Iron chelation in MDS: Practical issues

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Author takes full responsibility for presented information which reflect author’s stand/practice and might not be in line with locally approved SmPC.
Agenda

- Transfusion-dependence in MDS
- Management of Iron Overload
- Indications for chelation
- Management of adverse events
- Compliance and efficacy
- Survival and hematological improvement
A cross-sectional study (N = 907) of MDS patients who attended one of 74 French centres over a 1-week period.

### Prevalence of anemia and transfusion dependence at diagnosis*

- **Hb < 10 g/dL at diagnosis:** 77%
- **RBC transfusion(s) in 6 months prior to diagnosis:** 61%

### Reasons for attending a clinic: transfusion requirement**

- **Initial workup:** 10%
- **Follow-up:** 36%
- **Chemotherapy/hypomethylating agents:** 8%
- **Transfusion:** 39%
- **Infectious event:** 4%

*Cross-sectional study (N = 907). MDS patients who attended one of 74 French centres over a 1-week period.

MDS patients with Hb level of <10.7 g/dL risk cardiac organ damage

* Evidence of LVH based on LVM measurements according to the Devereux formula.
LVH, left ventricular hypertrophy; LVM, left ventricular mass;
RBC-TD, red blood cell transfusion-dependent;
RBC-TI, red blood cell transfusion-independent.

Hb levels in patients with evidence of cardiac re-modelling

<table>
<thead>
<tr>
<th>Cardiac re-modelling</th>
<th>Mean Hb, g/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>8.7</td>
</tr>
<tr>
<td>No</td>
<td>11.3</td>
</tr>
</tbody>
</table>

p < 0.0001

Hb levels predictive for LVH (multivariate analysis p = 0.017)

Area 0.84 (IC 0.61–0.99) p < 0.0001

Transfusion dependence is associated with comorbidities

- Age-related comorbidities may increase susceptibility to iron toxicity
- Iron overload may play a key role in inducing comorbid conditions or worsening pre-existing comorbidities

2003-2005, incidence of comorbidities

Gattermann N, Rachmilewitz EA. Ann Hematol 2011
Transfusion dependence is associated with mortality

Cumulative proportion surviving

Survival HR 1.58 (p = 0.005)

Time (months)

HR, hazard ratio.
Chronic anemia is associated with an increased risk of non-leukemic death

840 MDS patients from a single centre

Rates of NLD in males
(n = 504)

Rates of NLD in females
(n = 336)

NLD, non-leukemic death.

Pathological mechanisms and consequences of iron overload

- **Labile iron**
- **Iron chelation**
- **Blood transfusion**
- **High iron absorption**

**Neoplasia**

- **Anti-apoptotic**
  - **NF-κB activation**
  - **ROS**

- **Caspase activation**
  - **DNA damage**
  - **Organelle damage**
  - **Lysosomal fragility**
  - **Genomic instability**
  - **Enzyme leakage**
  - **Cell death**

- **Infection**
  - **TGF-β1**
  - **Lipid peroxidation**
  - **Collagen synthesis**
  - **Fibrosis**

**NF-κB, nuclear factor-κB**; **TGF, transforming growth factor**.

Patients with lower risk MDS according to transfusion requirement

<table>
<thead>
<tr>
<th></th>
<th>Not requiring transfusions (n = 109)</th>
<th>Requiring transfusions (n = 39)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hb, g/dL</strong></td>
<td>10.88 ± 1.99</td>
<td>8.70 ± 1.25</td>
</tr>
<tr>
<td><strong>Cytopenias, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>74 (67.9)</td>
<td>11 (28.2)</td>
</tr>
<tr>
<td>2</td>
<td>28 (25.7)</td>
<td>21 (53.8)</td>
</tr>
<tr>
<td>3</td>
<td>7 (6.4)</td>
<td>7 (17.9)</td>
</tr>
<tr>
<td><strong>Bone marrow blasts, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5%</td>
<td>95 (87.2)</td>
<td>25 (64.1)</td>
</tr>
<tr>
<td>5–10%</td>
<td>10 (9.2)</td>
<td>12 (30.8)</td>
</tr>
<tr>
<td>&gt;10%</td>
<td>4 (3.7)</td>
<td>2 (5.1)</td>
</tr>
<tr>
<td><strong>IPSS degree, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>50 (51.0)</td>
<td>6 (16.7)</td>
</tr>
<tr>
<td>Int-1</td>
<td>42 (42.9)</td>
<td>22 (61.1)</td>
</tr>
<tr>
<td>Int-2</td>
<td>6 (5.5)</td>
<td>8 (22.2)</td>
</tr>
<tr>
<td>NA</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td><strong>ECOG PS, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>77 (70.6)</td>
<td>17 (43.6)</td>
</tr>
<tr>
<td>1</td>
<td>26 (23.9)</td>
<td>18 (46.2)</td>
</tr>
<tr>
<td>2</td>
<td>6 (5.5)</td>
<td>4 (10.3)</td>
</tr>
</tbody>
</table>

Transfusion-dependence is associated with more severe MDS and worse performance status

p < 0.05 for all listed comparisons

ECOG PS, Eastern Cooperative Oncology Group Performance Status

Trasfusion-dependence and quality of life

- Dependence on hospital and staff
- Inability to travel
- Anxiety to receive transfusion
- Adverse events
- Fluctuations in Hb
- Symptoms (dyspnea, difficulty in climbing stairs)
Agenda

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Mean LIC and ferritin in patients with MDS treated with deferasirox

Mean LIC (MRI R2) and SF (± SEM) for completed patients

Patients, n

<table>
<thead>
<tr>
<th></th>
<th>BL</th>
<th>Month 6</th>
<th>Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>9</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>LIC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SF</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean LIC + SD (mg Fe/g dry wt)

Mean SF + SD (µg/L)

SEM, standard error of the mean.

LIC=liver iron content
Diagnosis of LIC: transfusion load vs ferritin levels

Threshold for RBC units = 13 and ferritin 1019 μg/l for LIC

In MDS, ferritin levels are *surrogate* markers of LIC but do not correlate with the entity of overload

Cardiac T2*: relationship with left ventricular ejection fraction (LVEF)

T2* < 20 ms is associated with a progressive and significant decline in LVEF

Cardiac T2* value of 37 ms in a normal heart

Cardiac T2* value of 4 ms in a significantly iron-overloaded heart

Cardiac T2*:
relationship with heart failure and arrythmia

Low T2* is associated with a high risk of heart failure and arrythmia

T2* < 10 ms: relative risk 159 (p < 0.001)
T2* < 6 ms: relative risk 268 (p < 0.001)

T2* < 20 ms: relative risk 4.6 (p < 0.001)
T2* < 6 ms: relative risk 8.65 (p < 0.001)
Summary

Transfusion-dependent myelodysplastic (MDS) patients are prone to iron overload. We evaluated 43 transfused MDS patients with T2* magnetic resonance imaging scans. 81% had liver and 16.8% cardiac iron overload. Liver R2* (1000/T2*), but not cardiac R2*, was correlated with number of units transfused \((r = 0.72, P < 0.0001)\) and ferritin \((r = 0.53, P < 0.0001)\). The area under the curve of a time-ferritin plot was found to be much greater in patients with cardiac iron loading (median 53.7 \(\times 10^5\) Megaunits vs. 12.2 \(\times 10^5\) Megaunits, \(P = 0.002\)). HFE, HFE2, HAMP or SLC40A1 genotypes were not predictors of iron overload in these patients.

HAMP, hepcidin antimicrobial peptide; HFE, haemochromatosis protein; SLC40A1, solute carrier family 40, member 1.
Cardiac iron overload

Identified by MRI after 75 units of RBC transfusions

….but the heart may be more vulnerable to the oxidative effects of iron with respect to the liver
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Treatment Algorithm

Lower-risk MDS

Transfusion-dependent anaemia?  
Yes

Has a life expectancy ≥ 1 year?  
Yes

Serum ferritin > 1,000 μg/L  
Yes

Start ICT

Candidate for HSCT?

Yes

Higher-risk MDS? a,1,2

---

a Eligible for disease-modifying therapy or SCT

b Duration: as needed to maintain serum ferritin < 1,000 μg/L.

Initiation of ICT: Barriers

1. Patient’s life expectancy is < 6 months
   - Does not prevent (at all) (Score 1–2): 7%
   - Score 3–5: 21%
   - (Strongly) prevents (Score 6–7): 72%
   - Mean: 5.8

2. Patient is aged ≥ 85 years or older
   - Does not prevent (at all) (Score 1–2): 20%
   - Score 3–5: 31%
   - (Strongly) prevents (Score 6–7): 50%
   - Mean: 4.9

3. Patient’s life expectancy is < 12 months
   - Does not prevent (at all) (Score 1–2): 15%
   - Score 3–5: 44%
   - (Strongly) prevents (Score 6–7): 41%
   - Mean: 4.7

4. Comorbidity that would limit prognosis
   - Does not prevent (at all) (Score 1–2): 13%
   - Score 3–5: 53%
   - (Strongly) prevents (Score 6–7): 34%
   - Mean: 4.6

5. Renal health concerns
   - Does not prevent (at all) (Score 1–2): 15%
   - Score 3–5: 58%
   - (Strongly) prevents (Score 6–7): 27%
   - Mean: 4.3

6. Expected non-compliance of the patient
   - Does not prevent (at all) (Score 1–2): 23%
   - Score 3–5: 49%
   - (Strongly) prevents (Score 6–7): 28%
   - Mean: 4.2

7. High-risk MDS: (e.g. High, Int-2 [IPSS] or RAEB, CMML [WHO])
   - Does not prevent (at all) (Score 1–2): 25%
   - Score 3–5: 44%
   - (Strongly) prevents (Score 6–7): 31%
   - Mean: 4.1

Row percentages may not add up to 100% because of rounding.
CMML = chronic myelomonocytic leukaemia.

Clinical cases
Case 1. Low risk MDS, non transfused

Ferritin: 828 ng/mL
Patient is concerned.............
Case 2. Low risk MDS, transfusion-dependent unchelated

Diagnosis October 2014 - Ferritin: 450 ng/mL

12 RBC units until April 2015: Ferritin 1200 ng/mL

<table>
<thead>
<tr>
<th>Average Liver Iron Concentration</th>
<th>16.0 mg/g dry tissue (NR: 0.17-1.8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>286 mmol/kg dry tissue</td>
</tr>
</tbody>
</table>

Normal range (NR) is taken from Bossett et al., Hepatology 1986; 6: 24-29
Case 3. Low risk MDS transfusion dependent and ring sideroblasts, inadequate chelation

Diagnosis November 2010 - Ferritin 110 ng/mL; 3 RBC Units/months from November 2011
Inadequate chelation for increases in creatinine

- Ferritin 2200 in March 2015

<table>
<thead>
<tr>
<th>Average Liver Iron Concentration</th>
<th>4.4 mg/g dry tissue (NR: 0.17-1.8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>79 mmol/kg dry tissue             (NR: 3-33)</td>
</tr>
</tbody>
</table>

*Normal range (NR) is taken from Bassett et al., Hepatology 1986; 6: 24-29*
Case 4. High risk MDS at diagnosis before hypomethylation treatment

Diagnosis October 2015 - Ferritin: 1050 ng/mL

2 RBC units in September 2015
Agenda

1. Transfusion-dependence in MDS
2. Diagnosis of Iron Overload
3. Indications for chelation
4. Management of adverse events
5. Compliance and efficacy
6. Survival and hematological improvement
Most common drug-related side effects of deferasirox treatment in the study setting

N = 341

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>74 (21.7)</td>
<td>29 (8.5)</td>
<td>8 (2.3)</td>
<td>111 (32.6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>34 (10.0)</td>
<td>10 (2.9)</td>
<td>1 (0.3)</td>
<td>45 (13.2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>21 (6.2)</td>
<td>5 (1.5)</td>
<td>-</td>
<td>26 (7.6)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>14 (4.1)</td>
<td>11 (3.2)</td>
<td>1 (0.3)</td>
<td>26 (7.6)</td>
</tr>
<tr>
<td>Upper abdominal pain</td>
<td>16 (4.7)</td>
<td>8 (2.3)</td>
<td>1 (0.3)</td>
<td>25 (7.3)</td>
</tr>
<tr>
<td>Rash</td>
<td>13 (3.8)</td>
<td>6 (1.8)</td>
<td>4 (1.2)</td>
<td>23 (6.7)</td>
</tr>
<tr>
<td>Constipation</td>
<td>16 (4.7)</td>
<td>5 (1.5)</td>
<td>-</td>
<td>21 (6.2)</td>
</tr>
<tr>
<td><strong>Total number</strong></td>
<td>188</td>
<td>74</td>
<td>15</td>
<td>277</td>
</tr>
</tbody>
</table>

Most common drug-related side effects of deferasirox treatment in the real-life medical practice

<table>
<thead>
<tr>
<th>AEs, n (%)</th>
<th>Chelation-naïve (n = 123)</th>
<th>Prior chelation (n = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>13 (10.6)</td>
<td>4 (9.1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>11 (8.9)</td>
<td>3 (6.8)</td>
</tr>
<tr>
<td>Increased serum creatinine</td>
<td>6 (4.9)</td>
<td>4 (9.1)</td>
</tr>
<tr>
<td>Rash</td>
<td>8 (6.5)</td>
<td>2 (4.5)</td>
</tr>
</tbody>
</table>

Safety profile of deferasirox in real-life medical practice is comparable to previous reported clinical trials

GIMEMA prospective single-arm trial, deferasirox in low risk MDS:
>69% unrelated adverse events

- Grade 3-4 drug-related AEs (14 events, 11 patients)
- Grade 1-2 drug-related AEs (79 events, 55 patients)
- Grade 1-4 non drug-related AEs (211 events, 41 patients)

Half did not complete 1 year in study due to drop-out (28%) and progression (25%)

Management of adverse events

Type of side effect

- Organ toxicity
  - Symptoms delayed

- Annoying symptoms
  - Usually not lethal

Goal

- Preserve organ functions
- Relieving symptoms
  - Maintaining adherence

Intervention

«Physician-centred» management

- Active monitoring
- Dose adjustments

«Patient-centred» management

- Dose adjustments
- Information
- Increase motivation

Adapted from Bor-Sheng Ko, National Taiwan University Hospital
Management of gastro-intestinal disturbances

- Explain that deferasirox may cause GI disturbances
  - to avoid patient self-limiting (or interrupting) treatment

- Disperse deferasirox in water
  - not juice

- Deferasirox may be taken
  - in the evening (rather than morning), 30 min before or 2 h after dinner
  - with food

- With high-fat food, drug exposure could be doubled

Dose-dependent and transient

DFX, deferasirox.

Severity of Diarrhea: definitions

- **Mild**: < 4 daily episodes
- **Moderate**: 4–6 daily episodes
- **Severe**: > 6 daily episodes

# Summary of dosing recommendation

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Dose adjustment</th>
<th>Upon resolution of side effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>No DFX dose adjustment</td>
<td>Re-escalate DFX to target dose in increments of 5 mg/kg each week</td>
</tr>
<tr>
<td>Moderate</td>
<td>Reduce DFX dose to 10 mg/kg/day</td>
<td>Re-initiate deferasirox at 10 mg/kg/day and adjust dose in increments of 5 mg/kg each week</td>
</tr>
<tr>
<td>Severe</td>
<td>Discontinue deferasirox (if diarrhea is unmanageable)</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild-to-moderate</td>
<td>DFX dose reduction before treatment interruptions</td>
<td>Increase DFX dosing in steps of 5 mg/kg/day</td>
</tr>
<tr>
<td></td>
<td>Reduce DFX dose in steps of 5 mg/kg/day</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>Time rarely interrupt DFX</td>
<td>Restart at low dose and increase in steps</td>
</tr>
<tr>
<td>Nausea / vomiting (severe)</td>
<td>Reduce DFX dosing in steps of 5 mg/kg/day</td>
<td>Increase dosing in steps of 5 mg/kg/day</td>
</tr>
</tbody>
</table>

*Patients with constipation have to be managed by another algorithm

Renal events in 1/3 of patients

Non-progressive increase of mean serum creatinine levels

Cappellini et al. Blood 2006
Incidence of creatinine increase during treatment with deferasirox

References from the literature

Clinical trials

In clinical practice

sCR = Serum creatinine
ULN = upper limit of normality

Acute kidney insufficiency during deferasirox treatment

- AKI following initiation of deferasirox treatment has been associated with complete proximal tubulopathy or acute interstitial nephritis.

- **Proximal tubular dysfunction** in association with AKI is considered a severe manifestation of deferasirox toxicity on proximal tubular cells.

- **Acute interstitial nephritis** with reversible AKI is considered a hypersensitivity reaction.

AKI = acute kidney insufficiency

# Drug-induced Fanconi Syndrome

<table>
<thead>
<tr>
<th>Class</th>
<th>Drugs</th>
<th>Indications for use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkylating agents</td>
<td>Ifosfamide</td>
<td>Cancer</td>
</tr>
<tr>
<td>Aminoglycoside antibiotics</td>
<td>Gentamicin, Amikacin</td>
<td>Gram-negative bacterial infection</td>
</tr>
<tr>
<td>Anti-epileptics</td>
<td>Sodium valproate</td>
<td>Seizures, bipolar disorder</td>
</tr>
<tr>
<td>Anti/protozoals</td>
<td>Suramin</td>
<td>Trypanosomiasis</td>
</tr>
<tr>
<td>Dicarboxylic acids</td>
<td>Fumaric acid</td>
<td>Psoriasis</td>
</tr>
<tr>
<td>Iron chelators</td>
<td>Deferasirox</td>
<td>Iron overload (e.g. in thalassemia)</td>
</tr>
<tr>
<td>NRTIs</td>
<td>Didanosine, Stavudine</td>
<td>HIV</td>
</tr>
<tr>
<td>NtRTIs</td>
<td>Tenofovir, Adefovir, Cidofovir</td>
<td>HIV, Hepatitis B, CMV</td>
</tr>
<tr>
<td>Platinum compounds</td>
<td>Cisplatin/carboplatin</td>
<td>Cancer</td>
</tr>
<tr>
<td>Salicylates</td>
<td>Aspirin</td>
<td>Analgesia, anti-inflammatory</td>
</tr>
<tr>
<td>Tetracycline antibiotics</td>
<td>Degraded tetracycline</td>
<td>Bacterial infection</td>
</tr>
<tr>
<td>Tyrosine kinase inhibitors</td>
<td>Imatinib mesylate</td>
<td>Chronic myeloid leukaemia</td>
</tr>
</tbody>
</table>
Normal renal physiology

DCT = distal convoluted tubule
PCT = proximal convoluted tubule
Solute transportation in the proximal renal tubule and signs of renal Fanconi syndrome

Aminoaciduria
Organic aciduria
Low molecular weight proteinuria
Hypophosphatemia
Normoglycemic glicosuria
Metabolic acidosis
Hypouricemia
Hypokalemic
Polyuria

Proximal tubular dysfunction
La disfunzione tubulare prossimale associata all’insufficienza renale acuta è considerata una manifestazione severa della tossicità di deferasirox sulle cellule tubulari prossimali.
Incidence of deferasirox-associated Fanconi syndrome

- Develops within a mean of 18 months (range 1–36 months) following initiation of therapy and to be reversible within a mean of 3 weeks (range of 3 days to 6 weeks) following its discontinuation
- Commonly reported to occur in very young (≤16 years) and elderly patients (aged ≥65 years)

Risk factors of deferasirox-associated Fanconi syndrome

- Elevated doses
- Pre-existing renal disease
- Reduced renal mass
- Age > 65 anni or pediatric
- Pharmacological interactions (NSAIDS, cyclosporine)
- Low body weight
- Dehydration (ex. diarrhea or vomiting)
- High risk MDS
Diagnosis of renal damage

- An increase in serum creatinine is a surrogate marker of reduced GFR with low sensitivity.
- For serum creatinine levels to reach ULN GFR is reduced to 50–60 ml/min/1.73 m².

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Interpretation</th>
<th>Criterion for CKD</th>
<th>Mentioned in FDA recommendations</th>
<th>Mentioned in EMA recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Markers of decreased GFR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sCr</td>
<td>No specific cut-off value provided</td>
<td>Should be reported</td>
<td>&gt;33% over baseline or &gt;ULN (in duplicate)</td>
<td>&gt;33% over baseline (in duplicate)</td>
</tr>
<tr>
<td>Ccr (estimated by Cockcroft–Gault formula)</td>
<td>Not used</td>
<td>Not used</td>
<td>Yes</td>
<td>Yes; dose adjustment if it falls &lt;90ml/min</td>
</tr>
<tr>
<td>GFR (estimated from Ccr)</td>
<td>MDRD pathological if &lt;60ml/min/1.73 m²</td>
<td>Yes; estimate in adults with 2009 CKD–EPI creatinine equation and in children with Schwartz (creatinine) formula and 1B Equation (BUN)</td>
<td>No</td>
<td>Yes; estimate using MDRD formula in adults and Schwartz formula in children</td>
</tr>
<tr>
<td>Serum cystatin C</td>
<td>Use a cystatin C-derived GFR estimating equation rather than rely on serum cystatin C concentration alone</td>
<td>Suggest measuring cystatin C in adults with eGFR 45–59ml/min/1.73 m² who do not have markers of kidney damage if confirmation of CKD is required</td>
<td>No</td>
<td>Yes (albeit just the serum level, not GFR estimated according to serum cystatin C)</td>
</tr>
</tbody>
</table>

GFR = Filtrato Glomerulare; ULN = superiore al limite normale
## Diagnosis of renal damage

<table>
<thead>
<tr>
<th>Parameter</th>
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<th>Mentioned in EMA recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Markers of kidney damage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albuminuria</td>
<td>Pathological if &gt;3 mg/mmol or &gt;30 mg per day</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>Pathological when &gt;15 mg/mmol or &gt;150 mg per day</td>
<td>Yes</td>
<td>Yes, urine protein:creatinine ratio &gt;0.6 mg/mg (60 mg/mmol)</td>
<td>Yes</td>
</tr>
<tr>
<td>Markers of renal tubular function</td>
<td>No specific cut-off value provided</td>
<td>Yes; for example, renal tubular acidosis, renal potassium wasting, renal magnesium wasting, Fanconi syndrome, nonalbumin proteinuria</td>
<td>No</td>
<td>Glycosuria in patients without diabetes; low serum potassium, phosphate, magnesium or urate; phosphaturia; aminoaciduria</td>
</tr>
</tbody>
</table>

CKD = Chronic Kidney disease

# FDA vs EMA recommendations

<table>
<thead>
<tr>
<th>Initial assessment</th>
<th>Monitoring</th>
<th>Contraindications</th>
<th>Dose adjustment</th>
<th>Problems in routine clinical practice</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FDA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measure sCr in duplicate</td>
<td>Measure sCr weekly during the first month and at least monthly thereafter</td>
<td>Ccr &lt;40 ml/min or sCr more than twice the age-appropriate ULN</td>
<td>Initial dose: 10–20 mg/kg per day; if Ccr 40–60 ml/min, reduce starting dose by 50%</td>
<td>Estimation of Ccr by Cockcroft–Gault is obsolete</td>
</tr>
<tr>
<td>Estimate Ccr by Cockcroft–Gault formula</td>
<td>Monthly monitoring for proteinuria</td>
<td></td>
<td>In response to changes in sCr: reduce dose by 10 mg/kg per day; if sCr increases by ≥33% above baseline, repeat sCr measurements within 1 week, and if still elevated ≥33% or more, interrupt therapy if the dose is 5 mg/kg, or reduce by 50% if the dose is 10 or 20 mg/kg</td>
<td>Age-adjusted ULN not provided by many labs; Proximal tubular dysfunction not assessed; No action suggested for proteinuria changes</td>
</tr>
<tr>
<td></td>
<td>Mentions renal tubular damage but no monitoring</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EMA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measure sCr in duplicate</td>
<td>Measure sCr</td>
<td>Ccr &lt;60 ml/min</td>
<td>Initial dose: 10–20 mg/kg per day</td>
<td>MDRD not a precise estimation method when eGFR &gt;60 ml/min/1.73 m²</td>
</tr>
<tr>
<td></td>
<td>Estimate Ccr* by Cockcroft–Gault or MDRD formula in adults, and by the Schwartz formula in children, and/or measure plasma cystatin C levels weekly in the first month after initiation or modification of therapy and monthly thereafter</td>
<td></td>
<td>In response to changes in sCr: dose can be reduced by 10 mg/kg if sCr increases by &gt;33% above the average of the pretreatment measurements and estimated Ccr* decreases &lt;90 ml/min at two consecutive visits and cannot be attributed to other causes</td>
<td>Proximal tubular dysfunction not routinely assessed</td>
</tr>
<tr>
<td></td>
<td>Monthly monitoring for proteinuria</td>
<td></td>
<td></td>
<td>No action suggested for proteinuria changes</td>
</tr>
<tr>
<td></td>
<td>Markers of renal tubular function (for example, glycosuria in patients without diabetes; low levels of serum potassium, phosphate, magnesium or urate; phosphaturia, or aminosiduria) can also be monitored</td>
<td></td>
<td></td>
<td>Contraindications and dose adjustment strategy differ from those suggested by FDA</td>
</tr>
</tbody>
</table>
Deferasirox Summary of Product Characteristics: Prevention of renal dysfunction

1. Serum creatinine
   - If progressive increase > 33% compared to baseline in 2 consecutive visits*
     - Reduce deferasirox to 5–10 mg/kg/daily
     - If creatinine > ULN, interrupt treatment and restart at a lower dose

2. Proteinuria
   - Monitor

* Not attributable to other causes
ULN= Upper limit of normality
Case 1. Creatinine vs GFR

GFR Calculators: Serum Creatinine and Cystatin C (2012)
(With SI Units)

4 variable MDRD Study Equation, CKD-EPI Creatinine Equation (2009), CKD-EPI Cystatin C Equation (2012) and CKD-EPI Creatinine-Cystatin C Equation (2012) (with SI Units) using standardized serum creatinine, age, race, gender and serum cystatin C

programmed by Stephen Z. Fadem, M.D., FACP, FASN and Brian Rosenthal

Serum creatinine
- mg/dL  μmol/L

Serum Cystatin C (mg/L)

NOTE: CKD-EPI GFR is only valid with serum creatinine methods are traceable to IDMS

Age

Race

Gender

TRACEABLE TO IDMS (What is this?)

EQUATION:

CKD-EPI CREATININE (2009)
CKD-EPI CYSTATIN C (2012)
CKD-EPI CREATININE-CYSTATIN C (2012)

MDRD STUDY EQUATION

in a 80 year old Non African American male.

Chronic kidney disease (GFR less than 60 or kidney damage for at least three months)

80 years
- African American  All other races*
- Male  Female
- No  Yes

VALUE:
(mL/min/1.73 m²)

71

72
Case 1. Creatinine > 33% baseline value vs GFR

GFR Calculators: Serum Creatinine and Cystatin C (2012) (With SI Units)

4 variable MDRD Study Equation, CKD-EPI Creatinine Equation (2009), CKD-EPI Cystatin C Equation (2012) and CKD-EPI Creatinine-Cystatin C Equation (2012) (with SI Units) using standardized serum creatinine, age, race, gender and serum cystatin C

programmed by Stephen Z. Fadem, M.D., FACP, FASN
and Brian Rosenthal

Creatinine increase > 33%:
what to do?

Serum creatinine
• mg/dL • µmol/L

Serum Cystatin C (mg/L)

NOTE: CKD-EPI GFR is only valid with serum creatinine methods are traceable to IDMS

Age

Race

Gender

TRACEABLE TO IDMS (What is this?)

EQUATION:

CKD-EPI CREATININE (2009)
CKD-EPI CYSTATIN C (2012)
CKD-EPI CREATININE-CYSTATIN C (2012)
MDRD STUDY EQUATION:
in a 80 year old Non African American male.

80 years

African American • All other races

Male • Female

No • Yes

VALUE:
(mL/min/1.73 m²)

50

52
Case 2. Creatinine vs GFR

Creatinine 0.9 = clearance 60 ml/min
Case 2. Creatinine > 33% baseline value vs GFR

GFR Calculators: Serum Creatinine and Cystatin C (2012)
(With SI Units)

4 variable MDRD Study Equation, CKD-EPI Creatinine Equation (2009), CKD-EPI Cystatin C Equation (2012) and CKD-EPI Creatinine-Cystatin C Equation (2012) (with SI Units) using standardized serum creatinine, age, race, gender and serum cystatin C

programmed by Stephen Z. Fadem, M.D., FACP, FASN
and Brian Rosenthal

Serum creatinine
mg/dL µmol/L
Serum Cystatin C (mg/L)

Creatinine increase > 33%:
what to do?

1.33

80 years

<table>
<thead>
<tr>
<th>African American</th>
<th>All other races*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

VALUE:
(mL/min/1.73 m²)
38

38
Renal adverse events: Conclusions

- Deferasirox is potentially nephrotoxic
- The causes of nephrotoxicity, its epidemiology and clinical impact are not yet well-known
- Renal adverse events are generally asymptomatic; therefore monitoring is warranted for creatinine levels, serum and urinary electrolytes, GFR and urinalysis
- Renal damage is generally reversible with dose reduction or interruption
Agenda

- Transfusion-dependence in MDS
- Diagnosis of Iron Overload
- Indications for chelation
- Management of adverse events
- Compliance and efficacy
- Survival and hematological improvement
Adherence to deferasirox

- Adherence increases but <90%

EOS, end of study
*patients with prior history of ICT
**patients with no prior history of IC

Factors influencing non-adherence

Territory-specific
- Access to health services
- Provision of drugs

Center-specific
- Health and drug information (communication)
- Follow-up

Drug-specific
- Formulation, administration
- Side effects

Compliance determines morbidity and mortality

Reduction in Compliance

Reduction in survival

![Graph showing survival distribution function with time from diagnosis to death (months)]

- Non-chelated
- Weak chelation
- Adequate chelation

Median overall survival:
- 53 months if no chelation
- 85 months with weak chelation
- 124 months with adequate chelation

References:
Agenda

- Transfusion-dependence in MDS
- Diagnosis of Iron Overload
- Indications for chelation
- Management of adverse events
- Compliance and efficacy
- Survival and hematological improvement
## Iron chelation and survival in transfusion-dependent

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Design</th>
<th>Survival</th>
<th>Non-chelated patients</th>
<th>Chelated patients</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leitch 2008</td>
<td>36</td>
<td>Retrospective</td>
<td>Median OS</td>
<td>40 mo</td>
<td>Not reached</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4-year survival rate</td>
<td>43%</td>
<td>64%</td>
<td>0.003</td>
</tr>
<tr>
<td>Rose 2010</td>
<td>97</td>
<td>Prospective follow-up</td>
<td>Median OS from diagnosis</td>
<td>53 mo</td>
<td>124 mo</td>
<td>&lt; 0.0003</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Median OS with adequate vs weak chelation</td>
<td>NA</td>
<td>124 vs. 85 mo</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Neukirchen 2012</td>
<td>188</td>
<td>Matched pair analysis</td>
<td>Median OS</td>
<td>49 mo</td>
<td>75 mo</td>
<td>0.002</td>
</tr>
<tr>
<td>Neukirchen 2012</td>
<td>417</td>
<td>Retrospective, registry</td>
<td>Median time to death in TD patients</td>
<td>30 mo</td>
<td>67 mo</td>
<td>NR</td>
</tr>
<tr>
<td>Komrokji 2011</td>
<td>97</td>
<td>Retrospective</td>
<td>Median OS</td>
<td>34 mo</td>
<td>59 mo</td>
<td>0.013</td>
</tr>
<tr>
<td>Delforge 2012</td>
<td>186</td>
<td>Retrospective</td>
<td>Median OS in Low/Int-1</td>
<td>37 mo</td>
<td>126 mo</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Zeidan 2012</td>
<td>4,226</td>
<td>Retrospective, registry</td>
<td>Median survival</td>
<td>47 wk</td>
<td>110 wk</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HR for 27-52 wks on DFX</td>
<td>1</td>
<td>0.77</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HR for ≥ 53 wk on DFX</td>
<td>1</td>
<td>0.34</td>
<td>NR</td>
</tr>
<tr>
<td>Remacha 2012</td>
<td>228</td>
<td>Retrospective</td>
<td>Median OS</td>
<td>105 mo</td>
<td>133 mo</td>
<td>0.009</td>
</tr>
<tr>
<td>Lyons 2013</td>
<td>600</td>
<td>Prospective, registry</td>
<td>Median OS from diagnosis</td>
<td>48.7 mo</td>
<td>All 96.8 mo ICT &gt; 6 mo 102.5 mo</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>de Witte T 2012</td>
<td>1,000</td>
<td>Prospective, registry</td>
<td>Adjusted HR</td>
<td>1</td>
<td>0.51 (0.19-1.32)</td>
<td>NS</td>
</tr>
</tbody>
</table>
US22 prospective registry: chelated MDS patients experience less deaths from any cause

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Non-chelated (N = 328)</th>
<th>Chelated (N = 271)</th>
<th>Chelated ≥ 6 months (N = 202)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to death, median (min, max), months</td>
<td>47.8 (43.4, 53.1)</td>
<td>88.0 (78.4, 103.0) a,*</td>
<td>100.0 (83.4, 118.2) *</td>
</tr>
<tr>
<td>Deaths, n (%)</td>
<td>239 (72.9)</td>
<td>161 (59.4) a,**</td>
<td>115 (56.9) a,***</td>
</tr>
<tr>
<td>Cause of death, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDS/AML</td>
<td>103 (31.4)</td>
<td>73 (26.9)</td>
<td>53 (26.2)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>36 (11.0)</td>
<td>21 (7.7)</td>
<td>15 (7.4)</td>
</tr>
<tr>
<td>Infection</td>
<td>27 (8.2)</td>
<td>14 (5.2)</td>
<td>14 (6.9)</td>
</tr>
<tr>
<td>Other</td>
<td>16 (4.9)</td>
<td>16 (5.9)</td>
<td>10 (5.0)</td>
</tr>
<tr>
<td>Unknown</td>
<td>29 (8.8)</td>
<td>18 (6.6)</td>
<td>12 (5.9)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>14 (4.3)</td>
<td>2 (0.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>7 (2.1)</td>
<td>7 (2.6)</td>
<td>4 (2.0)</td>
</tr>
<tr>
<td>Multi-organ failure</td>
<td>3 (0.9)</td>
<td>3 (1.1)</td>
<td>3 (1.5)</td>
</tr>
<tr>
<td>CVA</td>
<td>1 (0.3)</td>
<td>5 (1.8)</td>
<td>3 (1.5)</td>
</tr>
<tr>
<td>GVHD/transplant</td>
<td>3 (0.9)</td>
<td>2 (0.7)</td>
<td>1 (0.5)</td>
</tr>
</tbody>
</table>

a Versus non-chelated. * p < 0.0001; ** p = 0.0002; *** p = 0.0005.

## MDS-CAN study

### Demographics

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Without Iron Chelation (n = 149)</th>
<th>With Iron Chelation (n = 70)</th>
<th>p-value *</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at diagnosis (years)</strong></td>
<td></td>
<td></td>
<td>0.0003</td>
</tr>
<tr>
<td>Median (Inter-quartiles)</td>
<td>74 (65, 80)</td>
<td>68 (61, 73)</td>
<td></td>
</tr>
<tr>
<td><strong>Time from diagnosis to TD (months)</strong></td>
<td></td>
<td></td>
<td>0.1002</td>
</tr>
<tr>
<td>Median (Inter-quartiles)</td>
<td>11 (3, 32)</td>
<td>17 (7, 48)</td>
<td></td>
</tr>
<tr>
<td><strong>ECOG distribution</strong></td>
<td></td>
<td></td>
<td>0.3982</td>
</tr>
<tr>
<td>0</td>
<td>45 (31.47%)</td>
<td>17 (25.37%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>79 (55.24%)</td>
<td>46 (68.66%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>15 (10.49%)</td>
<td>4 (5.97%)</td>
<td></td>
</tr>
<tr>
<td>3-4</td>
<td>4 (2.80)</td>
<td>0 (0.00%)</td>
<td></td>
</tr>
<tr>
<td><strong>Duration of follow-up from diagnosis (years)</strong></td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Median (Inter-quartiles)</td>
<td>2 (1, 4)</td>
<td>5 (2, 7)</td>
<td></td>
</tr>
<tr>
<td><strong>WHO at diagnosis (combined categories)</strong></td>
<td></td>
<td></td>
<td>0.0667</td>
</tr>
<tr>
<td>RA, RARS, 5q, NDS-U, Unclassified, RCUD-A, RCUD-T</td>
<td>52 (36.11%)</td>
<td>37 (54.41%)</td>
<td></td>
</tr>
<tr>
<td>RCMD/RCMD-RS</td>
<td>56 (38.89%)</td>
<td>24 (35.29%)</td>
<td></td>
</tr>
<tr>
<td>CMML, MDS/MPD</td>
<td>17 (11.81%)</td>
<td>4 (5.88%)</td>
<td></td>
</tr>
<tr>
<td>RAEB1</td>
<td>14 (9.72%)</td>
<td>2 (2.94%)</td>
<td></td>
</tr>
<tr>
<td>RAEB2</td>
<td>5 (3.47%)</td>
<td>1 (1.47%)</td>
<td></td>
</tr>
</tbody>
</table>

### IPSS, IPSSR, Karyotype at diagnosis

<table>
<thead>
<tr>
<th>IPSS at diagnosis</th>
<th></th>
<th></th>
<th>0.0404</th>
</tr>
</thead>
<tbody>
<tr>
<td>INT-1</td>
<td>97 (66.90%)</td>
<td>31 (50.82%)</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>48 (33.10%)</td>
<td>30 (49.18%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IPSSR at diagnosis (3 categories)</th>
<th></th>
<th></th>
<th>0.0243</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>65 (44.83%)</td>
<td>36 (59.02%)</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>58 (40.00%)</td>
<td>23 (37.70%)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>22 (15.17%)</td>
<td>2 (3.28%)</td>
<td></td>
</tr>
</tbody>
</table>
### MDS-CAN study
Multivariate analysis

<table>
<thead>
<tr>
<th>Final Model</th>
<th>Independent Covariate</th>
<th>Coefficient</th>
<th>SE</th>
<th>p-value</th>
<th>HR</th>
<th>95% CI of HR</th>
<th>R² (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predictive factors</td>
<td>Iron Chelation (No vs. Yes)</td>
<td>0.59912</td>
<td>0.24678</td>
<td>0.0152</td>
<td>1.821</td>
<td>1.122</td>
<td>2.953</td>
</tr>
<tr>
<td></td>
<td>Age at time of TD (years)</td>
<td>0.02471</td>
<td>0.00989</td>
<td>0.0125</td>
<td>1.025</td>
<td>1.005</td>
<td>1.045</td>
</tr>
<tr>
<td></td>
<td>IPSSR at time of TD (3 categories)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High vs. Low</td>
<td>1.05299</td>
<td>0.29718</td>
<td>0.0004</td>
<td>2.866</td>
<td>1.601</td>
<td>5.132</td>
</tr>
<tr>
<td></td>
<td>Intermediate vs. Low</td>
<td>0.42055</td>
<td>0.23824</td>
<td>0.0775</td>
<td>1.523</td>
<td>0.955</td>
<td>2.429</td>
</tr>
<tr>
<td></td>
<td>High vs. Intermediate</td>
<td>-</td>
<td>-</td>
<td>0.0292</td>
<td>1.882</td>
<td>1.066</td>
<td>3.322</td>
</tr>
</tbody>
</table>

**Graph:**
- Time since diagnosis (years) vs. Overall survival probability
- Legend: Without Iron Chelation, With Iron Chelation
- p-value = 0.0005
Hematological improvement during iron chelation

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>IPSS risk</th>
<th>RBC response</th>
<th>Neutrophil response</th>
<th>Platelet response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cilloni D, et al. 2011(^1)</td>
<td>57</td>
<td>Low/Int-1</td>
<td>45.6%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Molteni A et al. 2013(^2)</td>
<td>53</td>
<td>Low/Int-1</td>
<td>35.1%</td>
<td>76.4%</td>
<td>61%</td>
</tr>
<tr>
<td>Cheong JW, et al. 2013(^3)</td>
<td>96</td>
<td>Low/Int-1</td>
<td>Hb level</td>
<td>NS</td>
<td>PLTs increased</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>increased by 1.36 g/dL</td>
<td></td>
<td>by 10.7 x 10(^9)</td>
</tr>
<tr>
<td>List A, et al. 2012(^4)</td>
<td>173</td>
<td>Low/Int-1</td>
<td>15%</td>
<td>15%</td>
<td>22%</td>
</tr>
<tr>
<td></td>
<td>52/77</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gattermann N, et al. 2012(^5)</td>
<td>247</td>
<td>Low/Int-1</td>
<td>21.5%</td>
<td>22%</td>
<td>13%</td>
</tr>
<tr>
<td></td>
<td>50/100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nolte F, et al. 2012(^6)</td>
<td>50</td>
<td>Low/Int-1</td>
<td>11%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Angelucci E, et al. 2014(^7)</td>
<td>152</td>
<td>Low/Int-1</td>
<td>11%</td>
<td>3%</td>
<td>15%</td>
</tr>
</tbody>
</table>

RBC, platelet, and neutrophil responses are assessed according to IWG 2006 criteria (1–3).

GIMEMA prospective trial: hematological improvement in IPSS low and int-1 risk MDS

All responses to last ≥ 12 weeks; erythroid response: transfusion independence
Treated with ESAs (n = 403)
Untreated (n = 628)

ESA responders
Non responders
Untreated

Overall survival (%)

Years from diagnosis

p<0.001

Erythropoietic stimulating agents (ESAs) in MDS: longer survival in responders

Lenalidomide: Longer survival in responders

Oliva EN, et al. Leuk Lymph 2013
Azacitidine: Longer survival in responders

Adapted from List AF, et al. Oral presentation at ASCO 2008, Chicago, IL, USA
Quality of life: Hb and transfusion-dependence

MDS-Specific Quality of life questionnaire, QOL-E:

Efficacy of lenalidomide: transfusion independence and quality of life changes

QOL-E scores

Oliva EN, et al. Leuk Lymph 2013
Conclusions

- The MDS population is vulnerable and iron overload impacts morbidity and mortality.
- The indication for iron chelation should be established on guidelines and on an individual basis.
- Ferritin levels, units of pRBC and MRI evaluation should guide treatment.
- Renal toxicity must be monitored.
- Adverse events may be avoided and managed through an appropriate patient-physician relationship, which influences compliance.
- Iron chelation may improve survival and is associated with hematological improvements with a favorable impact on morbidity and quality of life.