Supportive care and chelation therapy in MDS: ARE WE SAVING LIVES OR JUST LOWERING IRON?

Leitch HA and Vickars LM. ASH education-2009:664-672
Dietary iron

Duodenum (average, 1–2 mg per day)

Utilization

Plasma transferrin (3 mg)

Muscle (myoglobin) (300 mg)

Liver parenchyma (1000 mg)

Storage iron

Circulating erythrocytes (hemoglobin) (1800 mg)

Bone marrow (300 mg)

Reticulo-endothelial macrophages (600 mg)

Utilization

Sloughed mucosal cells
Desquamation
Menstruation
Other blood loss (average, 1–2 mg per day)

Iron loss

Andrews N. C., 1999
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: \( \geq 20 \text{ g iron} \)

Normal body iron: 3-4 g
When physiological iron ligands (transferrin and ferritin) are saturated, 

FREE IRON SPECIES ARE GENERATED.
NTBI/LPI in serum/plasma

• In normal conditions all plasma iron is virtually bound to transferrin

• When plasma iron rises and surpasses transferrin’s iron binding capacity (at >70% saturation), it appears as NTBI (non transferrin bound iron).

• The forms of NTBI that are redox-active, chelatable and permeant to cells (via unregulated pathways) are collectively referred as labile plasma iron (LPI)

• Excessive ingress of LPI into cells leads to a rise in labile iron pool (LIP), attaining toxic levels

• LIP can engage in the formation of production of reactive O species (ROS) by catalyzing the formation of noxious OH· radicals

• LIP (Fe³⁺ and Fe²⁺) reacts with reactive O intermediates (O₂⁻ and H₂O₂ produced by respiration and other incomplete reductions of O₂) forming OH· radicals (Haber Weiss cycle)
  
  • Fe³⁺ + O₂⁻ → Fe²⁺ + O₂
  • Fe²⁺ + H₂O₂ → Fe³⁺ + OH· + OH⁻ (Fenton reaction)

Sustained levels of LIP impose a persistent oxidative stress

Courtesy of Professor IV Cabantchik
LPI appears as Tf saturation raises beyond 85%

85% Tf sat is a threshold level beyond which
Where and how does labile iron cause cell damage?

1. 33 g of ROI = reactive oxygen intermediates produced per day*

ROI are normally converted to water by resident enzymes SOD and GPX

2. LPI present in systemic iron overload leads to accumulation of labile iron pool (LIP)

3. ROI react with LPI producing noxious ROS, e.g. OH· radicals

4. OH· radicals are highly reactive and they can modify DNA, proteins and lipid components of cells

* Up to 3Kg ROI/d in inflammation!
LPI can be taken up into cardiac, endocrine and hepatic tissue.

- Uptake of LPI into liver cells leads to iron overload (IO), liver fibrosis, cirrhosis and carcinoma.
- Uptake of LPI into cardiac cells leads to atrial IO, cardiac arrhythmia and arrest.

Chelation of labile iron from cellular and extracellular sources is needed in order to reduce body iron overload and overcome iron toxicity.
NTBI levels in samples from normal individuals and MDS patients.
ROS generation by peripheral blood cells in MDS

Peripheral blood cells were stained with DCF

(A) Forward scatter (FCS) vs side scatter (SSC) dot plot. The gates indicate platelets (R1), RBC (R2), monocytes (R3), and PMN (R4)

(B–D) Histograms showing DCF fluorescence of platelets, RBC, and PMN of a normal donor (white) and of a patient with MDS (grey)

The mean fluorescent channel (MFC) of each population is indicated


DCF = 2’-7’-dichlorofluorescin diacetate; PMN = polymorphonuclear leukocytes.
Oxidative Stress Mechanisms in MDS

Farquhar and Bowen, Int J Hematology 77:342, 2003
STRUCTURE OF CHELATOR-IRON COMPLEXES

Deferoxamine
Hexadentate

Deferiprone
Bidentate

Deferasirox
Tridentate
Membrane-permeable iron chelators, such as deferiprone, can shuttle iron within the cell between endosomes (e), mitochondria (m), the nucleus, and the cytoplasm. Chelator-mediated mobilization of the metal from iron-overloaded organelles or cellular deposits reduces the local formation of toxic hydroxyl-radical and results in transport of the iron across membranes, delivery of the metal to transferrin, and subsequent transferrin receptor (TfR)—mediated acquisition of iron by erythroid progenitor (ep) cells to be used for heme biosynthesis.
Effects of monotherapy and combined therapy on LPI

Each colour represents LPI values of individual patients starting at 8AM and followed for the next 24 hours.

Changes in mean levels ±SD of (A) LIP in RBC and platelets (n=18), and (B) LPI (n=16)
Changes in mean levels of GSH in RBC, platelets and PMN, and ROS and lipid peroxidation in RBC

Cell fluorescence (MFC) is proportional to ROS and GSH but inversely proportional to lipid peroxidation.
Overall survival of low and intermediate-1 IPSS risk in 97 MDS patients according to intensity of iron chelation therapy. Median survival was 124 months in the adequately chelated patients – 85 months in those receiving weak chelation and 51 months in non-chelated patients – p< 0.01

(Rose C. et al, Leukemia Research 2010; 34(7):864-870)
Impact of iron chelation therapy prior to hematopoietic stem cell transplant (SCT) outcome. Improved survival in 74 patients was superior compared with 26 unchelated patients with SF>1000ng/ml prior to SCT.

Lee JW, et al. BMT 2009;44:793-797
(a) Overall survival and (b) treatment-related mortality in patients with myelodysplastic syndromes or acute leukaemia undergoing allogeneic stem cell transplantation according to serum ferritin level. Those with ferritin in the highest quartile had significantly inferior survival (p < 0.001) and treatment-related mortality (p = 0.005) [adapted from Armand et al.,[118] with permission from the American Society of Hematology].
Median serum ferritin in patients who completed 12 months of deferasirox versus baseline

Mean labile plasma iron over 12 months in patients with abnormal LPI at baseline

A.F. List et al. 2012
Hematologic Response rate on Deferasirox Therapy in Lower Risk MDS Patients with Iron overload

- Erythroid response: 15%
- Neutrophil response: 15%
- Platelet response: 22%

Median time to hematologic Response 169 days

A.F.List et al 2012, JCO
CONCLUSIONS

1. Several retrospective studies demonstrate prolonged overall survival in chelated vs. unchelated patients with low risk MDS (Malcovatti, Rose, Gattermann, Leitch)

2. Similar results were reported in chelated vs. unchelated MDS patients undergoing SCT

3. There might be a potential role of iron chelation in the treatment of AML and MDS by: a) Inhibition of tumor cell proliferation; b) inducing stem cell differentiation
HOWEVER
The main toxic effect of I.O. in LOW RISK MDS (RA, RARS) is due to the presence of toxic free iron species: NTBI, LPI and LIP generating formation of ROS
Therefore, free iron species should be eliminated (Irrespective whether the data that iron chelation prolongs survival are still statistically insignificant)