Deferasirox for iron overload patients: preserving organ functions

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Iron overload has a strong negative impact on survival of patients with β thalassemia major

Clinical sequelae of iron overload

- Pituitary → impaired growth
- Heart → cardiomyopathy, cardiac failure
- Liver → liver cirrhosis
- Pancreas → diabetes mellitus
- Gonads → hypogonadismus, infertility


Iron chelation has a strong positive impact on survival of patients with β thalassemia major.

Improvement in survival by later birth date reflects the availability of DFO treatment for IOL and the extent of patient compliance with treatment.


Why is it difficult to extrapolate this knowledge into the field of MDS?

- Exposure to iron overload is shorter in MDS
  - Transfusion therapy in MDS starts much later in life
  - Many patients with MDS do not live long enough to develop clinical complications of iron overload

- Iron-related complications in elderly MDS patients overlap with age-related medical problems
In elderly MDS patients, iron-related complications overlap with age-related medical problems.
Common causes of death in the elderly

- ↑ Vascular damage
- ↑ Heart failure
- ↑ Infections
- ↑ Liver dysfunction

Iron overload → Strong cumulative effect?
Survival of patients with MDS according to serum ferritin level

HR = hazard ratio; RA = refractory anemia; RARS = RA with ring sideroblasts.

Patients with RA/RARS/5q− (HR = 1.42; p<0.001)

Serum ferritin is an independent prognostic factor in MDS

Iron burden affects survival: > 1,000 µg/L SF threshold

A 30% greater risk of death was evident for every 500 µg/L increase in SF above a 1,000 µg/L threshold

European Leukemia Net (ELN) prospective MDS registry: Independent survival impact of SF

Besides transfusion burden, increasing levels of SF also had independent impact on the OS of transfusion-dependent patients with lower-risk MDS

ELN prospective MDS registry: Survival impact of labile plasma iron (LPI)

Possible relationship between bone marrow failure, iron overload and prognosis in patients with MDS
Possible relationship between bone marrow failure, iron overload and prognosis in patients with MDS

Severe bone marrow disease → Infections → Bleeding → Anemia → Transfusion dependency

Iron overload → Cardiac dysfunction → Overall Survival ↓

Overall Survival ↓
The heart is more vulnerable to iron overload than the liver.

Iron values derived from animal studies.

Clinically relevant cardiac dysfunction occurs at much lower tissue iron concentrations than clinically relevant liver dysfunction.

On T2* Magnetic Resonance and Cardiac Iron

John-Paul Carpenter, MB, MRCP*; Taigang He, PhD*; Paul Kirk, MB, MRCP; Michael Roughton, MSc; Lisa J. Anderson, MD, MRCP; Sofia V. de Noronha, PhD; Mary N. Sheppard, MD, FRCP; John B. Porter, MD, FRCP, FRCP; J. Malcolm Walker, FRCP; John C. Wood, MD; Renzo Galanello, MD; Gianluca Forni, MD; Gualtiero Catani, MD; Gildo Matta, MD; Suthat Fucharoen, MD; Adam Fleming, BSc; Michael J. House, PhD; Greg Black, MSc; David N. Firmin, PhD; Timothy G. St. Pierre, PhD; Dudley J. Pennell, MD, FRCP

**Background**—Measurement of myocardial iron is key to the clinical management of patients at risk of siderotic cardiomyopathy. The cardiovascular magnetic resonance relaxation parameter R2* (assessed clinically via its reciprocal, T2*) measured in the ventricular septum is used to assess cardiac iron, but iron calibration and distribution data in humans are limited.

**Methods and Results**—Twelve human hearts were studied from transfusion-dependent patients after either death (heart failure, n=7; stroke, n=1) or transplantation for end-stage heart failure (n=4). After cardiovascular magnetic resonance R2* measurement, tissue iron concentration was measured in multiple samples of each heart with inductively coupled plasma atomic emission spectroscopy. Iron distribution throughout the heart showed no systematic variation between segments, but epicardial iron concentration was higher than in the endocardium. The mean±SD global myocardial iron causing severe heart failure in 10 patients was 5.98±2.42 mg/g dry weight (range, 3.19 to 9.50 mg/g), but in 1 outlier case of heart failure was 25.9 mg/g dry weight. Myocardial ln[R2*] was strongly linearly correlated with ln[Fe] (R²=0.910, P<0.001), leading to [Fe]=45.0×(T2*)⁻¹.22 for the clinical calibration equation with [Fe] in milligrams per gram dry weight and T2* in milliseconds. Midventricular septal iron concentration and R2* were both highly representative of mean global myocardial iron.

**Conclusions**—These data detail the iron distribution throughout the heart in iron overload and provide calibration in humans for cardiovascular magnetic resonance R2* against myocardial iron concentration. The iron values are of considerable interest in terms of the level of cardiac iron associated with iron-related death and indicate that the heart is more sensitive to iron loading than the liver. The results also validate the current clinical practice of monitoring cardiac iron in vivo by cardiovascular magnetic resonance of the midseptum. (*Circulation. 2011;123:1519-1528.*)
Possible relationship between bone marrow failure, iron overload and prognosis in patients with MDS

- Severe bone marrow disease → Infections → Bleeding → Anemia
- Transfusion dependency
- Iron overload → ESA, transfusions
- Cardiac dysfunction
- Overall Survival ↓
- Iron chelation

Overall Survival ↓
Iron-related endothelial dysfunction: an underestimated clinical problem?

With increasing age, high circulating iron levels strongly enhance the severity of the atherosclerotic phenotype, indicating that systemic iron overload is a risk factor for atherosclerosis progression and predisposes to cardiovascular disease.

Pathophysiological model: a role for macrophage-retained iron in atherosclerosis

Iron Chelation Improves Endothelial Function in Patients With Coronary Artery Disease

Stephen J. Duffy, MB, BS, PhD; Elizabeth S. Biegelsen, MD; Monika Holbrook, MS; Judson D. Russell, BS; Noyan Gokce, MD; John F. Keaney, Jr, MD; Joseph A. Vita, MD

**Background**—Some epidemiological studies have shown that increased iron stores are associated with increased cardiovascular events. Redox-active iron may contribute to lipid peroxidation, endothelial cell activation, and generation of reactive oxygen species (especially hydroxyl radical, via Fenton chemistry). Increased oxidative stress is associated with impaired action of endothelium-derived nitric oxide in patients with atherosclerosis.

**Methods and Results**—To test the hypothesis that reducing vascular iron stores would reverse endothelial dysfunction, we examined the effects of the iron chelator deferoxamine (500 mg intra-arterially over 1 hour) on vasomotor function in forearm resistance vessels of patients with coronary artery disease by venous occlusion plethysmography. Patients with coronary artery disease had impaired endothelium-dependent vasodilation in response to methacholine compared with healthy control subjects ($P<0.001$). Deferoxamine infusion decreased serum iron levels ($P<0.001$). Deferoxamine improved the blood flow response to methacholine in patients with coronary artery disease ($P<0.01$ by 2-way repeated-measures ANOVA) but had no effect on the response to sodium nitroprusside. In normal volunteers, deferoxamine had no effect on the response to methacholine. The nitric oxide synthase inhibitor $N^\text{G}$-monomethyl-$L$-arginine abolished augmentation of the methacholine response associated with deferoxamine. The hydroxyl radical scavenger mannitol had no effect on the methacholine response.

**Conclusions**—Deferoxamine improved nitric oxide-mediated, endothelium-dependent vasodilation in patients with coronary artery disease. These results suggest that iron availability contributes to impaired nitric oxide action in atherosclerosis. (*Circulation.* 2001;103:2799-2804.)

**Key Words:** iron ■ nitric oxide ■ endothelium ■ coronary disease
Deferasirox has the ability to

- bind labile cell iron pools in the vascular wall
- diminish reactive oxygen species formation and
- attenuate nitric oxide inactivation.

**Effect of deferasirox on arterial function in patients with beta-thalassemia major**

Cheung et al. (2008)
Br J of Haematol. 141:728–33
Hepatic iron overload in MDS
EPIC Study: Reduction in serum ferritin associated with improvement in ALT

At 12 months, there were significant reductions in
- median serum ferritin (-253 µg/L; p=0.002)
- mean ALT (-27.7 ± 37.4 U/L; p<0.0001)

Mean actual deferasirox dose:
19.2 ± 5.4 mg/kg/day

Gattermann et al. Leuk Res. 2010 Sep;34(9):1143-50
Iron overload in lower international prognostic scoring system risk patients with myelodysplastic syndrome receiving red blood cell transfusions: Relation to infections and possible benefit of iron chelation therapy

Colleen A.C. Wong\textsuperscript{a}, Shannon A.Y. Wong\textsuperscript{a}, Heather A. Leitch\textsuperscript{b,*}

Clinical factors differing between ICT and non-ICT pts, respectively, were (median [range]):
- **age at 1st RBC transfusion**, 67 (31-88) and 75 (43-93) yrs
- **number of RBC units (U) transfused while lower risk**, 76 (10-675) and 24 (2-200)
- **number of RBCU/4 weeks**, 2.2 (0.5-9.1) and 2.0 (0.1-5.4)
- **serum ferritin**, 914 (49-15608) and 266 (12-5009) ng/mL
- **other treatments received**, 18 (30.5%) and 5 (6.3%) (\(p \leq 0.04\) for all)

Factors not differing between groups were:
- gender; FAB or WHO MDS diagnosis;
- marrow blast count;
- IPSS or IPSSR cytogenetic risk;
- IPSS or IPSSR risk;
- neutrophil count at first RBC transfusion or at first infection
- causes of death (\(p = \text{NS}\) for all)

In this retrospective, non-controlled analysis, for lower IPSS risk MDS patients receiving RBC transfusions, receiving iron chelation therapy was associated with superior overall survival. Though number and type of infections were similar between groups and despite similar neutrophil counts, **time to first infection was significantly longer in ICT patients.** These results should be confirmed in larger, prospective analyses.
The bone marrow may also be affected by iron overload

- Severe bone marrow disease
  - Infections
  - Bleeding
  - Anemia

- Transfusion dependency

- Cardiac dysfunction

- Overall Survival ↓

- Iron overload

- Overall Survival ↓
Clinical relevance?

- Hereditary hemochromatosis is **not** notorious for causing bone marrow dysfunction.

- Patients with β-thalassemia major and transfusional iron overload are **not** at risk of developing MDS or AML.

Is iron overload irrelevant for bone marrow function?
Iron overload: two different scenarios in the bone marrow

HH, TM

Iron overload

Polyclonal non-malignant hematopoiesis

Sufficient antioxidant defenses and DNA repair

No substantial bone marrow dysfunction

Clonal (pre)malignant hematopoiesis

MDS

Insufficient antioxidant defenses and DNA repair

Aggravation of bone marrow dysfunction
Increased oxidative stress in MDS


Antioxidant Enzyme Expression In Myelodysplastic And Acute Myeloid Leukemia Bone Marrow: Further Evidence Of A Pathogenetic Role For Oxidative Stress

D Bowen, L Wang, M Frew, R Kerr, M Groves
Haematologica January 2003 WW-1070-1072, 881

Enhanced growth of myelodysplastic colonies in hypoxic conditions

James Edwin Thompson, Joseph Patrick Conlon, Xiaowei Yang, Patricia Vanessa Sanchez, and Martin Carroll

Oxidative stress in red blood cells, platelets and polymorphonuclear leukocytes from patients with myelodysplastic syndrome

Hussam Ghoti, Johnny Amar, Asher Winder, Eliezer Rachmilewitz, Eltan Fibach

Oxidative DNA damage in bone marrow cells of patients with low-risk myelodysplastic syndrome

Bozena Novotna, Yana Bagryantseva, Magda Siskova, Radana Neuwirtova

Oxidative stress leads to increased mutation frequency in a murine model of myelodysplastic syndrome

Yang Jo Chung, Carine Robert, Sheryl M. Gough, Feyruz V. Rassool, Peter D. Aplan
Oxidative stress in the bone marrow is aggravated by iron overload, with detrimental effects on hematopoietic progenitors and the stroma.
Contribution of IOL to bone marrow dysfunction in MDS

- Iron overload by itself is apparently not leukemogenic.

- In the context of pre-existing genomic instability of the MDS clone, iron overload may accelerate mutagenesis and clonal evolution.

- Iron overload may impair proliferation and maintenance of (residual) normal HSPCs.

- Erythropoiesis appears to be particularly vulnerable to IOL.

- IOL also perturbs the bone marrow stroma.
Iron overload damages the bone marrow stroma

- BM transplantation from normal donors to recipients with IOL showed delayed haemopoietic reconstitution, indicating that excess iron negatively impacts the haemopoietic microenvironment.
- MSC showed markedly reduced expression of surface molecules known to be involved in stem cell homing.
- IOL impairs the proliferation of mouse BM mesenchymal cells.
- Free iron catalyzes in vitro oxidative damage to mesenchymal cells attenuating haemopoiesis.
Where does iron overload contribute to MDS pathology?

Iron overload

Oxidative stress

Replicative stress

T cell attack

Radiation

Chemicals

Stem cell mutation

Genomic instability (MSI, CIN)

Clones with multiple mutations

Maladapted clones with survival advantage

Clonal evolution

AML

Cytokine release

Immune reaction

Inflammatory milieu

Epigenetic reprogramming

Immunogenicity

Selection pressure

Iron overload

Altered marrow stroma
Beneficial effect of **chelation with DFX** on oxidative stress in MDS: decreased ROS production, decreased lipid peroxidation, improved colony growth, and diminished iron-mediated oxidative DNA damage.

  
  **Changes in parameters of oxidative stress and free iron biomarkers during treatment with deferasirox is iron-overloaded patients with myelodysplastic syndromes.**
  
  Haematologica 95:1433-1434

  
  **Improvement of iron-mediated oxidative DNA damage in patients with transfusion-dependent myelodysplastic syndrome by treatment with deferasirox.**
  
  Free Radical Bio Med 53:643-648
Deferasirox can improve hematopoiesis in MDS

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk IPSS</th>
<th>RBC response</th>
<th>Neutrophil response</th>
<th>PLT response</th>
</tr>
</thead>
<tbody>
<tr>
<td>List A et al. J Clin Oncol. 2012; 30:2134-9</td>
<td>Low/Int-1</td>
<td>15% (n=173)</td>
<td>15% (n=52)</td>
<td>22% (n=77)</td>
</tr>
<tr>
<td>Gattermann N et al. Haematologica 2012; 97:1364-71</td>
<td>Low/Int-1</td>
<td>21.5% (n=247)</td>
<td>22% (n=50)</td>
<td>13% (n=100)</td>
</tr>
<tr>
<td>Angelucci E et al. Eur J Hematol 2014; 92:527-36</td>
<td>Low/Int-1</td>
<td>Transfusion independence in 15.5% (n=152)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Meunier M et al. Oncotarget 2017; 8:105510-105524</td>
<td>Low/Int-1</td>
<td>Transfusion independence in 100% (n=6)</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>
Potential benefits of iron chelation in MDS

- Lower incidence of cardiac events, diabetes, and hepatic impairment
- Fewer infectious complications
- Improved hematopoietic function
- Lower risk of leukemic transformation
- Improved outcome of allogeneic SCT
Iron chelation may improve survival in transfusion-dependent MDS patients

<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 40 mo</td>
<td>Not reached</td>
<td>40 mo</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4-year survival rate 43%</td>
<td>64%</td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>Rose 2010</td>
<td>97</td>
<td>Prospective follow-up</td>
<td>Median OS from diagnosis 53 mo</td>
<td>124 mo</td>
<td>&lt; 0.0003</td>
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<td></td>
<td></td>
<td></td>
<td>Median OS with adequate vs weak chelation NA</td>
<td>124 vs. 85 mo</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Neukirchen 2012a</td>
<td>188</td>
<td>Matched pair analysis</td>
<td>Median OS 49 mo</td>
<td>75 mo</td>
<td>0.002</td>
<td></td>
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<tr>
<td>Neukirchen 2012b</td>
<td>417</td>
<td>Retrospective, registry</td>
<td>Median time to death in TD patients 30 mo</td>
<td>67 mo</td>
<td>NR</td>
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<tr>
<td>Komrokji 2011</td>
<td>97</td>
<td>Retrospective</td>
<td>Median OS 34 mo</td>
<td>59 mo</td>
<td>0.013</td>
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<tr>
<td>Zeidan 2012</td>
<td>4,226</td>
<td>Retrospective, registry</td>
<td>Median survival 47 wk</td>
<td>110 wk</td>
<td>0.003</td>
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<td></td>
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<td></td>
<td>HR for 27-52 wks on DFX 1</td>
<td>0.77</td>
<td>NR</td>
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<tr>
<td></td>
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<td></td>
<td>HR for ≥ 53 wk on DFX 1</td>
<td>0.34</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>de Witte T 2012</td>
<td>1,000</td>
<td>Prospective, registry</td>
<td>Adjusted HR 1</td>
<td>0.51 (0.19-1.32)</td>
<td>NS</td>
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<tr>
<td>Delforge 2014</td>
<td>127</td>
<td>Retrospective</td>
<td>Median OS in Low/Int-1 3.1 yrs</td>
<td>10.2 yrs</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Lyons 2014</td>
<td>600</td>
<td>Prospective, registry</td>
<td>Median OS from diagnosis 47.8 mo</td>
<td>All 88.0 mo</td>
<td>&lt; 0.0001</td>
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<td></td>
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<td>ICT &gt; 6 mo</td>
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<td></td>
<td>100.0 mo</td>
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<tr>
<td>Remacha 2015</td>
<td>263</td>
<td>Retrospective</td>
<td>Median OS 105 mo</td>
<td>133 mo</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

The main problem with studies on the survival impact of iron chelation in MDS patients

- Patient populations are usually well characterized regarding disease-related parameters and risk factors.

- Patient populations are usually not characterized and not stratified according to overall performance status and comorbidities.

- Possible bias: Patients with better overall performance status may have been more likely to be started on iron chelation therapy. This may have had an impact on clinical outcome.
Overall survival with and without ICT
OS measured from start of transfusion dependence

in all patients

excluding pts. receiving HMA and/or lenalidomide

restricted to IPSS-R very low, low and intermediate, and excluding RARS, RARS-T and RCMD-RS

Leitch HA et al., Br J Haematol. 2017; 179:83-97
In order to further adjust for differences in baseline characteristics between groups, a \textit{matched pair analysis} (at the time of transfusion dependence) was performed, including 83 ICT and 83 non-ICT pts.

**Matching criteria:**

- Age
- IPSS-R
- Number of RBC units transfused per month
- Time from MDS diagnosis until RBC transfusion dependence

Leitch HA et al., Br J Haematol. 2017; 179:83-97
Overall survival in patients with or without iron chelation in matched pairs restricted to IPSS-R very low, low and intermediate, and excluding RARS, RARS-T and RCMD-RS including receiving hypomethylating agents (HMA) and/or lenalidomide in the matching, and further excluding pts. receiving HMA.

\[ P = 0.02 \]

\[ P = 0.03 \]

\[ P = 0.01 \text{ at 2.5 yrs from TD} \]

\[ P = 0.2 \]
Overall survival with and without ICT in matched pairs

In this prospective, nonrandomized analysis, receiving ICT was associated with superior OS in lower IPSS risk MDS, adjusting for age, frailty, comorbidity, disability, revised IPSS, TD severity, time to TD and receiving disease-modifying agents. This provides additional evidence that ICT may confer clinical benefit.

Leitch HA et al., Br J Haematol. 2017; 179:83-97
Impact of treatment with iron chelators in lower-risk MDS patients participating in the European Leukemia Net MDS (EUMDS) Registry

Kaplan-Meier survival estimate of Deferasirox vs non-ICT

Adjusted Overall Survival

OS of 192 chelated patients was significantly better when compared with a large control group of 573 patients, even after adjustment for all relevant prognostic factors, i.e.

- age
- sex
- comorbidity
- performance status
- number of RBC units transfused prior to start of chelation
### Table 2 Data of three chelated subgroups and control group at time of reaching the eligibility criteria

<table>
<thead>
<tr>
<th></th>
<th>Unchelated</th>
<th>Chelated</th>
<th>Deferasirox</th>
<th>Deferoxamine</th>
<th>Deferiprone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>657</td>
<td>205</td>
<td>154</td>
<td>39</td>
<td>12</td>
</tr>
<tr>
<td><strong>No. of countries with chelated patients</strong></td>
<td>17 / 17</td>
<td>17 / 17</td>
<td>14 / 17</td>
<td>10 / 17</td>
<td>6 / 17</td>
</tr>
<tr>
<td><strong>Mean age at eligible (sd)</strong></td>
<td>75 (10)</td>
<td>70 (9)</td>
<td>69 (9)</td>
<td>72 (8)</td>
<td>69 (11)</td>
</tr>
<tr>
<td><strong>Time from diagnosis (months)</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Inclusion, median (p10-p90)</td>
<td>0 (0 - 27)</td>
<td>0 (0 - 21)</td>
<td>6 (0 - 26)</td>
<td>0 (0 - 19)</td>
<td>0 (0 - 7)</td>
</tr>
<tr>
<td>Chelation median (p10-p90)</td>
<td>15 (4 - 44)</td>
<td>17 (4 - 46)</td>
<td>13 (2 - 39)</td>
<td>22 (5 - 51)</td>
<td></td>
</tr>
<tr>
<td><strong>Transfused prior to being chelated</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Yes</td>
<td>657 100%</td>
<td>199 97%</td>
<td>150 97%</td>
<td>37 95%</td>
<td>12 100%</td>
</tr>
<tr>
<td><strong>Total number of units, median (range)</strong></td>
<td>15 (1 - 210)</td>
<td>13 (2 - 91)</td>
<td>12 (2 - 75)</td>
<td>11 (2 - 75)</td>
<td>25 (2 - 91)</td>
</tr>
<tr>
<td><strong>Ferritin (μg/L)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>393 (5315)</td>
<td>665 (3087)</td>
<td>658 (3087)</td>
<td>668 (1941)</td>
<td>530 (913)</td>
</tr>
<tr>
<td><strong>Comorbidity (MDSCI)</strong></td>
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</tr>
<tr>
<td>Low risk</td>
<td>395 60%</td>
<td>153 75%</td>
<td>120 78%</td>
<td>26 67%</td>
<td>7 58%</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>225 34%</td>
<td>44 22%</td>
<td>29 19%</td>
<td>11 28%</td>
<td>4 33%</td>
</tr>
<tr>
<td>High risk</td>
<td>35 5%</td>
<td>7 3%</td>
<td>4 3%</td>
<td>2 5%</td>
<td>1 8%</td>
</tr>
<tr>
<td><strong>Performance status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unable to care for self</td>
<td>12 2%</td>
<td>0 0%</td>
<td>0 0%</td>
<td>0 0%</td>
<td>0 0%</td>
</tr>
<tr>
<td>Unable to work</td>
<td>161 29%</td>
<td>34 18%</td>
<td>20 15%</td>
<td>12 31%</td>
<td>2 18%</td>
</tr>
<tr>
<td>Able to work and normal activity</td>
<td>376 68%</td>
<td>152 82%</td>
<td>116 85%</td>
<td>27 69%</td>
<td>9 82%</td>
</tr>
<tr>
<td><strong>Duration of treatment with chelation (months)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (p10-p90)</td>
<td></td>
<td>16 (3 - 43)</td>
<td>9 (1 - 34)</td>
<td>14 (6 - 30)</td>
<td></td>
</tr>
<tr>
<td><strong>Overall Survival (OS)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1</td>
<td>0.66 (0.52 - 0.85)</td>
<td>1</td>
<td>1.77 (1.02 - 3.05)</td>
<td>0.43 (0.10 - 1.77)</td>
</tr>
<tr>
<td>Adjusted**</td>
<td>1</td>
<td>0.75 (0.50 - 1.15)</td>
<td>1</td>
<td>1.95 (0.85 - 4.50)</td>
<td>0.38 (0.04 - 4.06)</td>
</tr>
</tbody>
</table>

* HRs and 95% CI were estimated using receipt of chelation as a time-varying covariate.
** adjusted by age at eligibility criteria, sex, comorbidity, performance status, and number of units transfused.

Emanuele Angelucci,1 Junmin Li,2 Peter Greenberg,3 Depei Wu,4 Ming Hou,5 Efreen Horacio Montaño Figueroa,6 Maria Guadalupe Rodriguez,7 Xunwei Dong,8 Jagannath Ghosh,8 Miguel Izquierdo,9 and Guillermo Garcia-Manero10

1Hematology and Transplant Center, IRCCS Ospedale Policlinico San Martino, Genova, Italy; 2Ruijin Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China; 3Stanford University Medical Center, Stanford, CA, USA; 4Jiangsu Institute of Hematology, First Affiliated Hospital of Soochow University, Suzhou, China; 5Department of Hematology, Qilu Hospital, Shandong University, Jinan, China; 6Department of Hematology, Hospital General de México, Mexico City, Mexico; 7Department of Hematology, Hospital de Especialidades, Centro Médico Nacional La Raza, IMSS, Mexico City, Mexico; 8Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; 9Novartis Pharma AG, Basel, Switzerland; 10MD Anderson Cancer Center, University of Texas, Houston, TX, USA
**TELESTO – a Phase II, randomized, double-blind study**

**Key inclusion criteria:**
- Hematologically stable IPSS Low or Int-1-risk MDS, confirmed by bone marrow within 6 months prior to study entry
- Serum ferritin $>1000$ ng/mL
- History of transfusion of 15–75 pRBC units
- No history of hospitalization due to congestive heart failure and LVEF $\geq 50\%$ by echocardiography
- ALT or AST $\leq 3.5 \times$ ULN, total bilirubin $\leq 1.5 \times$ ULN, no previous diagnosis of liver cirrhosis; CrCl $\geq 40$ mL/min
- ECOG performance status $\leq 2$

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CrCl, creatinine clearance; ECOG, Eastern Cooperative Oncology Group; IPSS, International Prognostic Scoring System; LPFV, last patient first visit; LVEF, left ventricular ejection fraction; pRBC, packed red blood cell; ULN, upper limit of normal
TELESTO study design

Designed as a **Phase III trial**
with a target enrolment of **630** patients

Because of low enrolment, the target sample size was reduced,
based on the feasibility of enrolling patients
and consultations with the health authorities

Changed to a **Phase II trial**
with target enrolment of **210** patients
Trial was therefore not designed to make statistical comparisons
To evaluate event-free survival (composite endpoint)

- Defined as the time from randomization to first documented non-fatal event (worsening cardiac function, hospitalization for congestive heart failure, liver function impairment, liver cirrhosis, transformation to AML), based on review and confirmation by an independent adjudication committee, or death, whichever occurred first

To assess:

- Overall survival
- Change in serum ferritin level
- Hematologic improvement in terms of erythroid response (based on International MDS Working Group criteria¹)
- Change in endocrine function (thyroid and glycemic control)
- Safety

Serum ferritin trends

Boxes show lower and upper quartiles, horizontal line shows the median

Deferasirox

Placebo

Deferasirox

Placebo

Serum ferritin level (ng/mL)

Time (quarter)
## Primary endpoint EFS: Stratified log-rank test and Cox regression model

<table>
<thead>
<tr>
<th>All patients*</th>
<th>Log-rank test</th>
<th>Cox model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Event / % (N)</td>
<td>Median time to event (95% CI), days†</td>
</tr>
<tr>
<td>Deferasirox</td>
<td>41.6 (62/149)</td>
<td>1440 (1167, 1559)</td>
</tr>
<tr>
<td>Placebo</td>
<td>48.7 (37/76)</td>
<td>1091 (820, 1348)</td>
</tr>
</tbody>
</table>

*Both the log-rank test and Cox proportional hazards model were stratified by stratification factors; †Median time to event and 95% CI generated by Kaplan–Meier estimation; ‡Exploratory P value is one tailed and based on the stratified log-rank test; $Based on a Wald test from the Cox model

A **36.4%** risk reduction in EFS was observed in the deferasirox arm compared with the placebo arm (HR: 0.636; 95% CI: 0.42, 0.96; nominal P=0.015)
Kaplan–Meier plot of EFS

Stratification: All patients

Randomized treatment

- Deferasirox
- Placebo
+ Censored

**Patients**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Events</th>
<th>Median EFS, days</th>
<th>3-year EFS, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deferasirox</td>
<td>149</td>
<td>62</td>
<td>1440</td>
<td>61.5</td>
</tr>
<tr>
<td>Placebo</td>
<td>76</td>
<td>37</td>
<td>1091</td>
<td>47.3</td>
</tr>
</tbody>
</table>

HR (95% CI) = 0.636 (0.421, 0.961); nominal P=0.015

**Time (days)**

- 0
- 364
- 728
- 1092
- 1456
- 1820
- 2184
- 2548
- 2912

**No. of patients still at risk**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>149</th>
<th>104</th>
<th>82</th>
<th>61</th>
<th>23</th>
<th>13</th>
<th>4</th>
<th>1</th>
<th>0</th>
</tr>
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<tbody>
<tr>
<td>Deferasirox</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>76</td>
<td>43</td>
<td>27</td>
<td>15</td>
<td>8</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1st sensitivity analysis
HR = 0.599 (95% CI: 0.38, 0.95)

2nd sensitivity analysis
HR = 0.537 (95% CI: 0.30, 0.97)

3rd sensitivity analysis
HR = 0.593 (95% CI: 0.39, 0.91)
EFS events (non-fatal events or deaths) that occurred first as confirmed by the EAC (adjudication rate 44%)

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<tr>
<td>Non-fatal events confirmed by EAC*</td>
<td>N=149 n (%)</td>
</tr>
<tr>
<td>Progression to AML</td>
<td>14 (9.4)</td>
</tr>
<tr>
<td>Hospitalization for CHF</td>
<td>10 (6.7)</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Liver function impairment</td>
<td>0</td>
</tr>
<tr>
<td>Worsening of cardiac function</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Deaths during treatment</td>
<td>48 (32.2)</td>
</tr>
</tbody>
</table>

*Investigators were asked to report any event that was even remotely possible to be an event to the EAC; only events confirmed by the EAC are included; †A patient with multiple occurrences of the same event is counted only once in the component category
EFS events (non-fatal events or deaths) that occurred first as confirmed by the EAC (adjudication rate 44%)

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<td>Liver function impairment</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Worsening of cardiac function</td>
<td>2 (1.3)</td>
</tr>
<tr>
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*Investigators were asked to report any event that was even remotely possible to be an event to the EAC; only events confirmed by the EAC are included; †A patient with multiple occurrences of the same event is counted only once in the component category

**TELESTO was not powered to detect differences between deferasirox and placebo for single-event categories of the composite primary endpoint for EFS**
Possible relationship between bone marrow failure, iron overload and prognosis in patients with MDS

Severe bone marrow disease → Infections → Bleeding → Anemia

Transfusion dependency

Iron overload

Cardiac dysfunction

Overall Survival ↓

Overall Survival ↓
Forest plot for EFS

**BM blasts**
- <5% at baseline (N=193 – Ev: D=51, P=29)
- ≥5% at baseline (N=19 – Ev: D=8, P=6)

**Gender**
- Female (N=88 – Ev: D=19, P=12)
- Male (N=137 – Ev: D=43, P=25)

**Age group**
- <65 years (N=108 – Ev: D=23, P=12)
- ≥65 years (N=117 – Ev: D=39, P=25)

**Stratum**
- Low IPSS (N=75 – Ev: D=18, P=11)
- Int–1 IPSS (N=150 – Ev: D=44, P=26)

**Cytopenia**
- 0/1 (N=61 – Ev: D=14, P=14)
- 2/3 (N=118 – Ev: D=37, P=19)

**Cytogenetics: karyotype**
- Good (N=171 – Ev: D=43, P=27)
- Intermediate (N=31 – Ev: D=9, P=8)
- Poor (N=3 – Ev: D=2, P=0)

**Serum ferritin**
- 1000–<2000 ng/mL (N=131 – Ev: D=37, P=22)
- 2000–<3000 ng/mL (N=59 – Ev: D=19, P=9)
- ≥3000 ng/mL (N=32 – Ev: D=6, P=5)

**Region**
- Asian (N=100 – Ev: D=21, P=15)
- Non-Asian (N=125 – Ev: D=41, P=22)

**All patients (N=225 – Ev: D=62, P=37)**

**HR (D/P) and 95% CI**
- Deferasirox better
- Placebo better
### Summary of overall survival

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<td>Event/N (%)</td>
<td>Median time (95% CI), days†</td>
</tr>
<tr>
<td>Deferasirox</td>
<td>57/149 (38.3)</td>
<td>1907 (1440, NE)</td>
</tr>
<tr>
<td>Placebo</td>
<td>33/76 (43.4)</td>
<td>1509 (1095, 1804)</td>
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*Both log-rank test and Cox proportional hazards model were stratified by stratification factors; †Median time to event and 95% CI generated by Kaplan–Meier estimation; ‡Exploratory P value is one-tailed and based on the stratified log-rank test; §Based on a Wald test from the Cox model

Median OS was prolonged by **398 days** with deferasirox vs placebo

Following study drug discontinuation, 52.1% of placebo patients started ICT
Summary of Telesto study

• TELESTO is the first prospective, randomized study of ICT in patients with Low-/Int-1-risk MDS and iron overload
• Treatment with deferasirox led to longer EFS compared with placebo
• Exposure-adjusted AEs were similar in the two arms with the exception of non-severe increases in serum creatinine, with no new safety signals
• Considering the current treatment landscape, it is unlikely that a similar randomized trial will be performed

TELESTO provides evidence on the clinical benefit of ICT in lower risk MDS patients with iron overload
Conclusions

- There is no reason to believe that iron overload is less toxic in elderly MDS patients than young thalassemia patients.
- Cardiovascular problems seem to be the most relevant sequelae of IOL in elderly MDS patients.
- Age-related cardiac comorbidities may lead to increased vulnerability to the toxic effects of IOL.
- The impact of IOL is difficult to prove in elderly MDS patients, due to overlap with age-related clinical problems.
- In recent years, well-conducted registry studies have consistently shown a survival benefit of ICT in patients with lower-risk MDS.
- These results are now corroborated by the improved EFS demonstrated by the Telesto study.