Iron Overload in Bone Marrow Failure

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Ottawa, October 16, 2010
Iron Overload in Bone Marrow Failure: Questions and Answers

- How is iron regulated in the body?
- How does iron overload occur?
- Why is too much iron bad?
- How can we tell if there is too much iron?
- How do we get rid of excess iron?
- What are the guidelines for chelation therapy in MDS?
- Why don’t all physicians offer chelation?
- Future directions
Case presentation: M. S.

- June 2007: 77 yr old female
- 1 yr Hx anemia and macrocytosis
- Transfused intermittently (outside institution)
- 4 mos. Hx SOB, fatigue, unable to do ADL
- Refused to undergo marrow asp/ bx, agreed to transfuse if Hb < 90 due to CAD
Case presentation cont’d

- October 2007: FU visit: agreed to marrow biopsy (apply for ESA), prescribed Exjade (ferritin 1319)
Case presentation cont’d

DOB: 29APR02    SEX: FEMALE
DOCTOR: FORGIS MA
ENCOUNTER NO. 48656221

ADMITTED: 2007/10/09    DISCH: 2007/10/19    AC    PAGE: 2

DIAGNOSIS:
Bone marrow aspirate:
- Myelodysplastic syndrome.
- Refractory anemia with ringed sideroblasts (RARS).

JB /cas
Verified by: J. Bormanis, M.D., FRCP (Electronic signature)
Verified date: 07/10/15

Cytogenetics normal

Comment
There are no comments associated with this test
Case presentation cont’d
Feb. 2010: severe CHF, admits to never taking Exjade consistently (explains erratic ferritin, dose increases limited by kidney function)

T2* cardiac MRI signal 7.2

Prescribed DFO with transfusions and daily sc infusion through homecare
Case presentation cont’d: clinic note July 2010

advanced myelodysplasia, which has been complicated by transfusional associated iron overload. She developed congestive heart failure and was placed on home care for subcutaneous Deferoxamine infusions. She has had significant improvement in her cardiac symptomatology and her iron indices have improved significantly, with her Ferritin decreasing from 4000 to currently 1900. She is only being transfused approximately every two to three months and was transfusion free between February and June. Her most recent blood work shows hemoglobin of 90, white cell count of 11.4, platelet count of 192, a neutrophil.
How is iron regulated in the body?
Iron metabolism: homeostasis

- **Utilization**
  - Duodenum (average, 1-2 mg per day)
  - Muscle (myoglobin) (300 mg)
  - Liver (1,000 mg)

- **Storage iron**
- **Loss**
  - Sloughed mucosal cells
  - Desquamation/Menstruation
  - Other blood loss (average, 1-2 mg per day)

- **Dietary iron**
- **Plasma transferrin** (3 mg)

- **Utilization**
  - Bone marrow (300 mg)
  - Circulating erythrocytes (hemoglobin) (1,800 mg)
  - Reticuloendothelial macrophages (600 mg)
Iron uptake from macrophages for red blood cell synthesis
How does iron overload occur?

Iron overload

primary

Genetic: imbalance in metabolism

Hemochromatosis

secondary

Bypass normal homeostasis: transfusion, iron poisoning

Transfusion

Iron poisoning

MDS

Sickle cell/thalassemia

AA
How does iron overload occur?

- Each unit of blood contains approximately 250 mg of iron.
- That means an excess of 500 mg of iron with a 2 unit transfusion.
- Recall the body can excrete about 1-2 mg per day; each unit is 10X amount the body can excrete.
- Recall the body is good at storing iron.
Transfusion burden

Unit \times 20 = \text{Transfusional iron overload}

As few as 20 units of blood, transfused over a lifetime, can result in transfusional iron overload.

Organs that may be affected by iron overload:
- Placental gland
- Thyroid and parathyroid gland
- Adrenal gland
- Heart and circulation
- Liver
- Pancreas
- Testes
- Man
- Woman
- Ovary

Toxic iron builds up across the body and can cause serious damage to vital organs, including the heart and liver.
Why is too much iron bad?

- In addition to accumulation in organs which causes organ dysfunction, when transferrin saturation exceeds 75%, non-transferrin bound iron (NTBI) appears and leads to formation of labile plasma iron (LPI) and reactive oxygen species (ROS).
- LPI and ROS are directly toxic to tissues.
Consequences of iron overload

- Liver
- Immune
- Musculo-skeletal
- Endocrine
- Heart

Cellular damage
Okay, so it looks like too much iron may be a bad thing but show me the evidence...
Figure 1. Survival of patients with myelodysplastic syndrome (MDS) according to the severity of transfusion requirement; overall survival is shown in the left panel and leukemia-free survival on the right.

Figure 2. Overall survival of transfusion-dependent patients with myelodysplastic syndrome (MDS) according to ferritin level

How can we tell if there is too much iron?

- Start screening after 20 units
- Typically done with simple blood tests at first: serum transferrin saturation (> 45%), serum ferritin (>1000 ng/mL)
Pitfalls of blood tests

- Depending on cutoff for transferrin saturation
- Ferritin elevated with inflammation, excess alcohol, other liver diseases
- Discordance between ferritin and iron overload
Figure 2.

Olivieri, N. F. et al. Blood 1997;89:739-761
Screening and diagnosis of iron overload

- Blood tests
- Direct measurement: liver (LIC), cardiac biopsy
- Imaging: MRI, T2*MRI, SQUID, echo, radionuclide ventriculography
Olivieri, N. F. et al. Blood 1997;89:739-761
Liver and cardiac biopsy

- LIC: gold standard
- LIC > 15: high risk of cardiac complications and death
- LIC > 19: cirrhosis, fibrosis
- LIC used to guide chelation therapy and dosing
- Invasive, acceptable in BTM but not MDS (co-morbidities, cytopenias)
- Sampling errors
- Variability between labs
- Cardiac more invasive
Imaging

- R2 (T2*) MRI liver: non-invasive, evaluates entire organ

- T2* MRI: standard for cardiac iron
Superconducting Quantum Interference Device (SQUID)

- Low power magnetic field
- Measures iron interference with the field
- Sensor requires cryogenic environment
- Only 5 world-wide: none in Canada
- Piga et al., Blood, 2005 (abs)
T2* cardiac MRI and R2 liver
MRI General Campus
Ferriscan®

- Wider range of LIC than conventional T2* MRI
- May not be necessary for shorter term chelation but will allow for more precise titration of chelation
- Available at CHEO soon
Echo and radionuclide scanning

- Non invasive
- Widely available
- Diastolic dysfunction prognostic value
- Abnormalities develop late: T2*MRI earlier detection
- Measurement of LVEF superior with radionuclide angiography
Liver versus heart: predictors?

- No correlation
- Cardiac iron clearing 6X more slowly
- Cardiac dysfunction with low liver Fe
- LIC > 15 predictive of cardiac disease, early death (Anderson, Eur Heart J., 2001)
- Lower rates of cardiac iron deposition in MDS than with BTM (higher transfusion burden needed; 75-100 units)
Figure 4.

Olivieri, N. F. et al. Blood 1997;89:739-761
# Comparison of methods for assessment of iron overload

<table>
<thead>
<tr>
<th>Method</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum ferritin</td>
<td>Non-invasive, inexpensive, rapid, Longitudinal FU</td>
<td>Indirect, Poor correlation with gold standard, Varies by etiology</td>
</tr>
<tr>
<td>Liver biopsy:</td>
<td>Reference standard, direct measurement, correlates with morbidity and mortality</td>
<td>Invasive, painful, requires skilled personnel, may not be representative, of entire organ, difficult to FU, risky in some MDS patients</td>
</tr>
<tr>
<td>LIC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td>Non-invasive, whole organ, more available than LIC, longitudinal FU, T2* gold standard for cardiac imaging: Ferriscan®</td>
<td>Indirect measure, sedation for children or those with claustrophobia, specialized software</td>
</tr>
<tr>
<td>SQUID</td>
<td>Non-invasive, linear correlation with LIC</td>
<td>Limited availability, costly, complex, may underestimate LIC</td>
</tr>
</tbody>
</table>
Measurement of iron: liver versus heart

Liver
- LIC
- MRI R2 (T2*)
- SQUID
- Ferriscan®

Heart
- LVEF
- MRI T2*
Canadian Consensus Guidelines for chelation in MDS

- Ferritin > 1000
- Transferrin saturation > 50%
- 2 units RBC per month > 1 yr
- No response to primary treatment or ineligible
- Imminent transplant
- Survival > 1 yr
- Compromised organ function
Who should be offered chelation?

- Low to int 1 MDS
- Pre and post BMT
- Consider in higher risk MDS
- No clear data for AA; extrapolate from MDS data
Treatment of iron overload
Treatment of iron overload: based on mechanism of iron distribution

Hemochromatosis:
- gradual
- more in parenchyma, less in macrophages
- phlebotomy
- intermittent

Transfusional iron overload:
- anemia has already reduced RBC iron pool
- sudden
- increased NTBI
- morbidity greater than primary iron overload
- chelation
- constant
How does chelation work?

Iron chelation – getting rid of toxic iron

Toxic iron → Chelated iron → Urine (excreted via kidneys) OR Solid waste (excreted via colon)

The iron that isn’t bound up in haemoglobin and other proteins is toxic and can damage organs. Iron chelators bind this toxic iron and allow it to pass out of the body, either in your urine or in your stool, depending on the iron chelator.
Chelation therapy

The graph shows survival percentage over follow-up years for different treatment regimens:
- Effective
- With chelation
- Ineffective
- With transfusions
- Irregular
- Regular

Survival (%) is on the y-axis, and follow-up (years) is on the x-axis.
What do we hope to achieve with chelation?

- Improve survival
- Preserve heart function
- Preserve liver function
- Improve hematopoeisis (QOL)
- Preserve function of other organs: endocrine
# Comparison of iron chelators

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Deferoxamine (Desferal)</th>
<th>Deferasirox (Exjade)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Route administration</strong></td>
<td>sc or iv</td>
<td>oral</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>20 min.</td>
<td>8-16 hrs</td>
</tr>
<tr>
<td><strong>Routes iron excretion</strong></td>
<td>Urine, stool</td>
<td>stool</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>Eye and ENT q 1 yr; ferritin, assess liver Fe q 1 yr; assess cardiac Fe q 1 yr</td>
<td>Creatinine, urine, ALT monthly; ferritin, assess liver Fe q 1 yr; assess cardiac Fe q 1 yr</td>
</tr>
<tr>
<td><strong>Advantages</strong></td>
<td>Long term experience, effective in maintaining near normal Fe, reverses cardiac disease with intensive Rx</td>
<td>Orally active, OD, equivalency to deferoxamine at higher doses, trials in several disorders</td>
</tr>
<tr>
<td><strong>Side effects</strong></td>
<td>Eye, ENT, local skin reactions, growth</td>
<td>Eye, ENT, GI, rash, HA, ↑ LFT, ↑ Cr, cytopenias</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>Parenteral, eye, ear; bone toxicity, poor compliance, skin reactions</td>
<td>Monitor renal function, may not achieve negative iron balance in all patients</td>
</tr>
</tbody>
</table>
Does chelation work in MDS and AA

- Well established efficacy in hereditary anemias
- Some evidence that transfusion dependence and iron overload confer worse prognosis in MDS (recall slide 25; Leitch et al.)
- Chelation may actually improve survival
- All retrospective data, small numbers
Show me the evidence...

- **Does chelation work in MDS?**
  - EPIC trial: prospective, 341 MDS patients, 116 AA patients (1744 patients total); YES

- **Okay, so chelation lowers ferritin but does chelation improve survival?**
Figure 3. Overall survival in patients with myelodysplastic syndromes (MDS) according to receipt of ICT in a subgroup analysis

Okay, so chelation may improve survival but what about quality of life?

- May decrease transfusion requirements:
  - Jensen at al, Br J Haematol 1996
    - 11 patients: 64% had > 50% reduction in transfusion requirements, 46% became transfusion independent
How is it that some physicians do not prescribe chelation?

- Data is indeed limited and sometimes ambiguous
- Recall data from Malcovati demonstrating adverse effects of high ferritin in lower risk MDS; those with more advanced disease demonstrated that high ferritin did not significantly alter survival
Analyses are retrospective with small sample sizes: inherently biased data (patients who were offered and received ICT are likely to be systematically different from those who were not, small numbers may not reflect population).

Why are all of the consensus guidelines different (experts cannot agree because the data are weak)?

Neither chelator is totally safe (S/E, renal dysfunction, myelosuppression)
What should our physicians be telling us?

- Some data suggest benefit of chelation in terms of survival and quality of life but the data are not perfect
- Canadian Consensus Guidelines exist
- Phase III studies needed to resolve uncertainty
- Keep asking questions
Future Directions

- Randomized controlled trials: TELESTO
- Reliable measures of NTBI, LPI, ROS
- Long lasting blood substitutes
Aplastic Anemia and Myelodysplasia Association of Canada

TOH and CHEO

Colleagues

Nurses

Students and residents

Patients
Thank you