



Iron and Iron Overload in Myelodysplastic Syndromes (MDS)



 Aplastic Anemia & MDS International Foundation, Inc.
Fighting Bone Marrow Failure Diseases Through Patient Support & Research Since 1983
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"Thumbprinted" iron meteorite (Group IIAB)
 from the Sikhote-Alin fall, eastern Siberia, 1947
 (Steensma collection)

Blood Transfusions: The Good...



- Improves "oxygen carrying capacity" of blood
- Improves patients' ability to function
- RBCs can be given more or less indefinitely
- In AA/MDS, the "backup" when other treatments fail
- Benefit for donors: sense of altruism

... and the Bad



- Time-consuming
- Costly
- Small but real infection risk and associated fears
- Risk of transfusion reaction (febrile, allergic)
- Alloimmunization
- Each unit of blood carries ~250 mg elemental iron

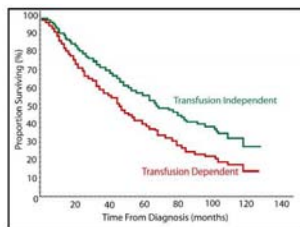
Incidence of RBC Transfusion Dependence In MDS

IPSS Category	Proportion RBC Transfusion Dependent
Low Risk	39%
Intermediate-1 Risk	50%
Intermediate-2 Risk	63%
High Risk	79%

28% in this survey (30 practices) were receiving chelation

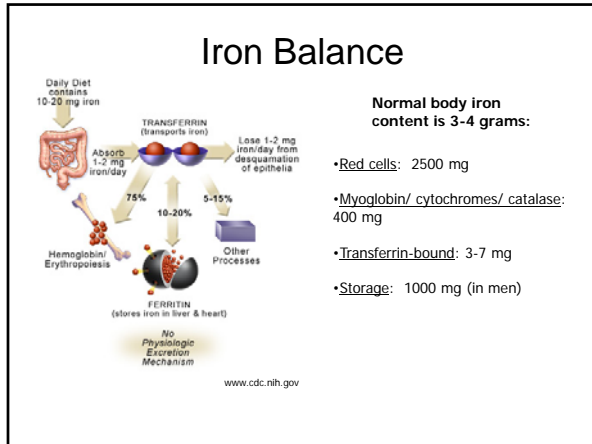
Brechignac S et al *Blood* 2004 104:236b (abstract 4716)

The Risk Of Transfusion Dependence In MDS



Cumulative Probability of Survival among 374 MDS Patients at Pavia, Italy, 1992–2002 (transfusion hazard ratio for death, 1.58; P=0.005).

Redrawn by DPS from Cazzola M and Malcovati L *NEJM* 2005; 352:536.



Normal body iron content is 3-4 grams:

- Red cells: 2500 mg
- Myoglobin/ cytochromes/ catalase: 400 mg
- Transferrin-bound: 3-7 mg
- Storage: 1000 mg (in men)

Ways To Augment Iron Overload

1 unit pRBCs = 200-250 mg Fe

"Medicinal" and vitamin-based exogenous iron (also vitamin C, A with iron)

Alcohol, especially iron-fortified wines (rare)

Steak: 1.73 mg Fe per 100 grams (3.5 ounces)

Ways To Decrease Net Iron...

Bleeding (trauma or medical bleeding)
Loss: variable

Menses
Loss: 15-20 mg/ period

Pregnancy
Net loss: 1000 mg (despite 9 months Amenorrhea)

Blood donation

More Ways To Decrease Net Iron

Malabsorb iron (e.g., sprue)

Abuse antacids

Eat only foods without much iron

Drink lots of tea and eat dark chocolate (polyphenols inhibit)

Eat only non-heme iron

Hemosiderosis

- Iron deposits in various tissues, causing damage

Netter Ciba collection 1957

Diagnosis of Iron Overload

Serology: Ferritin, Transferrin Sat.

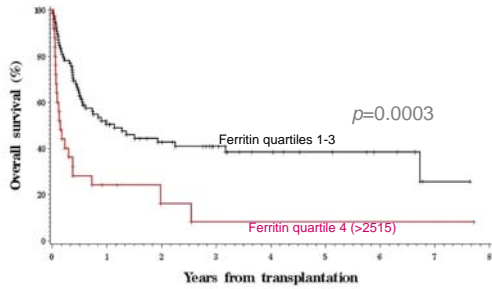
Liver biopsy: A small slender core of tissue is removed with a biopsy needle.

R2* MRI (Ferriscan™)

Category	Liver Iron Concentration (LIC)
Normal	< 6 mg/g
Mild iron overload	7.7 mg/g
Moderate iron overload	13.4 mg/g
Heavy iron overload	34.3 mg/g

©Peters T et al Blood 2005;105:654

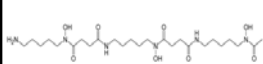
Overall Survival After Transplantation:*
Based on pre-transplant serum ferritin



Armand P, et al. *Blood*. 2007;109(10):4586-88.

* In MDS patients

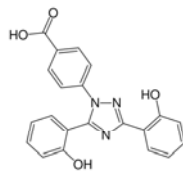
Iron Chelation Options



Deferoxamine (Desferal™)



Injectable – 8 to 12 hours
overnight 5-7 nights per week

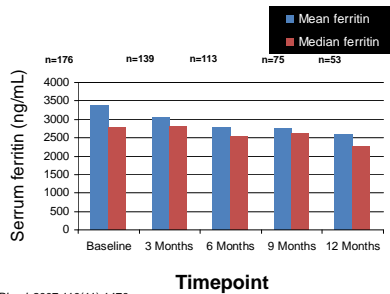


Deferasirox (Exjade™)



Oral – once daily

**Deferasirox US03 Study:
Reduction in Ferritin During Study**



List AF, et al. *Blood*. 2007;110(11):1470a.

Risks of Iron Chelation



- No proven benefit from iron chelation in AA/MDS
 - But benefit is well defined in congenital anemias like thalassemia
 - We worry about treating numbers rather than patients
- Deferoxamine:
 - Inconvenient (nightly pump)
 - Risk of cataracts/sensorineural deafness
 - Infections
 - Renal injury from overchelation
- Deferasirox:
 - Rash, mild gastrointestinal effects (diarrhea, nausea)
 - Need for periodic eye and auditory evaluations
 - Possibly liver injury
 - Renal injury

There is No Role for DFO “Chasers” After Transfusion

- Dynamics of iron chelation mean that it is ineffective



The Quaffer – a patented shot glass with a built in chaser

Clinical Guidelines



- Many organizations have guidelines for iron monitoring and iron chelation in MDS
 - At least 8 different ones in the last 10 years
 - Only partially evidence-based
- In general, these guidelines suggest:
 - Periodic ferritin monitoring, supplemented by other techniques for assessing iron burden
 - Consideration of iron chelation when patient has ferritin >1000 ng/mL or other evidence of iron overload, and lower-risk MDS
 - Start thinking about iron overload after 20-50 units RBCs

Questions about iron?