Iron Overload in MDS

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Iron Homeostasis

WHAT?!?!@!!!??!!
You're kidding…

Controversial and difficult topic…

The answers are not obvious!

Farquhar and Bowen, Int J Hematology 77:342, 2003
Iron Metabolism

• Normal iron balance: absorption in the intestine from diet (1-2 mg/day) and recycling from the hemoglobin of dying red blood cells (done by macrophages, 20 mg/day)
• Iron enters plasma, complexes with transferrin
• Transferrin-bound iron supplies red cells, liver cells and muscle cells
• Inside cells, iron complexes with ferritin, a large protein
• There is a small proportion of ferritin found in the blood

Porter, J. Pathophysiology of iron overload. Hematol/Oncol Clin N Am

Iron Metabolism, cont.

• When there is excess iron, transferrin gets saturated
• Increased NTBI (non-transferrin-bound iron)
• This is the bad stuff that damages tissues and organs

Causes of Iron Overload

• Hereditary
  – HFE hemochromatosis
  • Homozygous C282Y mutation in HFE gene
  • Defective regulatory receptor in intestine
  – Other genetic mutations
• Acquired (secondary) iron overload
  – Transfusional
  – Ineffective erythropoiesis
  – Toxic ingestion (rare)
Diseases Associated With Chronic Iron Overload Due To Blood Transfusions

- β thalassemia (major and intermedia)
- Sickle cell anemia
- Aplastic anemia
- Myelodysplastic syndromes (pts also have increased intestinal absorption due to ineffective hematopoiesis)
- Congenital chronic anemias
  - Fanconi’s anemia (hypoplastic anemia)
  - Blackfan-Diamond anemia (red cell aplasia)
  - Congenital dyserythropoietic anemias

Iron Loading From Blood Transfusions

- 1 unit of blood contains approximately 200 – 250 mg of iron
- Transfusion-dependent patients have iron excess of ~ 0.4 – 0.5 mg/kg/day
- With repeated infusions, iron accumulates

Moderate transfusion requirement:
- 2 units / month
- 24 units / year
- ~ 100 units / 4 years

High transfusion requirement:
- 4 units / month
- 48 units / year
- ~ 100 units / 2 years

100 units ≥ 20 g iron
Normal body iron: 3-4 g

Courtesy of E. Rachmilewitz
Excess Iron is deposited in multiple organs, resulting in organ damage

Iron overload
Capacity of serum transferrin to bind iron is exceeded

NTBI circulates in the plasma; Labile forms of NTBI (e.g. LPI) enter cells and raise the levels of labile cell iron (LCI)

Chelation aims:
- preventing LPI formation
- & LCI accumulation

Excess iron promotes the generation of free hydroxyl radicals, propagators of oxygen-related tissue damage

Irreversible damage occurs

Insoluble iron complexes are deposited in body tissues and end-organ toxicity occurs

Cardiac failure  liver cirrhosis/ fibrosis/cancer  Diabetes mellitus  infertility  infarcted kidneys  growth failure

Liver biopsy – Gold standard for kids, not feasible in most MDS

Magnetic resonance imaging (MRI) – Investigational, potential for broad access
- T2* cardiac MRI

Magnetic susceptibility (SQUID) – Investigational, very limited access

Ok, so how do we know if there’s too much iron?

Assessing Iron Overload

- Serum ferritin concentration
  – Used in clinical practice globally
- Liver biopsy
  – Gold standard for kids, not feasible in most MDS
- Magnetic resonance imaging (MRI)
  – Investigational, potential for broad access
  – T2* cardiac MRI
- Magnetic susceptibility (SQUID)
  – Investigational, very limited access
Magnetic Susceptometry (SQUID)

- Superconducting QUantum Interference Device
  - High-power magnetic field
  - Iron interferes with the field
  - Changes in the field are detected
- Noninvasive, sensitive
- Limited availability
  - Superconductor requires high maintenance
  - Only 4 machines worldwide

Photograph courtesy of A. Piga

Serum Ferritin Concentration

- Relatively noninvasive
- Inexpensive
- Useful for tracking changes in iron status over time
- Changes are confounded by
  - Inflammation (acute phase reactant)
  - Liver function abnormalities

Complications of iron overload: keep in mind...

- Most of the data are from children with thalassemia: severe anemia, chronic transfusions starting at age 1
- Iron-related heart disease most common cause of death
- Clear evidence that chelation with deferoxamine improved survival and helped liver and endocrine complications
Deferoxamine (Desferal®)

- Most clinical experience, dosing and administration well-known
- Reduces morbidity and mortality for sure in kids with thal, less clear in adults

Challenges of therapy
  - Subcutaneous or IV administration
  - Continuous 12-hour infusion 5 - 7 days/week rec'd
  - Infusion-site reactions and pain
  - Eye and ear side effects, need periodic exams
  - Infectious complications
  - High degree of noncompliance

- Survival correlated with compliance

Deferasirox (Exjade®)

- No studies directly comparing to deferoxamine
- Oral, taken once daily
- Effectively chelates
- Studied in > 700 adult and pediatric patients with transfusion-dependent anemia (data most limited in MDS, studies ongoing)
- Nausea, vomiting, diarrhea, rash, increased liver function tests
- Several instances of renal failure, have to watch in patients with abnormal renal function
- VERY expensive

The $6 billion question

- Does this mean iron overload is bad for everyone and chelation (treatment to get rid of iron) is good for everyone at risk of iron overload?
What do we know about clinical consequences of iron overload in non-thalassemic adults?

- Several studies suggest iron overload contributes to cardiac, liver and endocrine dysfunction in adults with MDS, but mainly small and retrospective.
- Also, although some laboratory abnormalities were found, not clear how clinically important they were.
- No prospective data comparing age-matched subjects from the general population to confirm the associations of these findings to iron overload.

MDS Outcome and Transfusion Burden: Univariate Analysis

![Graph showing survival time in months against cumulative proportion surviving.](image)

Malcovati, L. / Haematologica 2006;91:1588

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


(Spanish Registry of MDS)

50th Annual Meeting of the American Society of Hematology
San Francisco, CA, December 8, 2008
Patients & Methods

- Retrospective multicenter study
- 2,994 patients with de novo MDS according to FAB criteria (2,207 MDS according to WHO 2001 criteria)
  - Transfusional record in 2,241 (75%)
  - Successful karyotyping and IPSS in 2,074 (69%)
  - WPSS in 1,228 (41%)
  - Serum ferritin levels in 1,634 (55%)

Overall Survival
By RBC transfusion dependency (n = 2,241)

Leukemia-Free Survival
By RBC transfusion dependency (n = 2,241)
**BUT...**

- Limited evidence showing that iron causes clinically significant organ damage in MDS patients
- Unclear how to measure iron overload (ferritin, transferrin saturation, NTBI, liver biopsy, SQID, liver MRI, cardiac T2* MRI)
- No prospective data demonstrating that chelation improves survival
- Unclear which chelator to use (deferoxamine, deferiprone, deferasirox) and how to measure efficacy

**Critical questions...**

- Does iron overload shorten survival in MDS? Maybe
- Does iron overload hasten transformation to leukemia? Maybe
- Does iron overload worsen hematopoiesis? Maybe
- Does iron overload worsen outcomes of stem cell transplantation by increasing infections and/or VOD? Probably
- Does chelation treatment get rid of excess iron? Seems to

**So, now what do I do? Consider...**

- Transfusion-dependent patients with IPSS low or int-1 MDS (or WHO RA, RARS, 5q syndrome)
- Life expectancy > 1 year
- Serum ferritin > 1000 µg/L or evidence of iron-related organ damage; target serum ferritin < 1000
- Higher risk MDS patients who are candidates for stem cell transplant
- Deferoxamine or deferasirox with close clinical and lab monitoring
- Don’t just use deferoxamine at times of transfusion
Most importantly…
Let’s get more information
Participate in clinical trials!!!