MANAGEMENT OF IRON OVERLOAD IN MDS

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Iron overload in myelodysplastic syndromes: Evidence based guidelines from the Canadian consortium on MDS

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Canadian Guidelines for management of iron overload in MDS

Lower-risk MDS

Transfusion-dependent anemia?

Yes

Life expectancy ≥ 1-2 years?

Yes

Documented IOL?

Yes

Candidate for HSCT?

Higher-risk MDS?\(^a\)

Yes

Candidate for rx inducing transfusion independence?

Yes

Reduce IOL

Phlebotomy

Chelation

Levels of evidence & grades of recommendations

Future directions

References

\(^a\)Eligible for disease-modifying therapy or SCT

Case

- 56 year old man presented with fatigue
- Physical examination normal
- WBC 5.3, ANC 2.7, Hb 99 MCV 102, platelets 336
- Ferritin 800 (ULN 370), transferrin saturation 70%
- EPO level 168.1 IU/mL
- Smear showed macrocytosis
- Bone marrow aspirate showed increased cellularity, blasts 1%, erythroid dysplasia, ringed sideroblasts
- Cytogenetics, normal male karyotype
- Diagnosis: RARS, IPSS low risk
- Requiring transfusion of 2U PRBC every 3 weeks
Canadian Guidelines for management of iron overload in MDS

Lower-risk MDS

Transfusion-dependent anemia? Yes

Life expectancy ≥ 1-2 years? Yes

Documented IOL? Yes

Candidate for rx inducing transfusion independence? Yes

Reduce IOL

Phlebotomy Yes

Chelation No

Candidate for HSCT? Yes

Higher-risk MDS?a


aEligible for disease-modifying therapy or SCT
How would you manage iron overload in this patient?

- 1. ESA
- 2. lenalidomide
- 3. IST
- 4. AZA
- 5. SCT
- 6. ICT
How would you manage iron overload in this patient?

- 1. ESA
- 2. lenalidomide
- 3. IST
- 4. AZA
- 5. SCT
- 6. ICT
TREATMENT RECOMMENDATION:
ERYTHROPOIESIS STIMULATING AGENTS OR SUPPORTIVE CARE

FOR PATIENTS WITH SYMPTOMATIC ANEMIA WITH EPO<500 U/L CONSIDER ESAs.
ESAs: dosing and monitoring

INFO

ESAs: DOSING AND MONITORING

Dosing and monitoring (package insert dosing schedule):

- **Epoetin alfa**
  - Initial Dose:** 40,000 U SC
  - Titration for No Response

- **Darbepoetin alfa**
  - Initial Dose:** 500 µg every 2 weeks SC
  - Titration for No Response

Dosing and monitoring (alternative regimens):

- **Epoetin alfa**
  - Initial Dose:** 60,000 U every 2 weeks SC
  - Titration for No Response

- **Darbepoetin alfa**
  - Initial Dose:** 100 µg every 2 weeks SC
  - Titration for No Response

*Consider the starting dose if no response: 20,000 U 3 times/week or 30,000 U 2 times/week. Epo, epoetin alfa; ESA, erythropoiesis-stimulating agent; G-CSF, granulocyte colony-stimulating factor; Hb, hemoglobin; SC, subcutaneous.

www.MDSClearPath.org

Developed by the Canadian Consortium on MDS.
Eligible for agents that induce transfusion independence?

- Why ESA?
- LEN not approved for normal karyotype MDS in Canada
- lived remotely so IST would be difficult
- Azacitidine is not approved for lower risk MDS in Canada
- SCT considered but deferred because of good prognosis MDS & no sibling donor
- ICT – use active treatment + phlebotomy (if reasonable Hb) to reduce IOL
Case

- Trial of EPO 40,000 units weekly
  - No increment in Hb, still transfusion dependent
- Increased EPO to 60,000U weekly
  - Hgb 110-120
  - Ferritin 1115, transferrin saturation 81%
  - (here is where I could have started serial phlebotomy)
- 1 year later, remained transfusion independent
  - Ferritin 896, tsat 70%
- 6 years of transfusion independence & improved QOL

- Why TS?
Non-transferrin-bound iron

The portion of NTBI with the weakest binding to plasma biomolecules is labile plasma iron (LPI)

- Most toxic fraction of NTBI
- Chelatable

LPI can permeate into key organs, such as the liver, heart, and pancreas

LPI Appear at a Transferrin Saturation Above 80%

Courtesy of E. Rachmilewitz
Cellular Targets of Labile Iron

- Ability to transfer electrons
  \( \text{Fenton reaction: } \text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{3+} + \text{OH}^- + \cdot \text{OH} \)
- Production of free \( \text{O}_2 \) radicals:

ROS = Reactive Oxygen Species

Case

- 6 years later presented with exacerbation of anemia & renal stones
- Repeat BMBx showed stable MDS
- Developed a regular transfusion requirement
  - Initially 2U every 4 weeks
- Ferritin increased to >2500, tsat 90%
How would you manage iron overload in this patient?

- 1. ESA
- 2. lenalidomide
- 3. IST
- 4. AZA
- 5. SCT
- 6. ICT
How would you manage iron overload in this patient?

- 1. ESA
- 2. lenalidomide
- 3. IST
- 4. AZA
- 5. SCT
- 6. ICT
Canadian Guidelines for management of iron overload in MDS

1. Lower-risk MDS
   2. Transfusion-dependent anemia?
      3. Yes
   4. Life expectancy ≥ 1-2 years?
      5. Yes
   6. Documented IOL?
      7. Yes
   8. Candidate for rx inducing transfusion independence?
      9. Yes
   10. Reduce IOL
      11. Phlebotomy
      12. Chelation

1. Higher-risk MDS?
   2. Yes
   3. Candidate for HSCT?

Levels of evidence & grades of recommendations

References


aEligible for disease-modifying therapy or SCT
Eligible for agents that induce transfusion independence?

- Answer: no

- **ESA refractory**
  - LEN not approved for normal karyotype MDS in Canada
  - lived remotely so IST would be difficult
  - AZA not approved for lower risk MDS in Canada
  - SCT considered but deferred because of good prognosis MDS & no sibling donor
  - ICT is reasonable
How to treat iron overload in MDS:

- The literature provides no evidence-based studies of high quality to guide the best approach to treating MDS patients with IOL.
- Previous Canadian consensus recommendations published in 2008 are based mainly on thalassemia patients, although evidence in MDS has accumulated in the decade since the initial Canadian guidelines were published.
- Three iron-chelating agents are available: deferoxamine (DFO), deferasirox (DFX), and deferiprone (DFP), and additionally, eltrombopag (ELT) has iron chelating activity.
- DFO and DFX are Health Canada approved for use in MDS.

*Patients becoming transfusion independent with other agents used to treat MDS may undergo phlebotomy.*

(evidence level II-2, recommendation grade B)

Baseline:

Prior to initiation of ICT, the following baseline investigations should be completed

- (evidence level III, recommendation grade B):
  - Ophthalmological examination (slit lamp, retinal & corneal assessments)
  - Audiometry
  - Complete blood count and differential
  - Creatinine

Routine follow-up of patients receiving ICT should reflect Health Canada recommendations & include

- (evidence level III, recommendation grade B)
- (see next slide)

Table 6. Monitoring: Assessment of iron overload and common adverse events of chelators. Ideal assessments are listed and mandatory assessments bolded.

<table>
<thead>
<tr>
<th>Observation</th>
<th>Frequency</th>
<th>IOL assessment</th>
<th>AE monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron intake rate</td>
<td>Each transfusion</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Chelation dose and frequency</td>
<td>3 monthly</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Renal function&lt;sup&gt;1&lt;/sup&gt;</td>
<td>As frequently as required</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Liver function</td>
<td>3 monthly</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Sequential serum ferritin, transferrin saturation&lt;sup&gt;2&lt;/sup&gt;</td>
<td>3 monthly</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>GTT, thyroid, calcium metabolism (BMD&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>Yearly in adults</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Liver iron (T2* MRI)&lt;sup&gt;4&lt;/sup&gt;</td>
<td>At baseline where feasible and subsequently as clinically indicated</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Cardiac function (echo, MRI, ecg)</td>
<td>At baseline then as clinically indicated</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Cardiac iron (T2* MRI)</td>
<td>For patients receiving &gt;50U RBC prior to ICT, or with CHF or arrythmias</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Slit lamp examination, audiometry</td>
<td>Yearly</td>
<td>❌</td>
<td>✓</td>
</tr>
</tbody>
</table>

Abbreviations: AE, adverse event; BMD, bone mineral density; CHF, congestive heart failure; ecg, electrocardiogram; echo, echocardiogram; GTT, glucose tolerance test; ICT, iron chelation therapy; IOL, iron overload; MRI, magnetic resonance imaging; RBC, red blood cells; U, units.

<sup>1</sup>Creatinine should be measured at least every two weeks with each dose increase until stable.

<sup>2</sup>Transferrin saturation >80% may indicate the presence of oxidative stress (reference [70]).

<sup>3</sup>Based on early/suggestive data in transfusion dependent hemoglobinopathies (reference [259]).

<sup>4</sup>Up to 25% of hepatic IOL is underestimated by serum ferritin level (reference [185]).

Reprinted from Leitch HA. 2014 Canadian Perspectives in Clinical Hematology; 2:4-10, with permission and from Leitch HA et al; Crit Rev Oncol Hematol 2017 May;113:156-170 with permission.
ICT/DFX:

- DFX has been studied in hundreds of patients with transfusional IOL, including MDS\textsuperscript{1-4}.
  - For patients with ongoing transfusional iron loading, a DFX dose of 20 mg/kg/day (DF, Exjade®), appears sufficient to maintain iron levels, while often 30 mg/kg/day is required to achieve reduction in iron stores, depending on RBC transfusion requirements.
  - The most common adverse effects are GI symptoms (15.2%) & skin rash (10.8\%)\textsuperscript{2, 3, 5}.
  - Dose-dependent increases in serum creatinine, usually reversible, were seen in one third of patients.
    - Postmarketing surveillance identified several instances of fatal renal failure & cytopenias with DFX.
    - Recommended: weekly serum creatinine for >the first 8 weeks of treatment & following dose increases.
  - Rare adverse events include elevated ALT (0.6\%), deafness (0.3\%) & cataracts (0.3\%).
  - The DFX film coated tablet (FCT, Jadenu®) appears to have fewer GI side effects
  - however renal function and other side effects appear to be similar to the DF\textsuperscript{6}.
  - **Doses must be adjusted down by 30\% for the FCT vs the DF, due to better GI absorption & bioavailability.**

\textsuperscript{4}https://clinicaltrials.gov/ct2/show/NCT00940602.
DFX dosing

The frequency and severity of adverse effects of deferasirox may be minimized by a strategy of gradual dose escalation.

- Evaluation of transfusion need
- Definition of target dose (e.g., 20 mg/kg)
- Recommended initial deferasirox dose
- Up to 5 mg/kg/day (250 or 500 mg/day)
- Re-evaluate weekly for 4 wks for AEs
- Dose increase by one tablet per week
- If intolerable side effect
- Reduce dosage, maintain at highest tolerated level

EXJADE® DOSE (mg/kg/day)
- 20
- 30
- 40

JADENU™ DOSE (mg/kg/day)
- 14
- 21
- 28
### Table 1. Assessment of iron overload.

<table>
<thead>
<tr>
<th>Diagnostic tool</th>
<th>Characteristics</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calculation of transfusion iron burden</td>
<td>Provide a direct quantitative estimate of the body iron burden</td>
<td>Easy to calculate, inexpensive</td>
<td>Unreliable in patients with bleeding or chelation therapy</td>
</tr>
<tr>
<td>Serum ferritin level</td>
<td>Indirect serologic estimation of body iron burden</td>
<td>Widely available; easy to perform; low-cost; repeatable</td>
<td>Unreliable in patients with inflammation, liver function deficiency, and ascorbate deficiency</td>
</tr>
<tr>
<td>Serum transferrin saturation</td>
<td>High sensitivity and specificity in untransfused patients</td>
<td>Widely available; easy to perform; low-cost; repeatable</td>
<td>No quantitative correlation to iron burden</td>
</tr>
<tr>
<td>Imaging (T2* MRI, R2 MRI, SQUID)</td>
<td>Instrumental estimation of tissue iron concentration</td>
<td>Noninvasive, repeatable, validated*</td>
<td>Expensive; not widely available</td>
</tr>
<tr>
<td>Liver biopsy</td>
<td>Provides a direct estimation of iron overload</td>
<td>Validated and quantitative method to estimate hepatic iron concentration (gold standard)</td>
<td>Invasive (cannot be employed in many patients with hematologic malignancies)</td>
</tr>
<tr>
<td>Non-transferrin bound iron (NTBI), labile plasma iron (LPI), reactive oxygen species (ROS)</td>
<td>Research tool at present</td>
<td>Noninvasive method; estimates generation of the toxic iron fraction</td>
<td>Not validated and not widely available. Not currently useful in clinical practice</td>
</tr>
<tr>
<td>Enhanced labile plasma iron (eLPI)</td>
<td>Research tool at present</td>
<td>Noninvasive; estimates generation of toxic iron fraction; elevated eLPI associated with increased NRM and inferior OS in stem cell transplant</td>
<td>Not validated and not widely available. Not currently useful in clinical practice</td>
</tr>
<tr>
<td>Serum hepcidin level</td>
<td>Research tool at present</td>
<td>Noninvasive method that identifies patients at high risk of iron loading</td>
<td>Not widely available. Not currently useful in clinical practice</td>
</tr>
</tbody>
</table>


*R2 MRI validated in the liver, reliable up to LIC of 15mg/g DW; T2* MRI validated in the heart, requires skilled radiologist
Management of GI intolerance with DFX:

<table>
<thead>
<tr>
<th>Nausea &amp; vomiting</th>
<th>Diarrhea</th>
<th>Abdominal pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Use anti-emetics</td>
<td>• Hydration*</td>
<td>• Switch to pre-prandial dosing</td>
</tr>
<tr>
<td>• Switch to pre-prandial dosing</td>
<td>• Loperamide</td>
<td>• For upper abdominal pain, use anti-acids</td>
</tr>
<tr>
<td>• Reduce dose or interrupt treatment</td>
<td>• Lactaid if indicated</td>
<td>• Consider spasmolytic drugs</td>
</tr>
<tr>
<td></td>
<td>• Dose at night</td>
<td>• Reduce dose or interrupt treatment</td>
</tr>
<tr>
<td></td>
<td>• Use water to disperse tablets</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Reduce dose or interrupt treatment</td>
<td></td>
</tr>
</tbody>
</table>

- To avoid GI intolerance DFX may be started at a lower dose & titrated up


*ensuring adequate volume status may minimize renal insufficiency
Severe skin rash with DFX (dispersible formulation):

Desensitization Protocol

Dosage adjustment:

- For comparison:
- Reduce dose of DFO when SF <2000 ng/mL (evidence level III, recommendation grade B)
- Discontinue DFO when SF <1000 ng/mL (evidence level III, recommendation grade B)

- Discontinue DFX when SF <500ng/mL. However, for DFX, lower SF levels may be safer, though this has not yet been demonstrated in sizable studies (evidence level III, recommendation grade B)

- For DFX, follow the product monograph if the creatinine is elevated (evidence level III, recommendation grade B) [https://www.ask.novartispharma.ca/download.htm?res=exjade_scrip_e.pdf&resTitleId=689](https://www.ask.novartispharma.ca/download.htm?res=exjade_scrip_e.pdf&resTitleId=689)
  [https://www.ask.novartispharma.ca/download.htm?res=jadenu_scrip_e.pdf&resTitleId=1183](https://www.ask.novartispharma.ca/download.htm?res=jadenu_scrip_e.pdf&resTitleId=1183)

- Currently, no literature is available to support or guide the use of combination chelator therapy in MDS patients, therefore, no recommendations are made

Case

- For reasons of QOL:
- Started DFX (DF) at 20mg/kg/day
- Creatinine rose from 100 to 300
### Frequent adverse events with deferasirox and their management.

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Renal impairment</strong></td>
<td></td>
</tr>
<tr>
<td><strong>At initiation</strong></td>
<td></td>
</tr>
<tr>
<td>eGFR &gt;60ml/min/1.73m²</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td>eGFR 40-60ml/min/1.73m²</td>
<td>Decrease dose by 50%</td>
</tr>
<tr>
<td>eGFR &lt;40ml/min/1.73m²</td>
<td>contraindicated</td>
</tr>
<tr>
<td><strong>During treatment</strong></td>
<td></td>
</tr>
<tr>
<td>Creatinine increase 33% above baseline</td>
<td>repeat in 1 week, if still elevated reduce dose by 10mg/kg/day (Exjade) or 7mg/kg/day (Jadenu)</td>
</tr>
<tr>
<td>eGFR &lt;40ml/min/1.73m²</td>
<td>Discontinue</td>
</tr>
<tr>
<td><strong>Hepatic impairment</strong></td>
<td></td>
</tr>
<tr>
<td><strong>At initiation</strong></td>
<td></td>
</tr>
<tr>
<td>Mild (Child-Pugh class A)</td>
<td>No dose adjustment, monitor closely</td>
</tr>
<tr>
<td>Moderate (Child-Pugh class B)</td>
<td>Decrease dose by 50%, monitor closely</td>
</tr>
<tr>
<td>Severe (Child-Pugh class C)</td>
<td>Avoid use</td>
</tr>
<tr>
<td><strong>During treatment</strong></td>
<td></td>
</tr>
<tr>
<td>Severe/persistent increases in transaminases/bilirubin</td>
<td>Dose reduction or dose interruption</td>
</tr>
<tr>
<td><strong>GI intolerance</strong></td>
<td></td>
</tr>
<tr>
<td>Nausea &amp; vomiting</td>
<td>✓ Use anti-emetics&lt;br&gt; ✓ Switch to pre-prandial dosing&lt;br&gt; ✓ Reduce dose or interrupt treatment</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>✓ Hydration&lt;br&gt; ✓ Loperamide&lt;br&gt; ✓ Lactaid if indicated&lt;br&gt; ✓ Dose at night&lt;br&gt; ✓ Use water to disperse tablets&lt;br&gt; ✓ Reduce dose or interrupt treatment</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>✓ Switch to pre-prandial dosing&lt;br&gt; ✓ For upper abdominal pain, use anti-acids&lt;br&gt; ✓ Consider spasmolytic drugs&lt;br&gt; ✓ Reduce dose or interrupt treatment</td>
</tr>
</tbody>
</table>

*eGFR; estimated glomerular filtration rate*
Case

- What next?
ICT/DFO:

• Because of its short half-life (5-20 minutes), DFO 20–50 mg/kg/day is given by 12-24h SQ continuous infusion 5-7 days/week
  • for compliance reasons, SQ boluses or alternate routes of administration can be considered1-5.
  • The therapeutic index should be <0.025 (mean daily dose in mg/kg divided by ferritin).
• Allergic reactions can occur with rapid IV infusion. ARDS has followed excessive IV doses.
• In severe IOL, cardiac dysfunction can occur with concomitant vitamin C >500 mg daily
  • while vitamin C may augment urinary iron excretion in patients receiving DFO, it promotes free radical production that may initiate cardiomyocyte damage6.
• DFO should not be used in severe renal failure7.

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https://www.uptodate.com/contents/deferoxamine-drug-information?search=deferoxamine&source=panel_search_result&selectedTitle=1~33&usage_type=panel&kp_tab=drug_general&display_rank=1
Management of DFO side effects

- Common side effects include:
  - Injection site reactions: treat supportively
  - Infections: DFO is a siderophore and can deliver iron to microorganisms including Yersinia, mucormycosis and others, which supports their growth and replication.
    - DFO should be stopped during infections until the infection resolves.
    - (This is not the case with DFX, which sequesters iron & keeps it from microorganisms.)
- **DFO can cause ophthalmologic & ototoxicity, particularly at a ferritin level <1000ng/mL**.
  - These are likely reversible if abnormalities are detected early.
  - **It is critical to monitor with slit lamp examinations & audiology tests at regular intervals**. 

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### Case

- Started on DFO 30mg/kg/day by continuous SQ infusion 12 hours/day, 7 days/week
- Routine audiology tests 2 years later showed severe sensorineural hearing loss compared to baseline
- DFO stopped

<table>
<thead>
<tr>
<th>Event</th>
<th>Timeline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dx RARS</td>
<td>11/2004</td>
</tr>
<tr>
<td>EPO 9/05</td>
<td></td>
</tr>
<tr>
<td>TI</td>
<td></td>
</tr>
<tr>
<td>Ferritin 1100, tsat 81%</td>
<td>12/2007</td>
</tr>
<tr>
<td>Loss of TI</td>
<td>11/2011</td>
</tr>
<tr>
<td>Creatinine tripled</td>
<td></td>
</tr>
<tr>
<td>DFX 7/2012</td>
<td></td>
</tr>
<tr>
<td>DFO 11/2012</td>
<td></td>
</tr>
<tr>
<td>Hearing loss</td>
<td></td>
</tr>
<tr>
<td>Ferritin 2000, tsat 81%</td>
<td>1/2014</td>
</tr>
<tr>
<td>DFO d/c</td>
<td></td>
</tr>
</tbody>
</table>

DFO, deferoxamine
ICT/DFP:

- DFP is effective at increasing iron excretion; however, its efficacy has been established chiefly in patients with hemoglobinopathies.
- The safety profile of DFP in MDS is unclear, and concerns about agranulocytosis in patients with preexisting neutropenia remain.
- In a study of 48 MDS patients receiving DFP, a 4% incidence of agranulocytosis was seen\(^1\).

**DFP is not Health Canada approved for use in MDS**

DFP:

- The occasional MDS patient may be unable to tolerate either DFX or DFO.

- DFP is given at a target dose of 75mg/kg/day in 3 divided doses. Some patients may be able to escalate to 100mg/kg/day.

- Common side effects of DFP are GI and arthralgias.
  - Patients should be initiated on 1/5-1/4 the target dose and dose increased gradually as tolerated.

- ***DFP is not Health Canada approved for use in MDS***.

Case:

- Weight 100kg, target DFP dose 7500mg daily in 3 doses or 2500mg tid
- Started on DFP 500mg tid and escalated to full dose (**off-label**)
- Further dose increase limited by severe nausea and severe arthralgias
- A few months later DFP was stopped by his GP
- (it turns out the arthralgias were pseudogout from iron overload)

- *DFP is not Health Canada approved for use in MDS*

ELT shows strong iron chelating activity in pre-clinical models, as a single agent or in combination with other chelators\textsuperscript{1-3}

***There are no clinical studies examining the iron chelating activity of ELT in MDS***

**A recent study suggests that ELT supports the growth and replication of hematopoietic stem cells via iron chelating activity**\textsuperscript{4}

***ELT is not Health Canada approved for use in MDS***


Case

Access to eltrombopag denied by:

- the manufacturer
- the public authority
- and his private insurer
Case

- Started on a very low dose of Jadenu (DFX film-coated tablet) 3.6mg/kg/2 days: goal is to
  - 1. “take the edge” off the non-transferrin bound iron
  - 2. try to keep him going until luspatercept availability (expected in 2020 in Canada)
- Creatinine remained stable at 150
- If tolerated was planning to add back a low dose of DFP**
Back to eligible for therapies that induce TI?

- Accessed lenalidomide on private insurance (**off-label use**)
  - Had a transient (7 day) improvement in Hb then back to baseline
What next?

- Eligible for therapies that induce TI?
- Waiting for luspatercept….
- And then….
229 Eltrombopag Improves Hematopoiesis in Patients with Low to Intermediate-2 Risk Myelodysplastic Syndrome (MDS)

- Vicente et al (NIH), ASH 2018
- Phase-2 dose escalation study, safety and effectiveness of ELT in low to intermediate-2 risk MDS (NCT 00961064).
- 30 patients; ELT was started at 50 mg/day, up to a maximal dose of 150 mg/day, increasing the dose by 25mg every 2 weeks.
- The primary endpoint was hematologic response, defined as:
  - (1) increase in platelets ≥20,000/uL or transfusion independence for ≥8 weeks
  - (2) hemoglobin (Hb) increase ≥1.5g/dL, or reduction in RBC transfusion of ≥50%; or
  - (3) increase in ANC ≥0.5x10^9/L or by ≥100% if baseline ANC <0.5x10^9/L.
- Robust response (RR) was: stable hematopoiesis (off ELT) with ≥an Hb >10g/dl & platelets >50,000/L & ANC>1000/L.
ELT for MDS treatment

- The primary endpoint was met in 14/30 patients (47%).
- 10/14 responders achieved a RR after a median treatment duration of 15 (7-27) months.
- However, blood counts significantly declined in 5/10 RR & ELT was restarted.
  - In 4 patients blood counts recovered.
  - 1 patient did not achieve a second response.
- 4/30 (13%) patients progressed; 3 non-responders & 1 responder, at a median follow-up of 4 (3-35) months.
ELT for MDS (3):

- Novel dose limiting toxicities were not observed.
- Three patients developed CTCAE grade III hepatic toxicities\(^1\).
  - Elevated transaminases returned to baseline after ELT discontinuation in 2 patients.
  - In both ELT was resumed at the same (150mg/day) or reduced dose (50mg/day) level.
- There were no treatment-related deaths.
- In conclusion, the results suggest that ELT is well-tolerated and effective in restoring hematopoiesis in low to int-2 MDS.
  - ELT was d/c for RR in most responders but declining blood counts were observed in about 50%.
- ELT appears **not** to selectively promote clonal expansion in this patient population.

Case:

- Re-applied to his private insurer for ELT (as an MDS treatment vs ICT)
  - Denied
  - Awaiting results of appeal
Clinical Benefit of ICT

- IOL might not always be straightforward to manage. In order to benefit our patients we need to believe that IOL management is important, as do the patients.
- What do we know about the clinical benefit of iron chelation in MDS?
  - Multiple non-controlled analyses indicate superior clinical outcomes in MDS patients receiving ICT.
  - However, the findings may be influenced by selection or referral bias, so that patients with a better performance status are selected to receive ICT.
  - To examine this, we turned to the Canadian MDS registry, which prospectively collects data on quality of life in MDS patients.
  - Four measures of QOL were included: the Clinical Frailty score; the Charlson Comorbidity index; the MDS-specific comorbidity index; and the Lawton-Brody disability score.
  - Importantly, these factors were not significantly different between ICT & non-ICT patients.
  - In addition, to minimize lead-time bias, we measured survival from the time of first RBC transfusion dependence.
Figure. Overall survival in lower IPSS risk MDS from red blood cell transfusion dependence by receipt of iron chelation therapy a) in all patients; b) in patients matched 1:1 for age (≤50, 51-60, 61-65, 66-70, 71-75, 76-80, and >80 years), IPSS-R score (very low + low, intermediate, and high + very high), number of RBC units/month transfused (0, >0-≤2, >2-≤4, >4-≤6, & >6), and time from MDS dx until RBC transfusion dependence (0, >0-<6, >6-36, >36 months).

Despite target enrollment being reduced by 2/3, making the study not powered to detect its endpoint,
• Despite half of placebo patients withdrawing from the study and subsequently receiving ICT,
• Despite the patient population being younger than is characteristic for MDS (mean age 61 years),
• There was superior EFS in ICT patients, which became more apparent over time.
• In multiple studies of DFX in MDS, the median treatment duration is around 12 months. These data give us rationale for continuing ICT wherever possible, as the clinical benefit appears to increase over time.

INFECTIONS:
Time from 1st RBC transfusion to 1st infection while Lower IPSS Risk MDS & Transfusion Dependent by Receipt of Iron Chelation Therapy

- ICT remained significant for TTI in a multivariate analysis, \( p=0.03, \text{HR } 0.3, 95\% \text{ CI } 0.09-0.9 \).


- Similar:
  - Neutrophil counts
  - Numbers of infections
  - Types of infections

- Median time to first infection (TTI):
  - 27.0 months ICT
  - & 7.8 mo non-ICT
  - \( p<0.0001 \)

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  - 27.0 months ICT
  - & 7.8 mo non-ICT
  - \( p<0.0001 \)
CARDIAC EVENTS:
Time from 1st RBC transfusion to 1st Cardiac Event while Lower IPSS Risk & Transfusion Dependent by Receipt of Iron Chelation Therapy

- Cardiac events:
  - CHF
  - CAD
  - Arrhythmia

- ICT remained significant for TTCE in a multivariate analysis, \( p=0.03 \), HR 0.93, 95% CI 0.87-0.99.

- Median TTCE:
  - 20.0 months ICT
  - & 7.0 months non-ICT
  - \( p<0.0001 \)

Summary/Conclusions:

- In summary,
- There is increasing evidence that ICT is of clinical benefit in MDS patients
  - The number of chelators we have access to is limited
  - Use of these chelators may be limited by side effects
  - Side effects must be managed aggressively to ensure optimal control of iron overload
- In future, we will hopefully have access to more therapeutic options to modify disease course in MDS
  - This in turn will induce transfusion independence
  - which will optimize
    - Overall survival
    - Quality of life
    - And minimize iron overload
Future directions (1)

Research agenda addressing iron overload and iron chelation therapy in MDS.

- Clarify the contribution of iron toxicity to symptoms and risk in MDS
- Does ICT improve overall survival in lower risk MDS?
- Does ICT decrease organ complications in lower risk MDS?
- **What clinical markers predict for hematologic improvement with ICT in lower risk MDS?**
- Does ICT decrease infection risk in lower risk MDS?
- **Which subgroups of lower risk MDS patients benefit most from iron reduction?**
- **Is there value to early intervention/prevention of iron overload vs rescuing damaged tissue?**
- Is there a benefit to chelating to a lower iron burden?
- Is there a benefit to combining standard of care with ICT for MDS?
- Does ICT delay progression to AML?
- Should ICT be offered to selected patients with higher risk MDS?
- Should ICT be offered to MDS patients undergoing SCT?
- **Can combinations of chelators be used safely and effectively in MDS?**
- **Develop newer chelators with fewer side effects?**

AML, acute myeloid leukemia; ICT, iron chelation therapy; MDS, myelodysplastic syndrome; SCT, stem cell transplantation; vs, versus
Future directions (2)

- Longer acting, less toxic formulations of DFO are being developed and may have clinical application in future\(^1\).
- Future work addresses organ-targeted chelators\(^2\)

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\(^2\)Canadian Institute of Health Research Grant Application Submitted, March 2019
Canadian Guidelines for management of iron overload in MDS

Lower-risk MDS

Transfusion-dependent anemia?

Yes

Life expectancy ≥ 1-2 years?

Yes

Documented IOL?

Yes

Candidate for rx inducing transfusion independence?

Yes

Reduce IOL

Phlebotomy

Chelation

Candidate for HSCT?

Yes

Higher-risk MDS?\(^a\)

Yes

Future directions

References

\(^a\)Eligible for disease-modifying therapy or SCT
