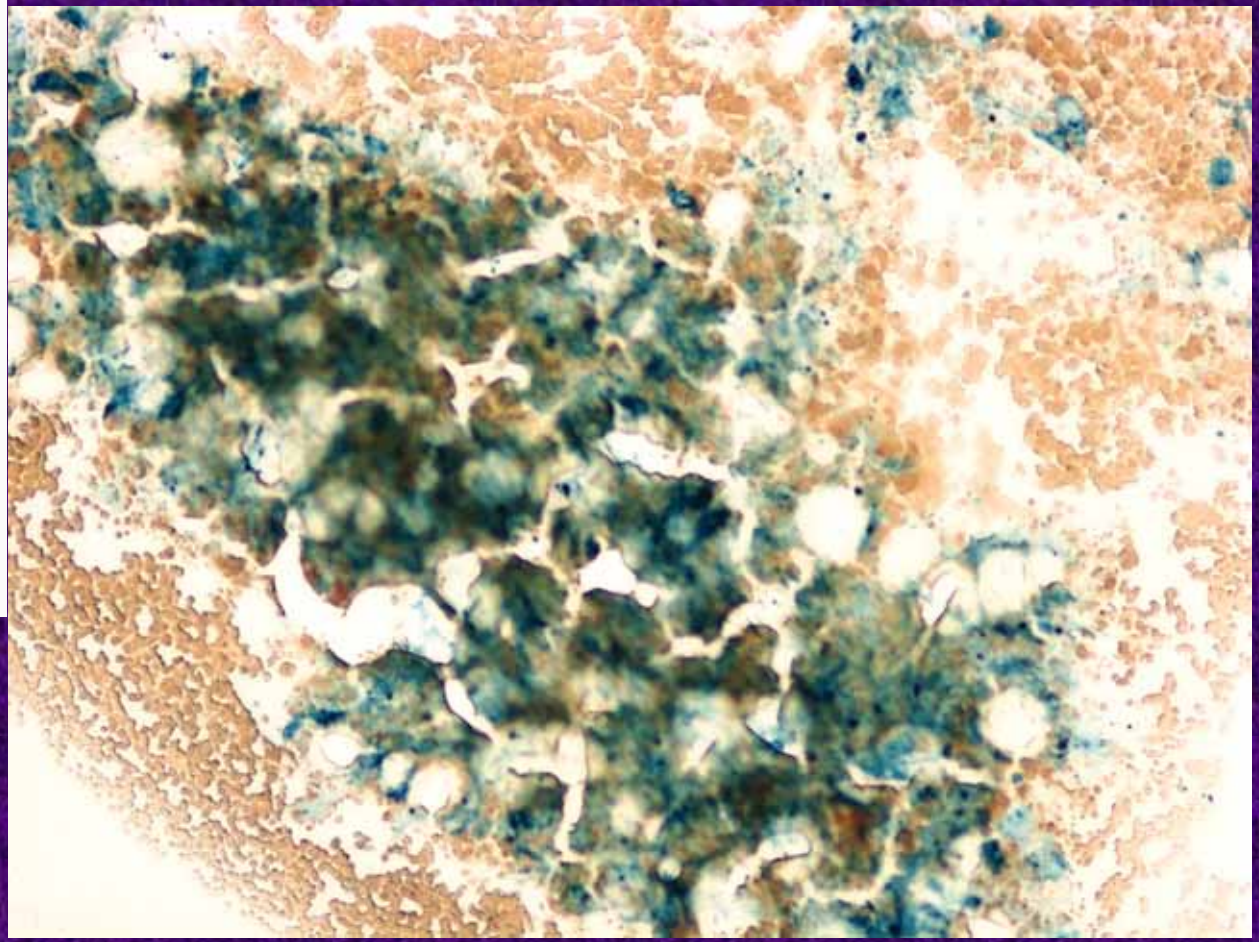
Adapted with permission from Andrews NC. *N Engl J Med*. 1999;341:1986–1995

Body Iron Balance

- After intake, iron is sequestered in complexes
  - Ferritin
    - Large protein: can bind 4500 Fe^{+3} ions
    - Mainly inside cells
    - Iron overload reflected by high serum levels
  - Hemosiderin
    - Iron storage protein deposited in organs
  - Serum transferrin
    - Iron transport protein in blood
    - Capacity can be exceeded resulting in Non Transferrin Bound Iron (NTBI)
      - *NTBI is the most toxic form of iron*

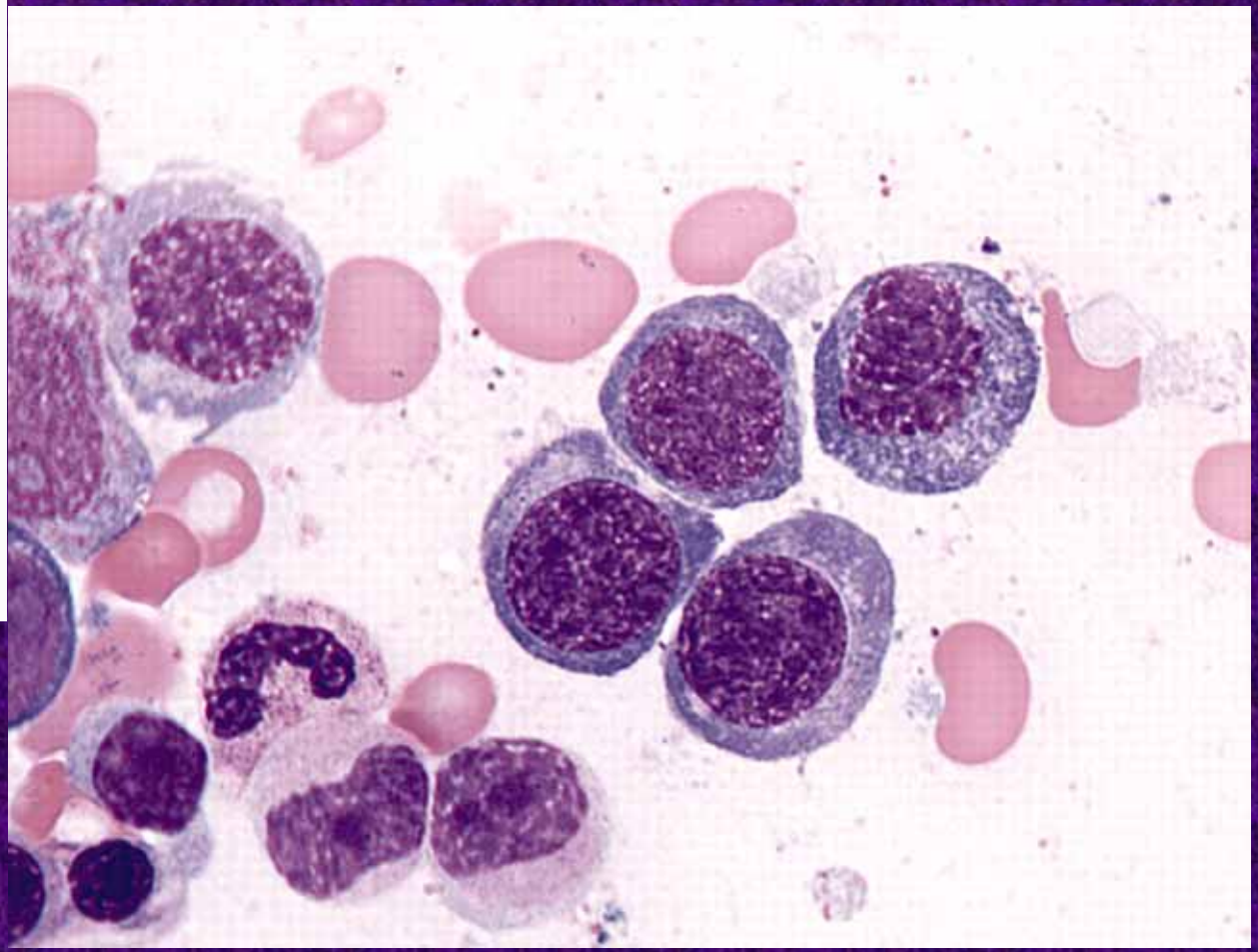
Andrews NC. *N Engl J Med*. 1999;341:1986–1995

Iron in the bone marrow



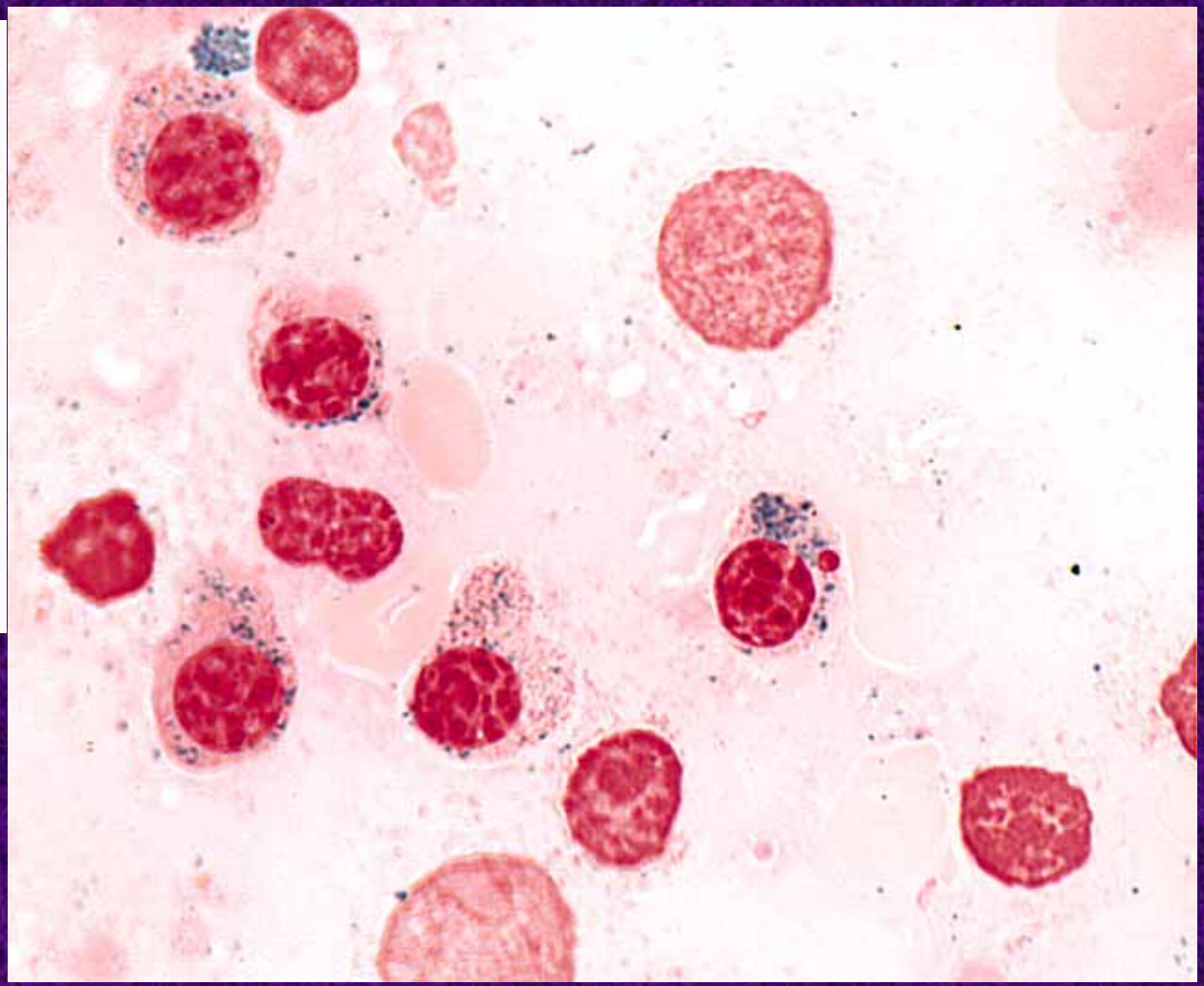
Maslak, P. ASH Image Bank 2004;2004:101141

Figure 1. Bone marrow aspirate is hypercellular with erythroid hyperplasia and prominent dyserythropoiesis



Maslak, P. ASH Image Bank 2004;2004:101135

Figure 7. RARS accounts for approximately 15%-20% of the myelodysplastic syndromes



Maslak, P. ASH Image Bank 2004;2004:101135

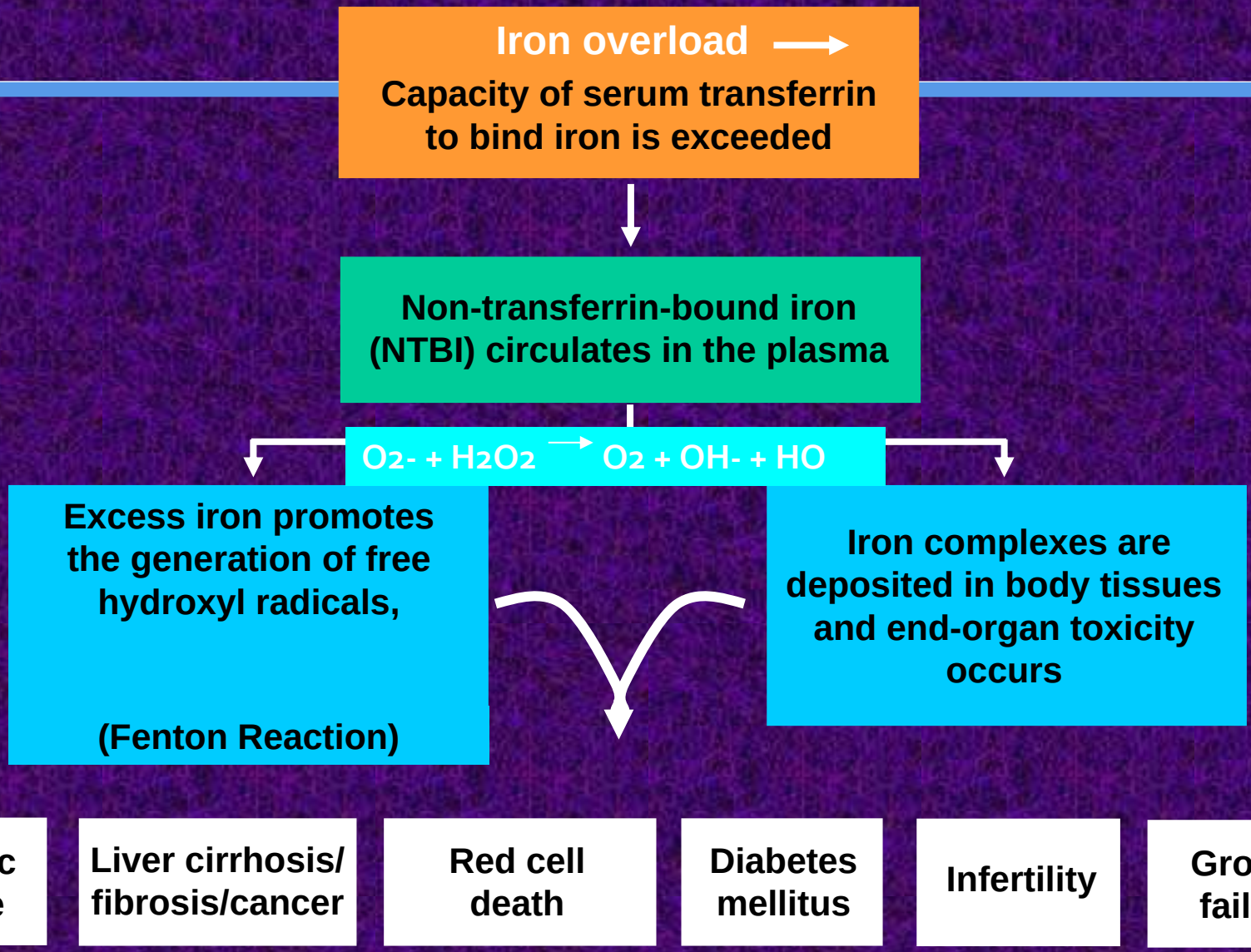
Chronic transfusion overwhelms the iron balance

- Normal daily iron flux:

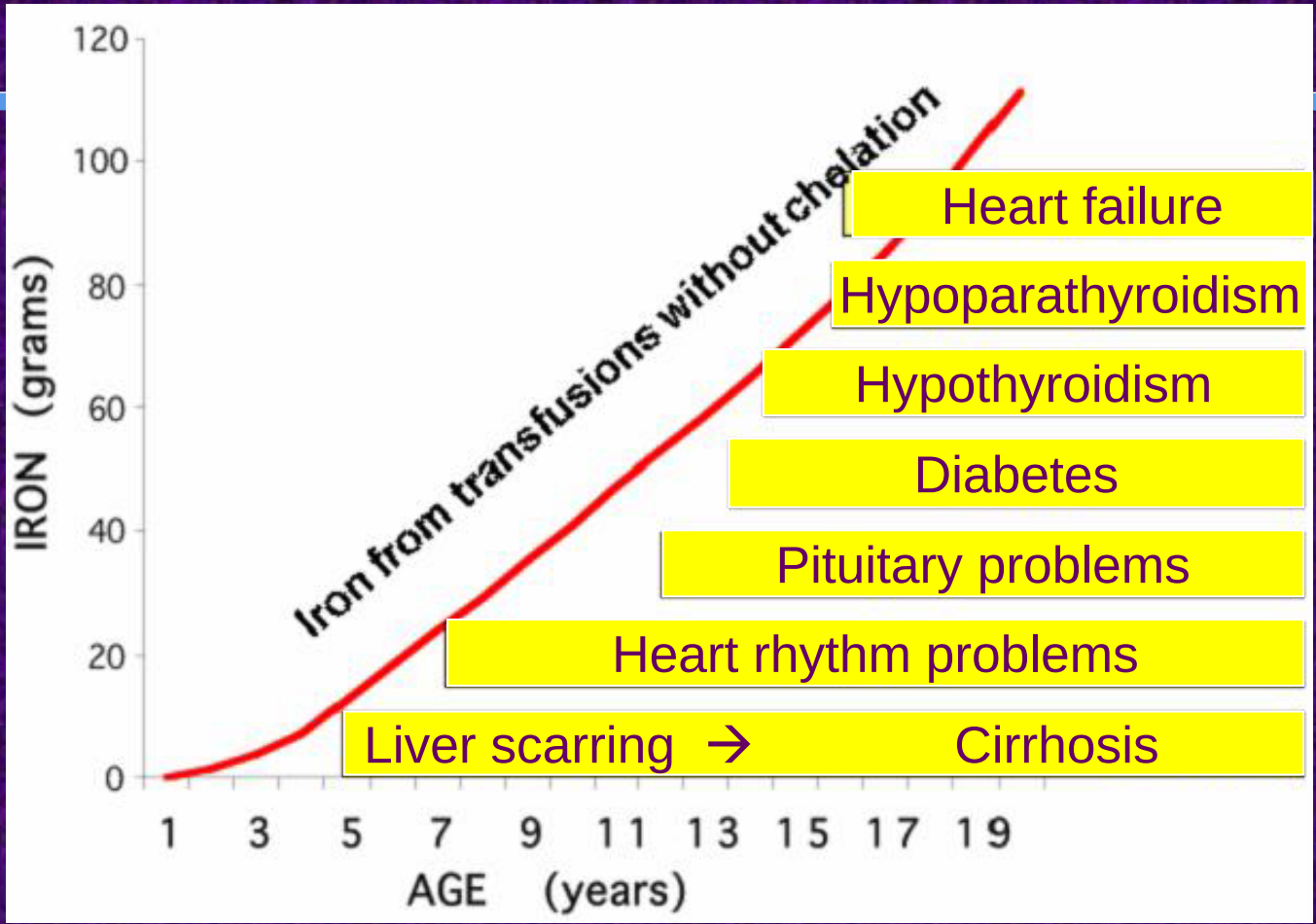
1-2 mg

- Each unit of PRBC:

Complications of Iron Overload: Lessons from Thallasemia



Lessons from thalassaemia



When does iron become a problem?

- Normally 2.5 – 3 g of iron in the body.
- Tissue damage when total body iron is 7 – 15 g
  - After 20-50 units of red blood cells

Monitoring Iron Overload

- Serum ferritin concentration
- Liver iron content[1]
  - Liver biopsy
  - MRI T2*

MRI = Magnetic Resonance Imaging

1. Brittenham GM, et al. *Blood.* 2003;101:15–19

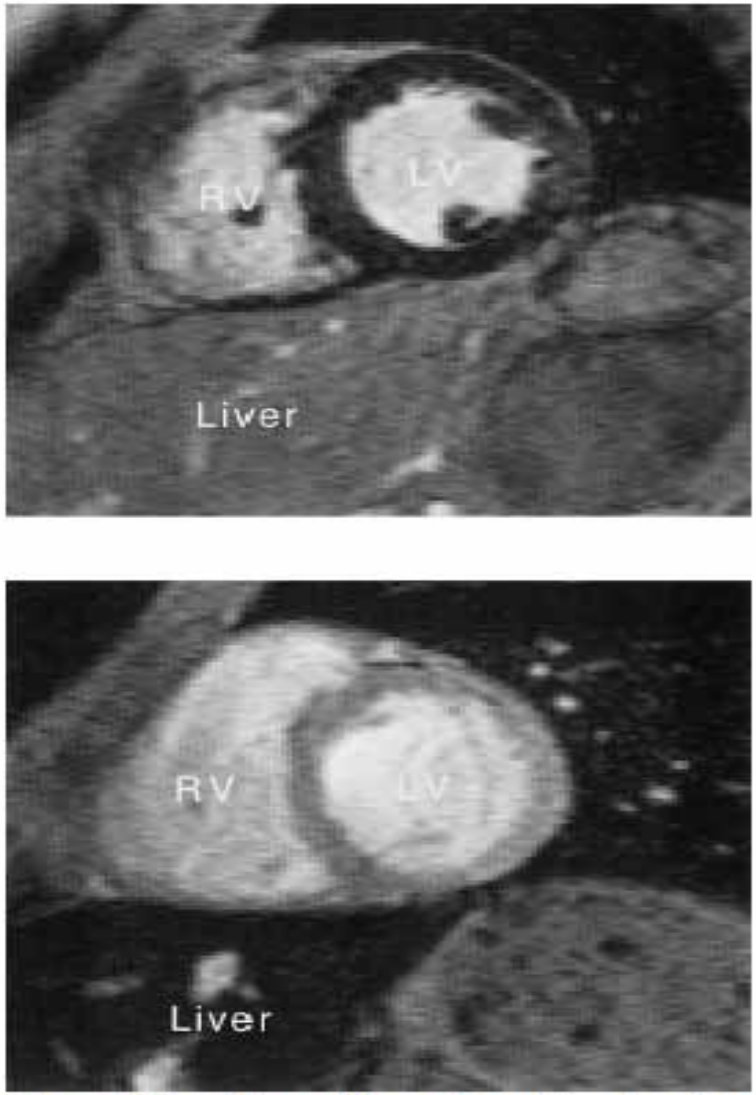


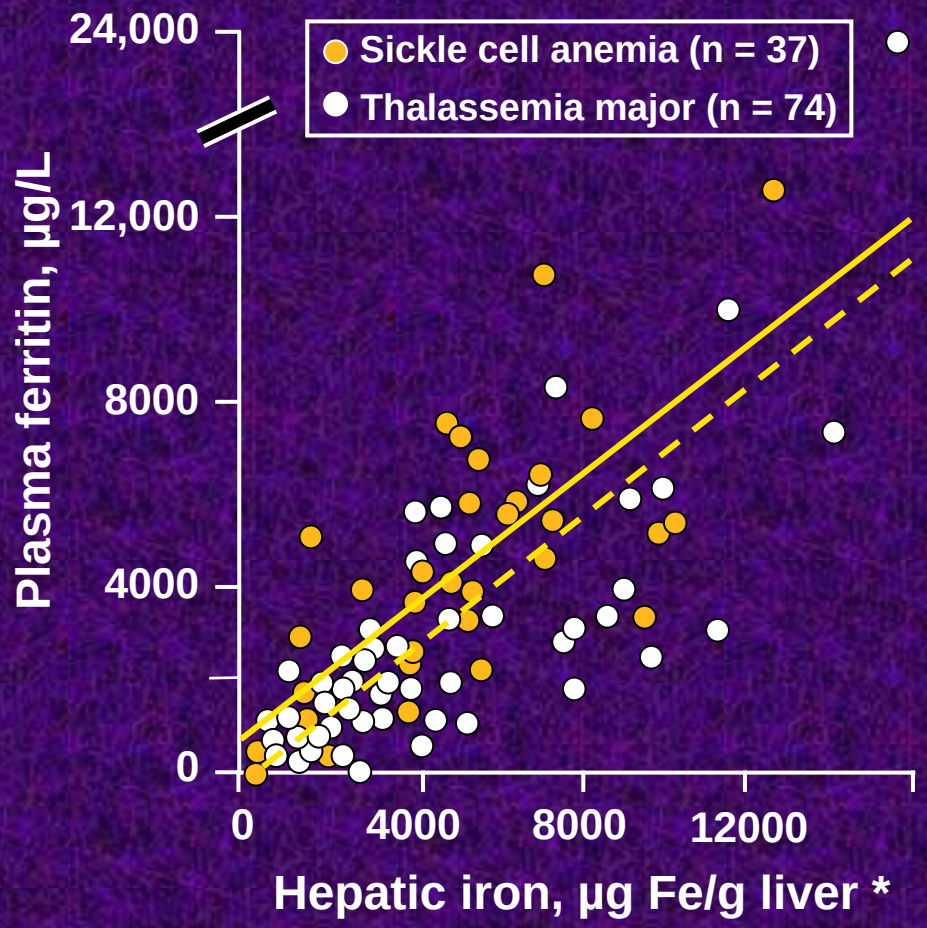
Figure 2 Discordance of liver and heart iron deposition. Short axis plane, including the adjacent liver (TE 5-6 ms). The top panel shows a patient with severe cardiac iron deposition but minimal liver iron deposition (heart darker than liver). The lower panel shows a patient with normal myocardial iron but severe liver iron overload (liver darker than heart).

Anderson, American Heart Journal 2001

Serum Ferritin

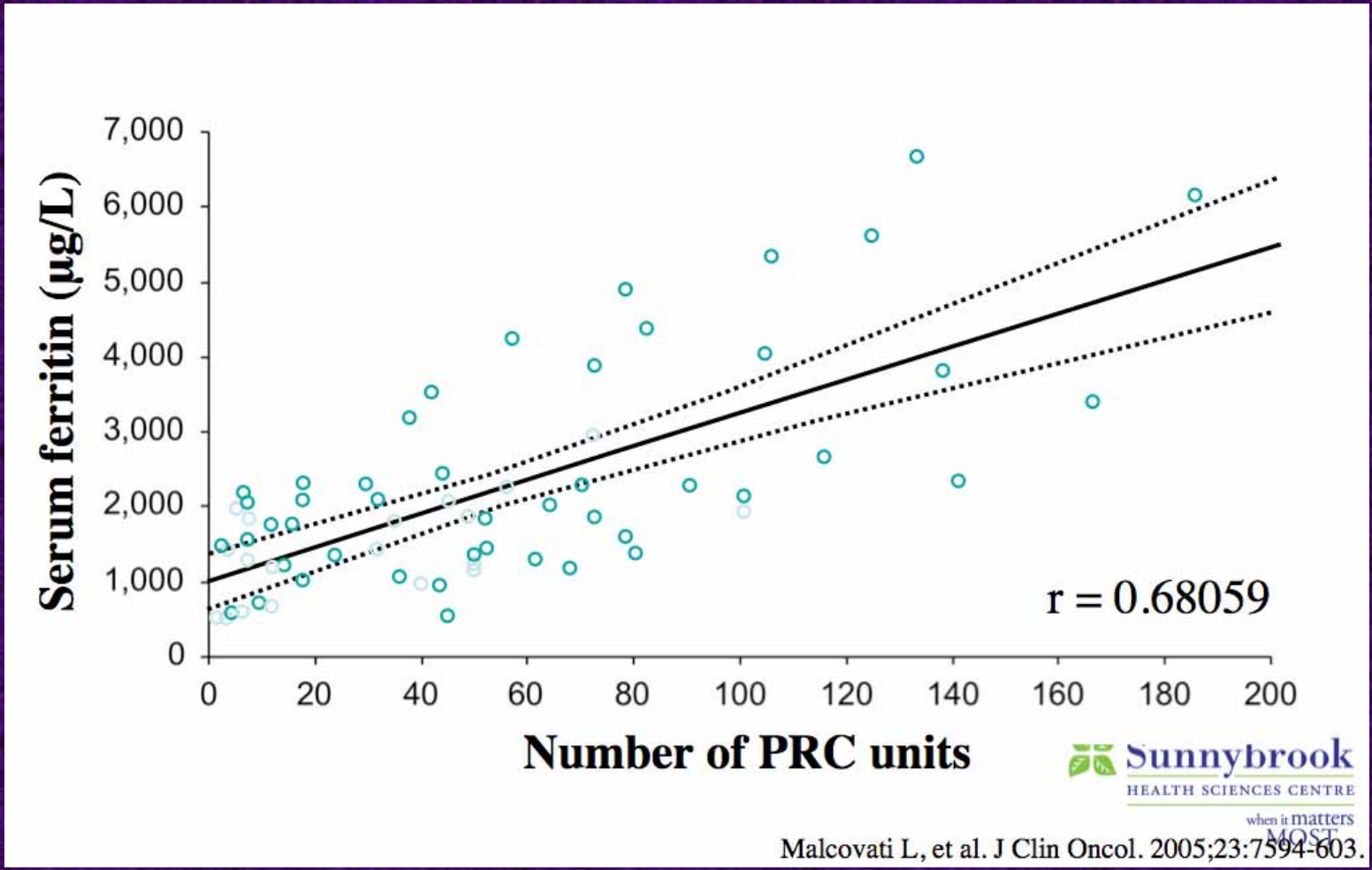
Serum Ferritin:

- Relatively non-invasive
- Inexpensive
- Obtained as routine laboratory assay
- Values confounded by
  - Inflammation
  - Liver function



Brittenham et al. Am J Hematol. 1993;42:81

Relationship between ferritin and # units of red blood cells



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

Transfusions in MDS

- 80% of MDS are anemic at time of presentation
- 40-80% require transfusions at some stage of their disease
  - Low: 39%
  - Int-1: 50%
  - Int-2: 63%
  - H: 79%
- Time from diagnosis to first transfusion:
  - < 6 mos: 48%
  - 6-12 mos: 7%
  - > 12 mos: 10%

Piedmont MDS registry Malocvati et al 2006

Why chelate in MDS?
Limited Published Data

- Thalassemia: no dispute
- Few published data on iron overload in MDS
  - Does iron overload cause problems or shorten life *in MDS patients*?
  - Does iron chelation decrease or prevent this *in MDS patients*?

Does iron overload cause excess organ dysfunction in MDS patients?

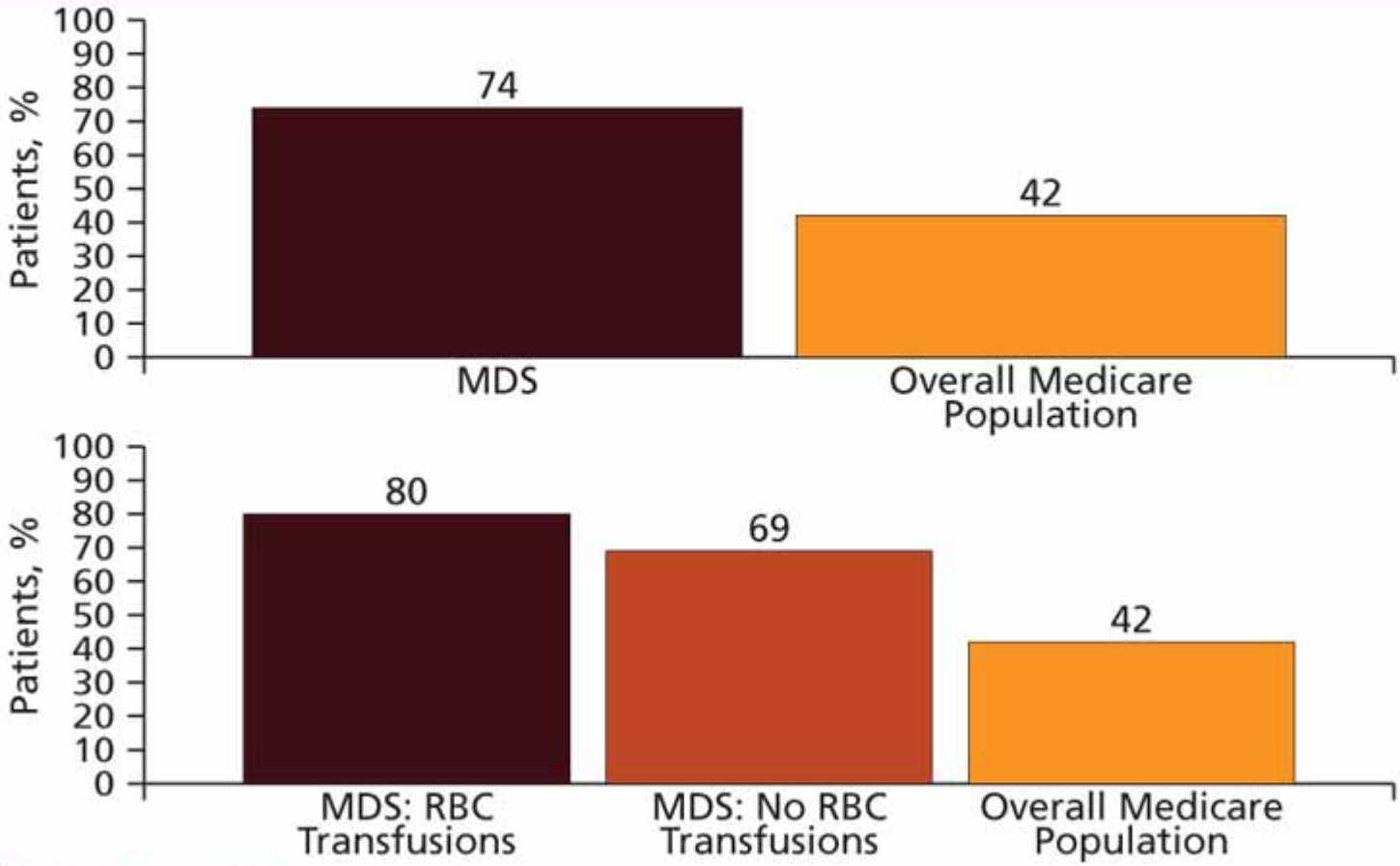
- Schafer AI et al., *N Engl J Med 1981*
  - (N=15) Heart failure and rhythm distrubances + glucose intolerance very common in highly transfused adults
- Jaeger M et al., *Münch Med Wochenschr 1992*
  - (N=46) Heart Failure seen in >40% of highly transfused MDS patients; frequently the cause of death
- Takatoku et al., *Eur J Haem 2007*
  - (n= 292; 152 MDS) Abnormal cardiac function in 22%, abnormal liver function in 73%, cardiac failure at time of death in 24%; strong correlation with ferritin > 1000

Incidence of cardiac events over a 3 year period in patients with MDS in US Medicare population

	Number of Patients %
Any cardiac related event	522 (74)
Heart attack (MI)	142 (29)
Congestive Heart Failure	344 (48)
Irregular Heart Rhythm	374(53)
Other cardiac events	415 (58)

Goldberg SL Leuk Res 2009

Development of Cardiac Complications in Patients With MDS*



* During 3 years of follow-up.

Impact of Transfusions

	MDS			Control
	Total	+TF	-TF	
Cardiac	74%	81%	65%	42%
DM	43%	45%	37%	32%
Hepatic	1.8%	2.1%	1.6%	0.4%
Infectious		81%	57%	

p=.001

p=.002

p=.001

p=.002

- Only 2% of transfused patients were receiving iron chelation therapy

Abstract 636: Goldberg et al; *Hackensack University Medical Center, Hackensack, NJ*

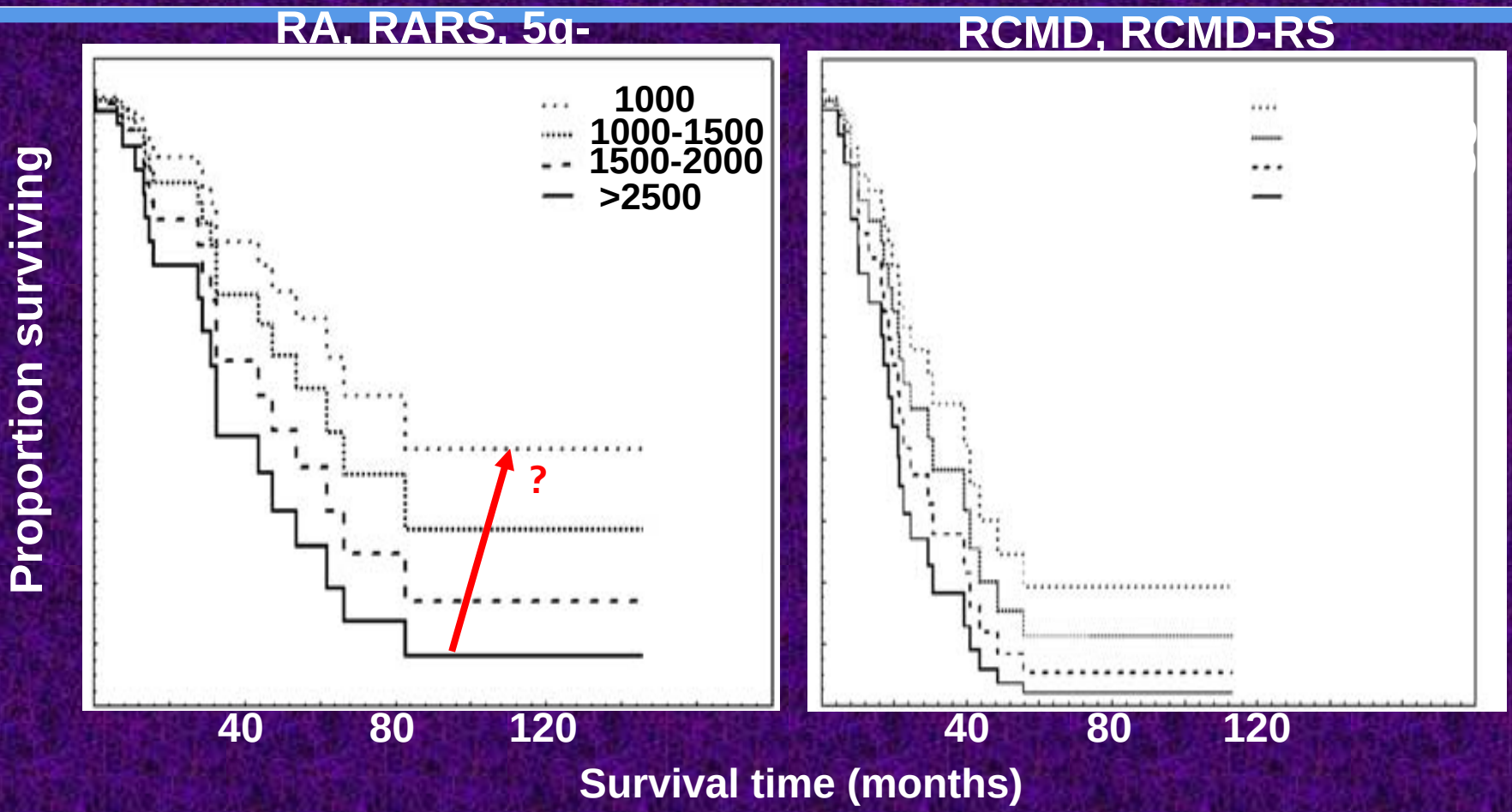
Evidence of increased mortality

- Pavia 10 year study (n=346)
  - Shorter survival in transfusion dependent patients with MDS
    - Excess of deaths cardiac failure (51%) and cirrhosis (8%)
  - Secondary iron overload (ferritin > 1000ng/ml) impaired survival (p=0.003) in patients with RA and RARS
    - Increased by 36% for every rise of serum ferritin of 500 ng/ml above 1000

Malcovati L et al. J Clin Oncol 2005, 23: 7594-7603

*independent of cytogenetics

Iron overload impairs survival in MDS



Malcovati, Haematologica, 2006

More indirect evidence…

Independent Impact of Iron Overload and Transfusion Dependency on Survival and Leukemic Evolution in Patients with MDS

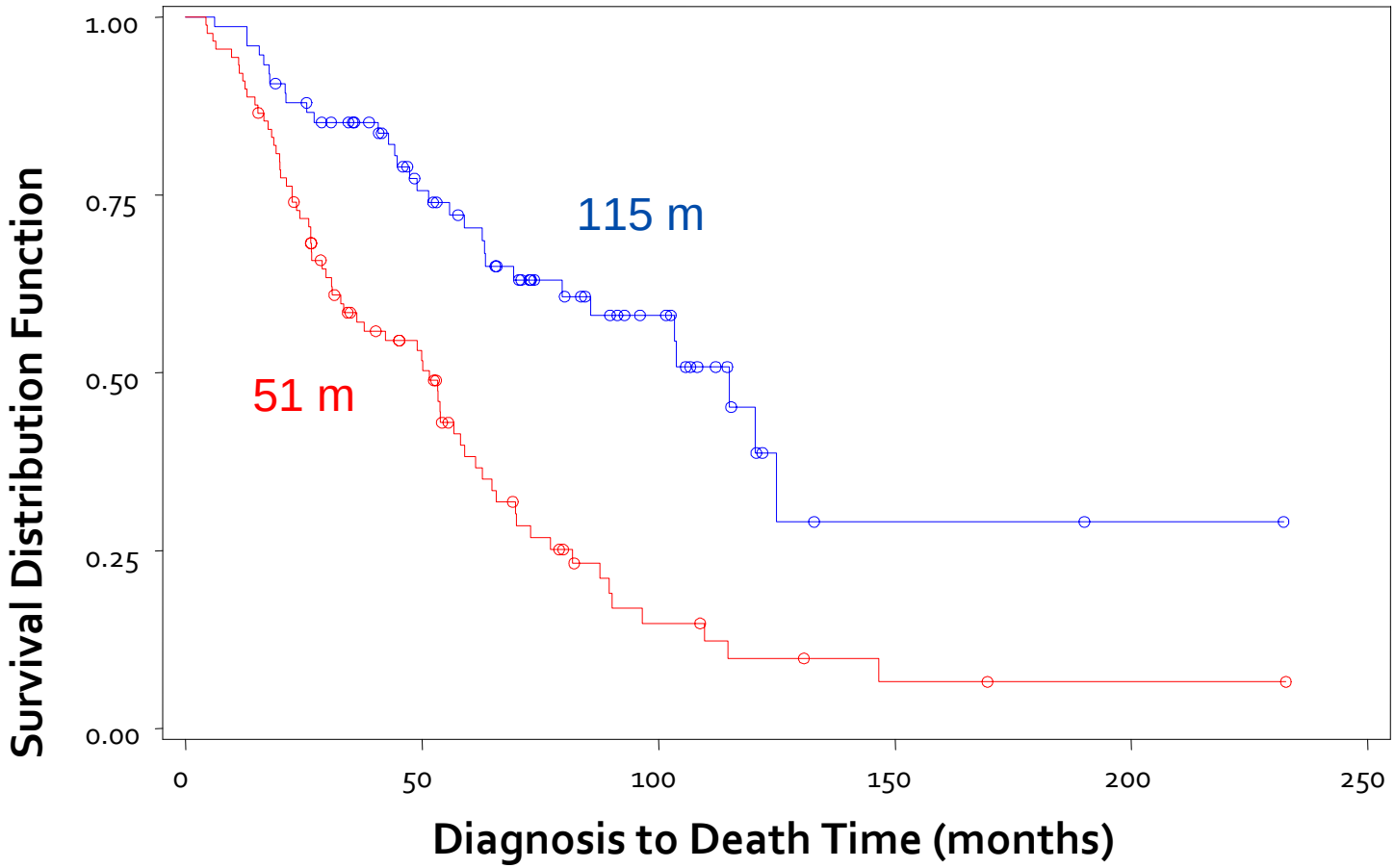
- Aim: Evaluate the independent prognostic value of transfusion dependency and iron overload in a large series of 2, 994 patients with de novo MDS
- Complete transfusional history was available in 2,241 patients at diagnosis

Sanz, G. ASH 2008 abstract 640

	OS		LFS	
	HR	p	HR	p
Transfusions	8.8	<.0001	3.5	<.003
F_{+3} Overload	52.4	<.0001	6.6	<.0001
IPSS	1.5	<.001	1.92	<.001
WPSS	1.6	<.001	2.24	<.001

Evidence for Iron Chelation?

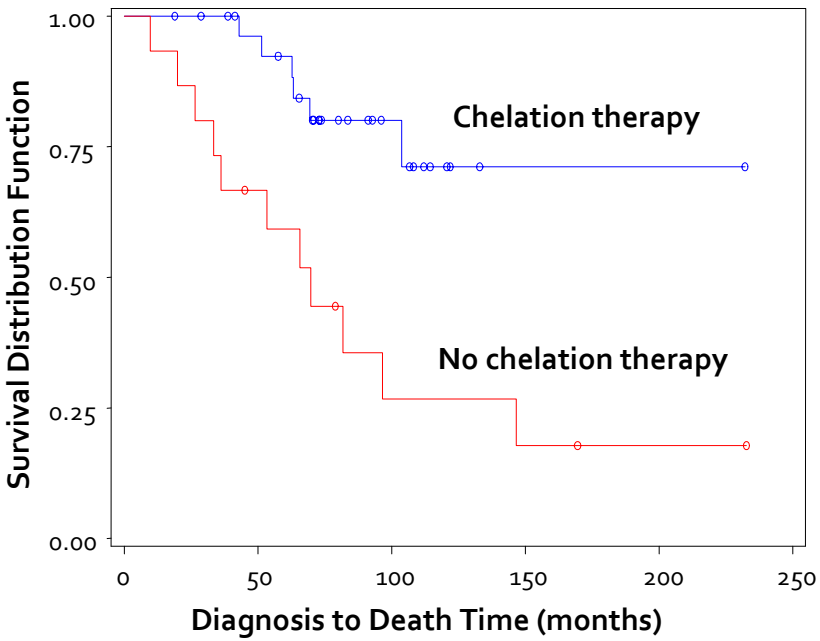
Iron Chelation Therapy Improves Survival in Regularly Transfused MDS Patients—A Prospective Analysis by the GFM in 2005: n=165



Survival–According IPSS

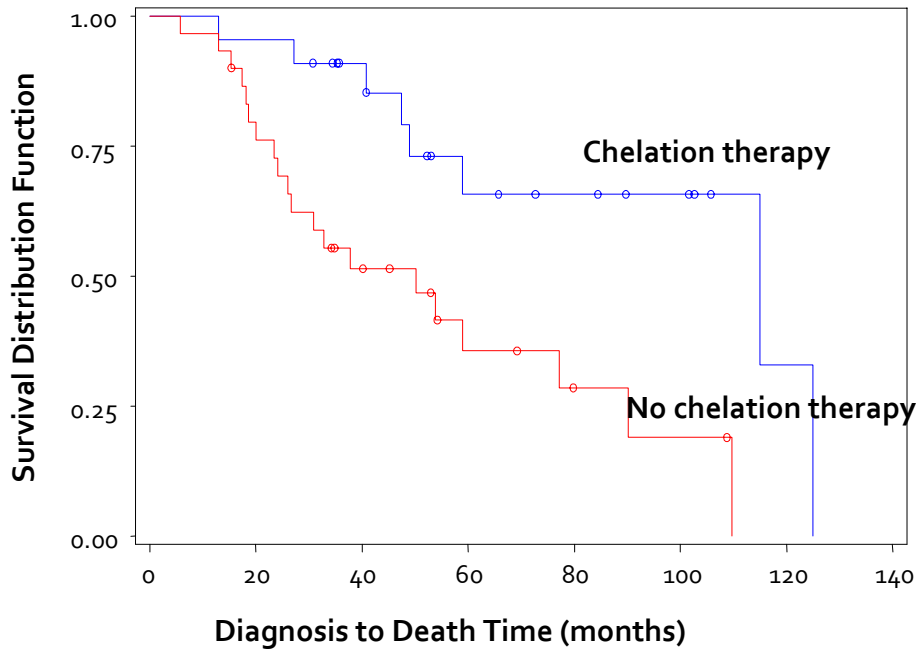
IPSS = low

Median: not reached vs 69 months (*P* <.002)



IPSS = int 1

Median: 115 vs 50 months (*P* <.003)

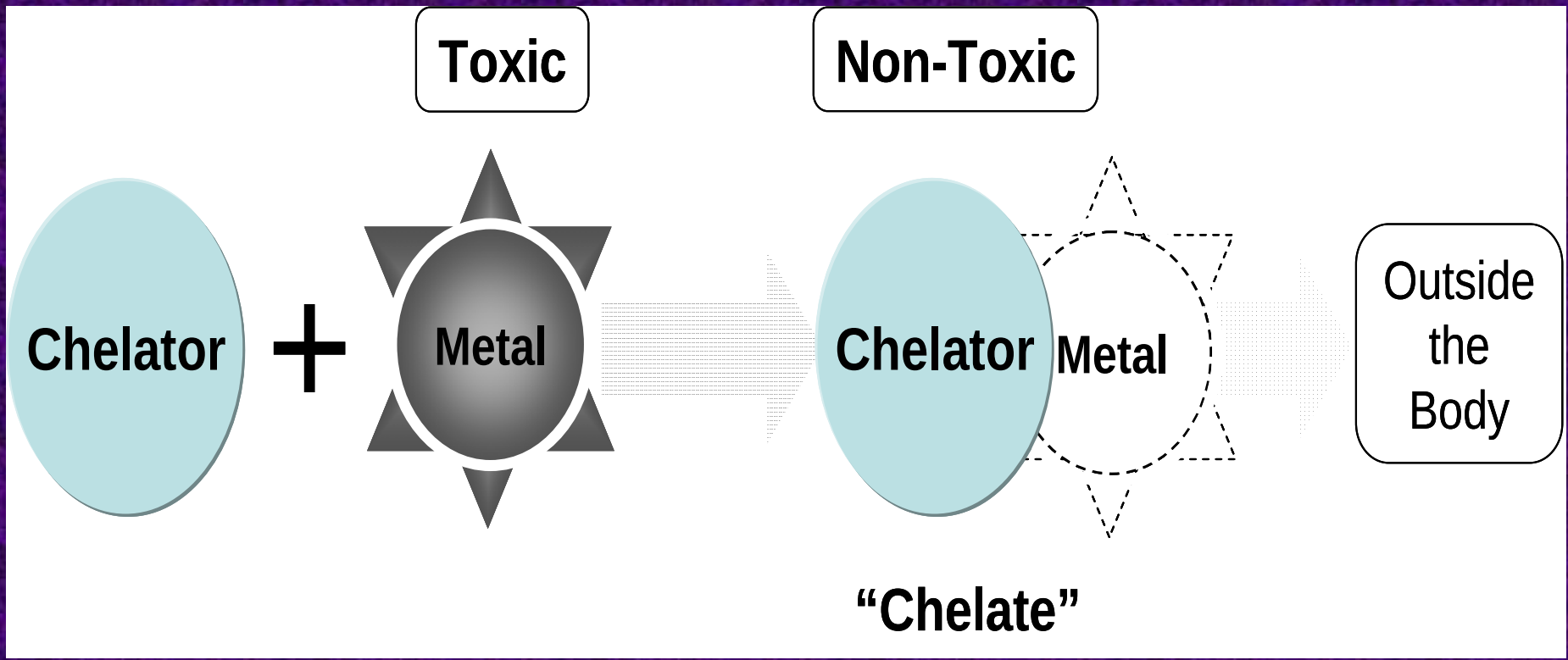


Rose C, et al. *Blood*. 2007:110:Abstract 249.

Summary: Why chelate?

- The relationship between iron overload and survival has been well-established in genetic anaemias
- Retrospective analyses indicate that transfusion dependence and iron overload is bad
- Canadian and GFM data suggest iron chelation in MDS associated with improved survival
- Is this convincing enough???
  - Biased population?
  - Is it the iron or the transfusion dependence?

What is Chelation Therapy?



How do chelators decrease toxicity?

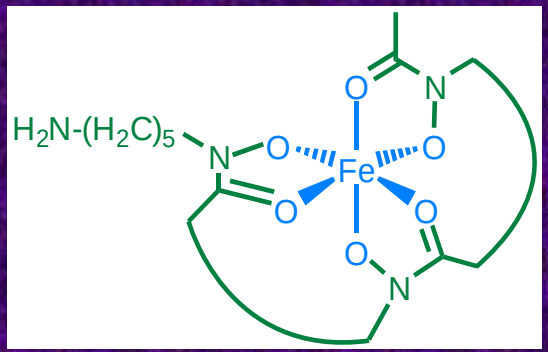
- They complex iron for removal in urine, feces and bile
  - Labile iron pools (organs) and NTBI (plasma)
  - Plasma NTBI declines rapidly in presence of chelator
  - Ferritin and hemosiderin: slower to chelate

Ultimate Goals of Chelation….

- Spare or improve heart function
- Spare or improve liver function
- Improve bone marrow function
- Quality of life? Cognitive function?

Chelators

Deferoxamine Hexadentate (1:1); high MW

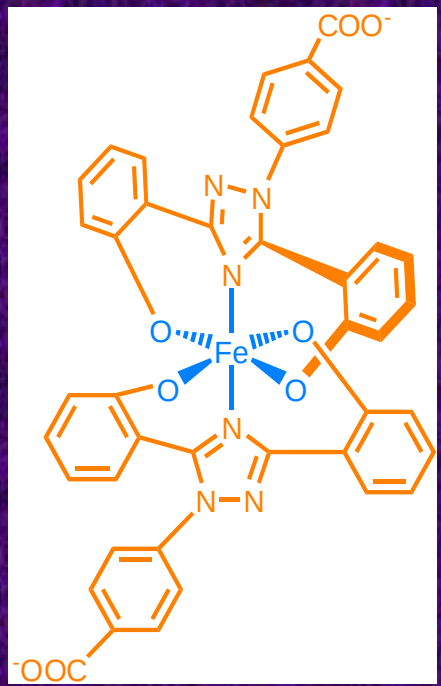


DFO

Subcutaneous infusion

Deferasirox

Tridentate (2:1); low MW

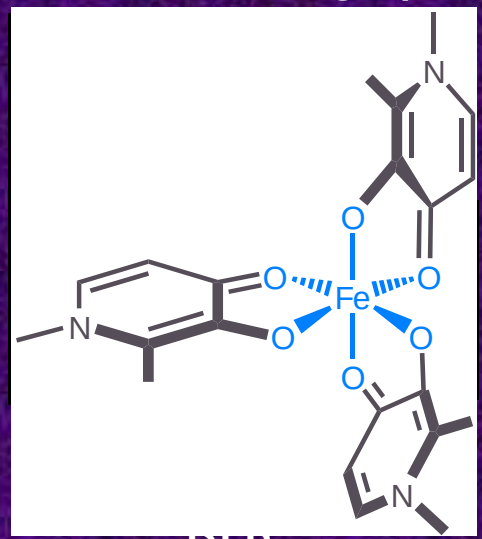


DFX

oral

Deferiprone

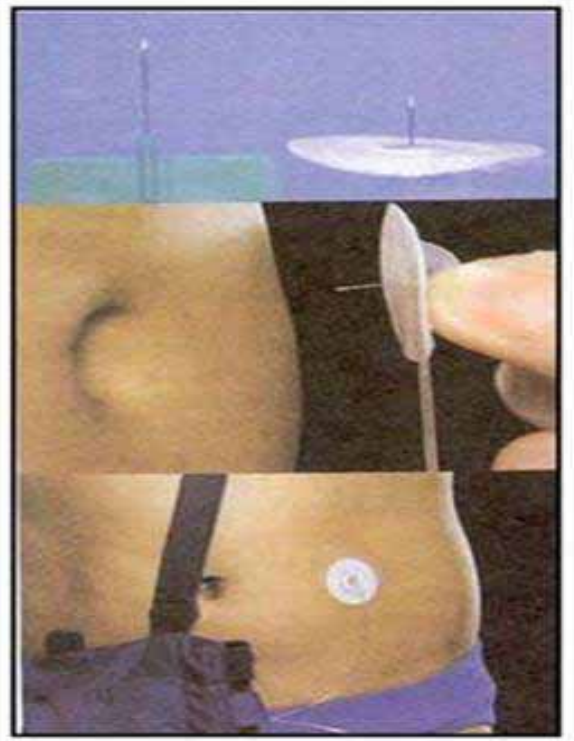
Bidentate (3:1); low MW



DFP

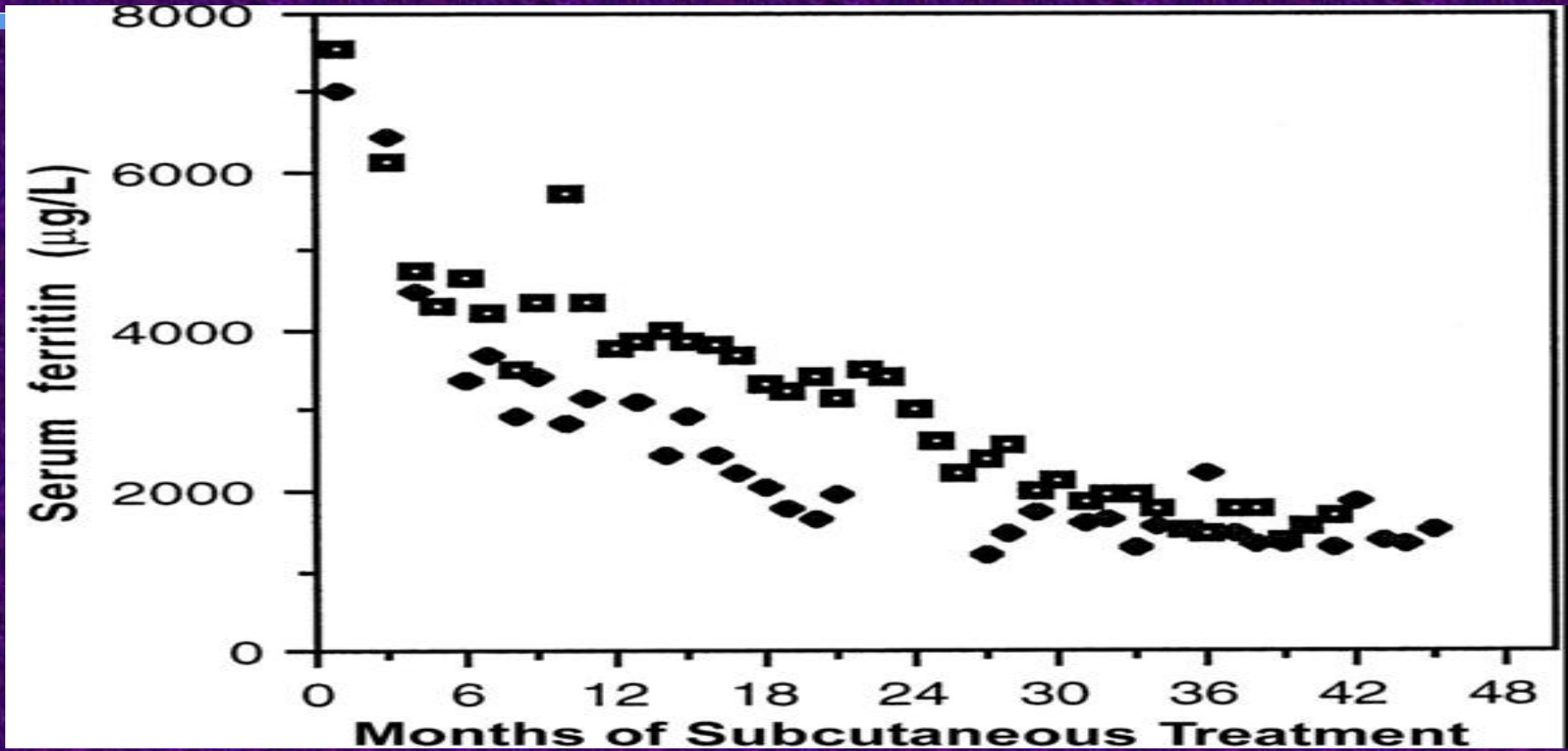
Oral – not available in North America

Deferoxamine



- "Gold standard"
- Used for 35+ years
- Hexadente chelator
- 1:1 binding with iron: excreted in bile or urine
- Large molecule: poor oral bioavailability
- Short half life- 30 mins
- 20-60 mg/kg every day over 10-12 hours parenteral or SC.

Deferoxamine: Efficacy

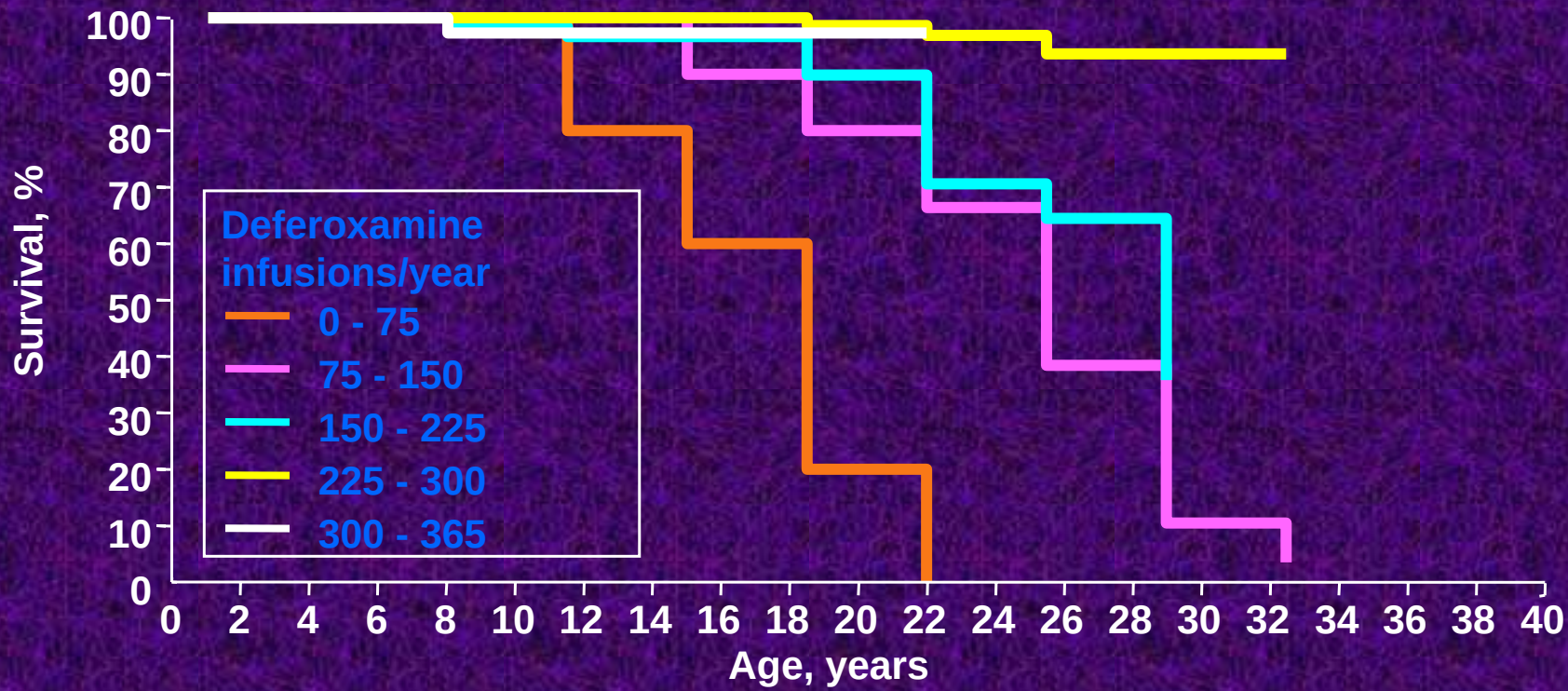


From Davis BA et al. Blood 2000;95:1229-1236

Why does desferal sometimes not work?

The Challenge of Compliance

Kaplan-Meier analysis of survival in 257 consecutive thalassemic patients according to the mean compliance with subcutaneous DFO therapy



Gabutti V and Piga A. Acta Haematol. 1995;95:26-36

Common Side Effects of Deferoxamine

- Local reactions
  - Redness
  - Swelling
  - Itchiness
- Hearing loss
- Zinc deficiency
- Eye
  - Reduced visual sharpness
  - Impaired color vision
  - Night blindness

Side Effects are more pronounced when

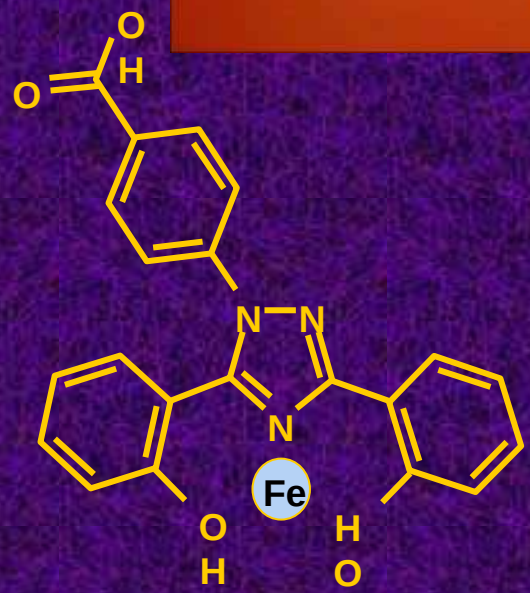
- Serum ferritin declines
- DFO dose increases

Summary: Iron chelation and deferoxamine

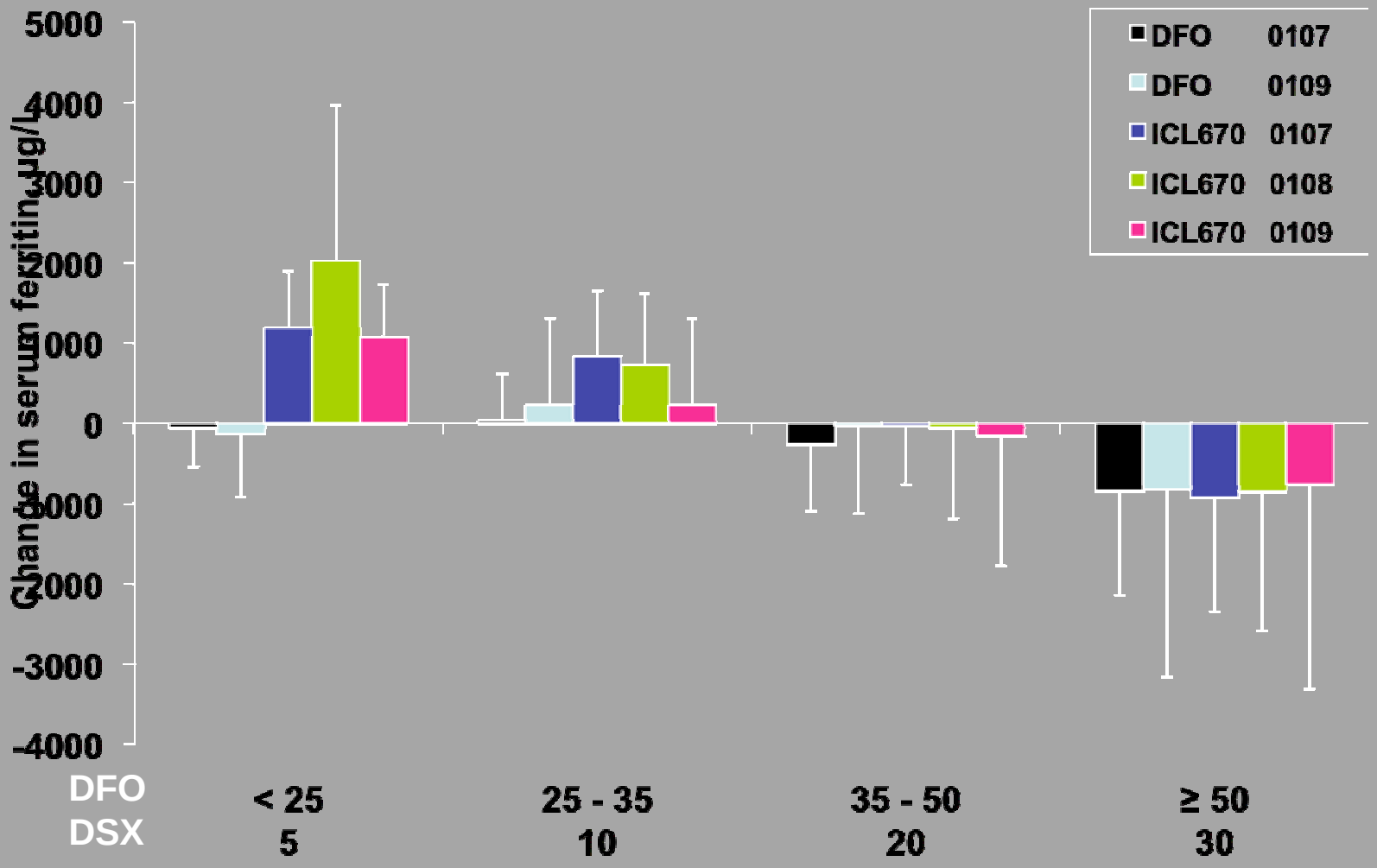
- Deferoxamine is nasty stuff…
  - Inconvenient and uncomfortable to take
  - Many nasty side effects
- …but it works
  - Enormous extension of lifespan in thalassaemia.

ICL670: Deferasirox, Exjade

- Oral, dispersible tablet
- Taken once daily
  - 12-16 h half life
- Highly specific for iron (2:1)
- Chelated iron excreted mainly in feces
- Less than 10% excreted in the urine

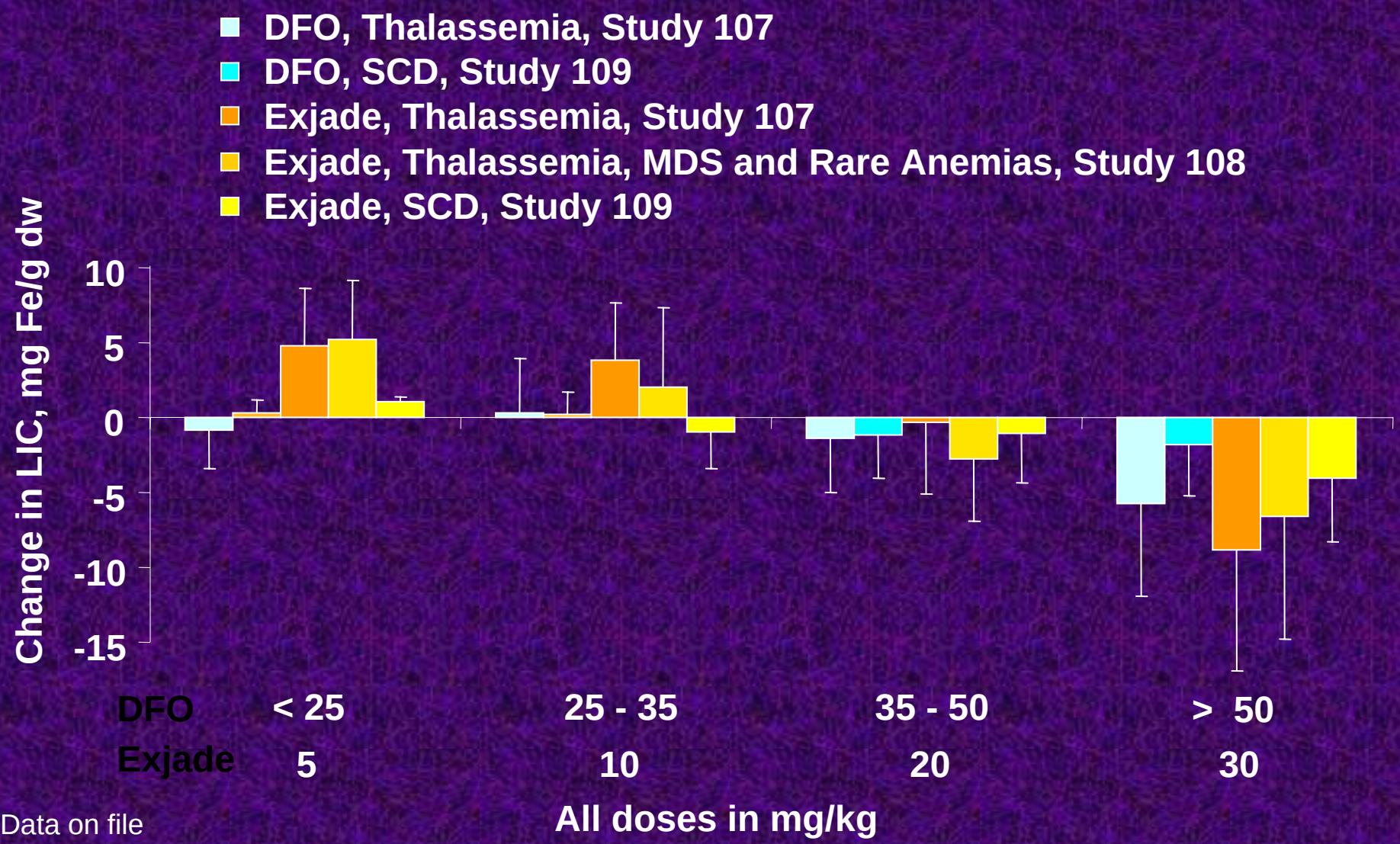


Mean Change in Ferritin by Dose Thalassemia, Sickle Cell Disease, Rare Anemia



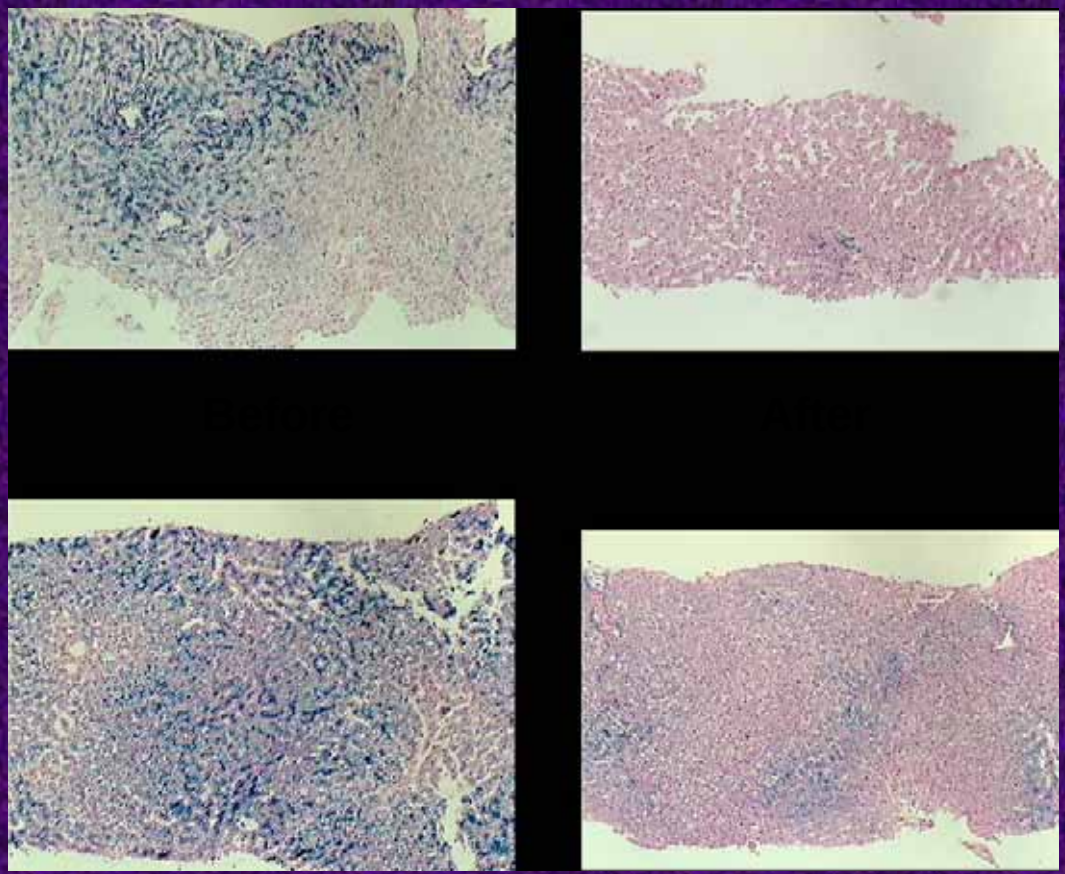
DFO, deferoxamine; DSX, deferasirox.

Consistent Effect on LIC
Studies 107, 108, 109



Data on file

Reduction In Hepatic Iron Loading



Magnification x10; Prussian blue staining

Exjade 30 mg/kg/day

- Female (28 years)
- LIC decreased from 16.2 to 3.3 mg Fe/g dw
- Average iron intake during study: 0.37 mg/kg/day
- Medical history: splenectomy, hepatitis C

Deferoxamine 56 mg/kg/day

- Male (18 years)
- LIC decreased from 18.4 to 5.2 mg Fe/g dw
- Average iron intake during study: 0.35 mg/kg/day
- Medical history: splenectomy

Cappellini M, et al. Presented at ASH 2004

Efficacy of Exjade

- 20 mg/kg/day maintains Liver iron content
  - Comparable to DFO 35-50 mg/kg/d
- 30 mg/kg/day reduces Liver Iron constne
  - Comparable to DFO ≥50 mg/kg/d
- The rate of transfusional iron loading has an important effect on the outcome of chelation therapy

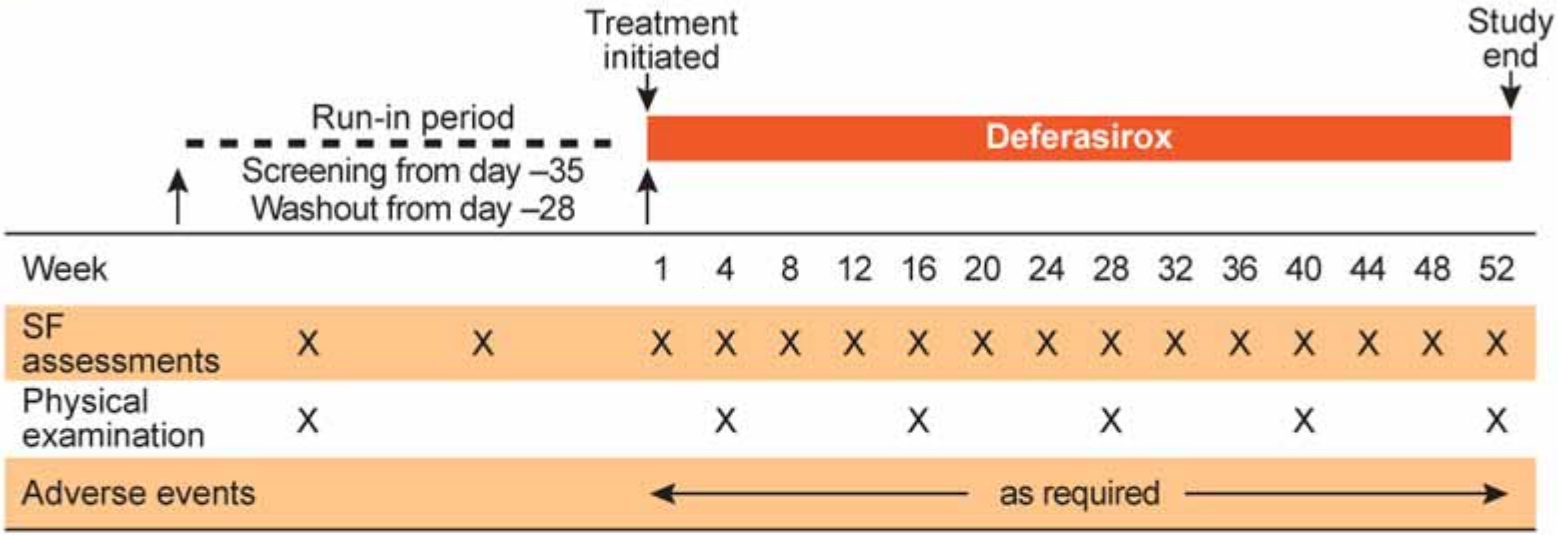
EPIC Study

Aim: To evaluate whether fixed starting doses of deferasirox, based on transfusional iron intake with subsequent dose titration, can provide clinically acceptable chelation, as measured by serum ferritin (SF), to iron overloaded patients with various transfusion-dependent anemias

- **1744 patients enrolled (β-thalassemia, n=1115; myelodysplastic syndromes [MDS], n=341; sickle cell disease [SCD], n=80; aplastic anemia (AA), n=116; other conditions associated with anemia, n=92)**

Cappellini et al. *Blood* 2008;112(11). Abstract #3875.

MDS in EPIC: Study Design



Efficacy Evaluation

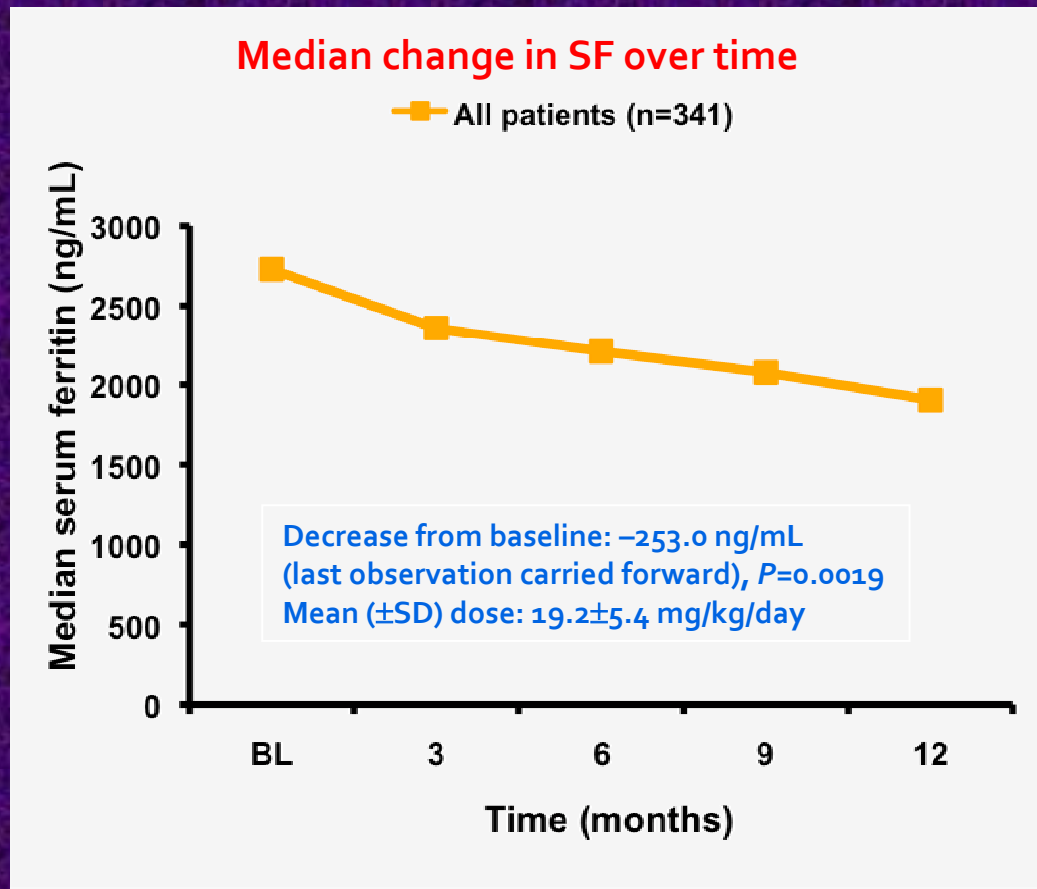
- Primary endpoint: change in SF from BL to 52 weeks
- SF assessed at BL and every 4 weeks thereafter

Safety Evaluation

- Monitoring and recording of all adverse events, serious adverse events, and routine laboratory assessment

Results From EPIC Trial [#633] Gattermann *et al*. Efficacy and Safety of Deferasirox (Exjade®) During 1 Year of Treatment in Transfusion-dependent patients with Myelodysplastic Syndromes:

- 341 MDS patients enrolled
- 48.4% received no prior chelation therapy; 40.2% previously received DFO, 4.1% deferiprone, 7.0% combination DFO/deferiprone, 0.3% other therapy
- Mean transfusion duration: 3.6 years
- Patients received a mean of 116.4 mL/kg of blood in the year prior to study entry



Gattermann et al. *Blood* 2008;112(11). Abstract #633.

MDS in EPIC: Adverse Events With Deferasirox*

Adverse Event	Total,† n (%)
Diarrhoea	110 (32)
Nausea	45 (13)
Vomiting	26 (8)
Abdominal pain	26 (8)
Upper abdominal pain	25 (7)
Rash	23 (7)
Constipation	21 (6)

- 95% of these adverse events were mild to moderate

* Drug-related and investigator-assessed adverse events.
† N = 341.

Efficacy and Safety of Deferasirox (Exjade®) in Myelodysplastic Syndromes: Results From EPIC Trial

- 48.7% discontinued therapy, primarily due to AEs (22.9%)
  - 44 (13%) due to drug related side effects
    - 17 (5%) due to drug related GI side effects
- No treatment related deaths
- Eighty-five patients (24.9%) had an increase in serum creatinine >33% above baseline and ULN on two consecutive visits; there were no progressive increases

*Drug-related as assessed by the investigator

Gattermann et al. *Blood* 2008;112(11). Abstract #633.

Efficacy and Safety of Deferasirox (Exjade®) in Myelodysplastic Syndromes: Results From EPIC Trial

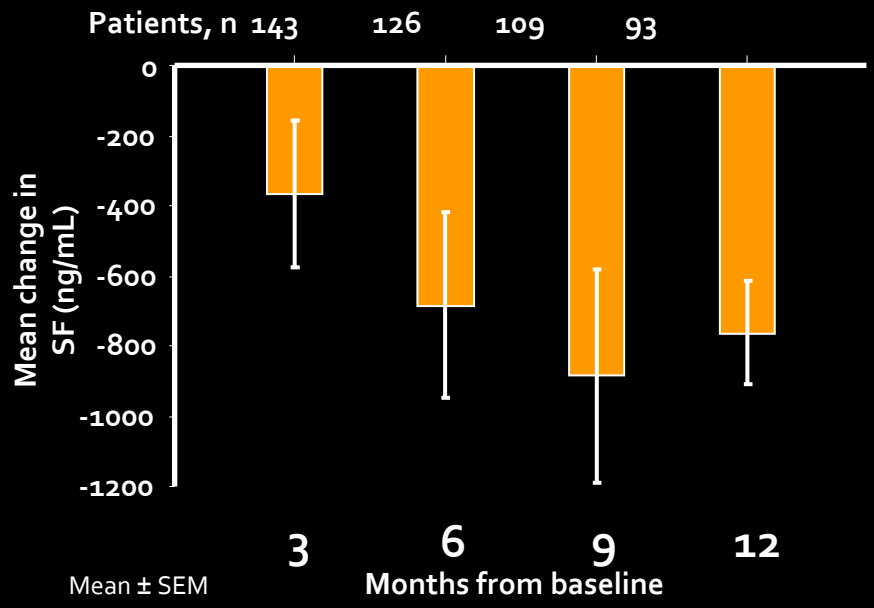
Summary:

- In this large cohort to MDS patients, deferasirox provided significant reduction in iron levels over 1 year treatment with appropriate dose adjustments every 3 months
- The safety profile and discontinuation rates were consistent with previously reported data in MDS patients

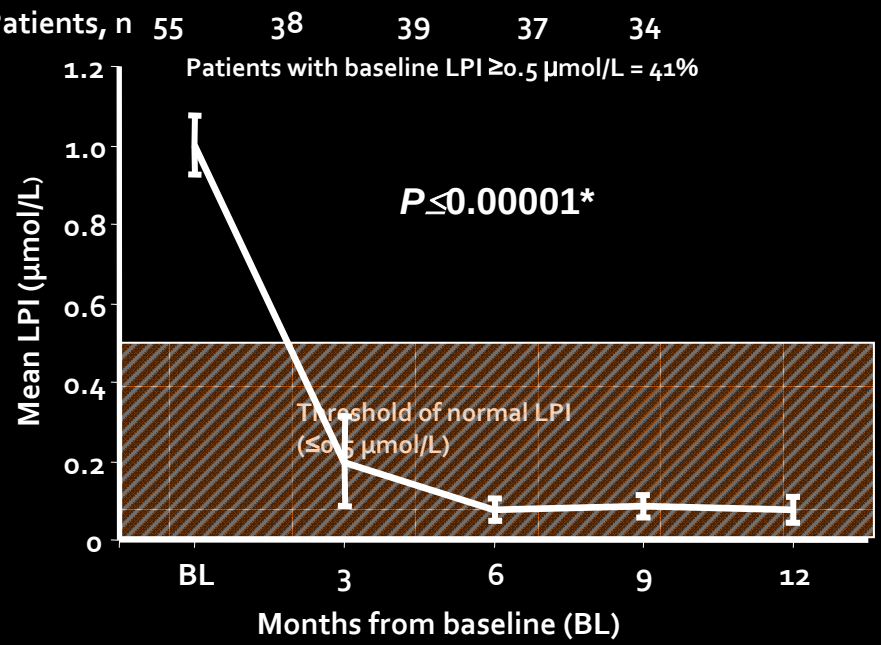
Gattermann et al. *Blood* 2008;112(11). Abstract #633.

List *et al*. Iron Chelation with Deferasirox (Exjade®) Improves Iron Burden in Patients with Myelodysplastic Syndromes (MDS) [oral #634]

Changes in SF and LPI over 12 months of therapy with deferasirox



P=0.0000015 (Baseline vs 12 month)



*Comparison of baseline LPI versus each treatment time point

- US03 study data - 93 out of 176 patients with Low/Int-1-risk MDS treated with deferasirox over 1 year

Summary: Deferasirox was effective in reducing SF and LPI in patients with Low-/Int-1-risk MDS

List et al. *Blood* 2008;112(11). Abstract #634.

Exjade Dosing

	Goal of daily therapy	
Transfusional rate	Maintain iron balance	Reduce iron burden
Low ≤ 2 units/month	10 mg/kg	20 mg/kg
Medium 2-4 units/month	20 mg/kg	30 mg/kg
High > 4 units/month	20 mg/kg	30 mg/kg

Proposed management strategies for side effects

- Diarrhea (8.8%): take in evening, keep hydrated, avoid lactose, use immodium or codeine
- Abdominal Pain (5%): sip water or clear fluids, avoid narcotics and NSAID, take in evening
- Skin rash: mild to moderate 4.3%: continue; If severe (0.4%) stop and resume at lower dose with or without steroids
- Eye and Ear (< 1%): assess yearly
- Liver function (2%): monthly, may need dose adjustment
- Kidney function (36%): 2 baseline assessments; weekly if impaired at baseline for first month then monthly. Otherwise monthly
  - If progressive increase to > 33% baseline (11%o: discontinue then resume at lower dose and increase cautiously

Recommended Monitoring on Exjade

Test	Frequency
Creatinine	Baseline, monthly
Ferritin	Baseline, monthly
Liver function	Baseline, monthly
Auditory/ophthalmic	Baseline, yearly

Availability of Deferasirox

- Health Canada approval received Oct 06
  - chronic iron overload in patients with transfusion-dependent anemias aged 6 years old and older.
  - chronic iron overload in patients with transfusion-dependent anemias aged 2 to 5 years old who cannot be adequately treated with deferoxamine

- Provincial formularies reimbursements vary for Deferasirox.

Who should be chelated

Management of IOL
Guidelines for Iron chelation in MDS

- Italian Society of Hematology (2002)
- United Kingdom MDS guidelines (2003)
- Nagasaki Consensus Statement (2005)
- National Comprehensive Care Network (2007)
- Canadian Consensus Guidelines (2008)
- Japanese guidelines (2008)
- Consensus statement (2008)
- Austrian guidelines (2008)
- Israeli Guidelines (2008)
- MDS Foundation International Guidelines (in dev)
- European LeukemiaNet Guidelines (in dev)

Canadian Guidelines 2007

- **Why:** to prevent end-organ complications of iron overload and extend lifespan
- **Whom:** transfusion-dependent patients with expected survival > 1 year *or* BMT candidates
- **When:** ferritin >1000, TfSat > 0.5
- **How:** DSX 20 mg/kg/d or DFO 50 mg/kg/d 5/7; target ferritin<1000

Guidelines - Indications for ICT

- Ferritin ≥1,000 ng/mL
- 2 RBC units/mo for at ≥ 1y
- no erythroid response to primary Rx or ineligible
- Pts in whom transplant is imminent
- Not pts with expected survival <1y
- Consider earlier in pts with compromised organ function
- IOL not always dependent on transfusion burden

mds foundation
the myelodysplastic syndromes foundation, inc.

Price vs Desferal

	Dose (mg/kg)	Body weight (kg)	Doses per week	Annual cost of drug	Annual cost of supplies *	Annual cost
Desferal	40	50	5	$13,650	$7,100	$20,750
Desferal	40	50	7	$19,110	$7,100	$26,210
Exjade	20	50	7	$28,756	$0	$28,756

*Average yearly cost over 3 years (including pump and nursing time)

Conclusions

- Iron overload is common in MDS do to blood transfusions and is linked to increased heart disease, diabetes and premature death
- There is evidence that MDS patients who get chelated live longer
- There are 2 effective chelators available in Canada
- Exjade is preferred by most patients do to convenience