Iron Overload and Chelation Therapy in Patients with Non-Transfusion-Dependent Thalassaemia

Ali Taher, MD, PhD, FRCP

Professor of Medicine, Hematology and Oncology
Associate Chair, Research, Department of Internal Medicine
American University of Beirut Medical Center
Beirut, Lebanon
Outline

• Overview of non-transfusion-dependent thalassaemia (NTDT)
• Mechanisms and consequences of iron overload (IO) in NTDT
• Assessment of IO in NTDT
• Treatment of IO in NTDT
• Practical recommendations
• Conclusions
Thalassaemia Syndromes

Asymptomatic carrier states

Non-transfusion-dependent thalassaemia

• Beta-thalassaemia intermedia
• Haemoglobin E/beta-thalassaemia (HbE/beta-thalassaemia)
• Alpha-thalassaemia intermedia (HbH disease)

Major, transfusion-dependent thalassaemia

Transfusions seldom required

Regular transfusions required

Non-Transfusion-Dependent Thalassaemia

• Does not require lifelong regular transfusions for survival\(^1,2\)
• Can require occasional or even frequent transfusions in certain clinical settings\(^1\)
• Includes several forms of thalassaemia arising from variants of genes regulating haemoglobin production\(^1\)
• Milder and progresses more slowly\(^2\)
• Different forms vary in clinical severity\(^2\)

Global Burden of Thalassaemias, Including NTDT


Burden of thalassaemia is spreading to Europe, North America, and Australia because of population migration

- **HbE/beta-thalassaemia**: ~1 million affected worldwide; >19,000 births annually
- **Alpha-thalassaemia intermedia**: 5% of global population are carriers; ~1 million affected worldwide; 10,000 births annually
- **Beta-thalassaemia**: 1.5% of global population are carriers; 23,000 births annually

Statistics are based on older studies and information from a limited number of centers. Thus, they are likely underestimates.
Problems with the Current Paradigm

• Non-transfusion-dependent thalassaemia (NTDT) considered a milder form of thalassaemia that requires little or no iron chelation\textsuperscript{1}
• Definition based on signs and symptoms early in life, but serious complications develop over time\textsuperscript{1}
• Regular monitoring and treatment initiation often delayed until complications are apparent\textsuperscript{2}
• **Guidelines needed to increase awareness of the monitoring and management requirements of NTDT**

Mechanism Underlying Iron Overload in NTDT

Ineffective erythropoiesis
Chronic anaemia/hypoxia

↑ Erythropoietin

↓铁蛋白
↑ Intestinal iron absorption

↓ Ferroportin

↑ Release of recycled iron from reticuloendothelial system

Iron overload
↑ Liver iron concentration
↓ Than expected serum ferritin level

# Iron Overload—Transfusion-Dependent Thalassaemia Versus NTDT

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Transfusion-Dependent</th>
<th>NTDT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary source of excess iron</td>
<td>Regular transfusions</td>
<td>Intestinal iron absorption</td>
</tr>
<tr>
<td>Preferential distribution of iron</td>
<td>Reticuloendothelial system and parenchyma</td>
<td>Hepatocytes</td>
</tr>
<tr>
<td>SF level*</td>
<td>High</td>
<td>Relatively low and likely to underestimate IO*</td>
</tr>
<tr>
<td>Rate of iron accumulation</td>
<td>Rapid</td>
<td>Slow (3–4 mg/day, 1000 mg/year)</td>
</tr>
<tr>
<td>LIC</td>
<td>HIGH</td>
<td>HIGH</td>
</tr>
</tbody>
</table>

*Ratio of SF to LIC lower in NTDT compared with transfusion-dependent thalassaemia.

Abbreviations: IO, iron overload; LIC, liver iron concentration; NTDT, non-transfusion-dependent thalassaemia; SF, serum ferritin.

Consequences of Iron Overload in NTDT

• Hepatic
  – Hepatic fibrosis¹
  – Hepatocellular carcinoma¹

• Vascular
  – Thrombosis¹
  – Pulmonary hypertension¹
  – Large cerebral vessel disease²

• Endocrine
  – Hypothyroidism¹
  – Hypogonadism¹

• Neurologic
  – Silent brain infarction²
  – Decreased neuronal function²

• Skeletal: osteoporosis¹

• Renal: tubular dysfunction¹

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Consequences of IO—NTDT versus Transfusion-Dependent Thalassaemia

Increasing Age is a Risk Factor in IO-Related Morbidity

- Study of 52 patients with beta-thalassaemia intermedia
- Incidence of morbidity higher among older patients
- Older patients likely to have or shift to SF levels of 800 ng/mL or higher
- Incidence of complications higher among patients who have or shift to SF levels of 800 ng/mL or higher

Assessing IO—Liver Iron Concentration
The gold standard for assessing overall iron concentration

<table>
<thead>
<tr>
<th>Method</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Needle biopsy²</td>
<td>Direct</td>
<td>Adverse events, such as pain at the needle site and, more rarely, sepsis or hemorrhage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Variable concentration based on processing, location in liver³</td>
</tr>
</tbody>
</table>
| Magnetic techniques (MRI, superconducting quantum imaging [SQUID])² | Noninvasive Reliable | Limited availability
SQUI not accurate for concentrations between 3 and 10 mg Fe/g dry weight |

RISK_THRESHOLDS⁴

- 9 mg/g dw
- 7 mg/g dw
- 6 mg/g dw
- 1.8 mg/g dw


Risk threshold graphic courtesy of Dr. Taher.
What Happens Around the LIC 5 mg/g Threshold?

Slide courtesy of Dr. Taher.
Patients with a LIC ≥5 mg/g dw Have a Higher Prevalence of Morbidities

Abbreviations: LIC, liver iron concentration; PHT, pulmonary hypertension.
LIC Treatment Thresholds—THALASSA Study

- LIC $\geq$ 5 mg Fe/g dw --> Treatment initiation
- LIC < 3 mg Fe/g dw --> Treatment withholding
- LIC $\geq$ 7 mg Fe/g dw --> Treatment dose escalation

However, LIC measurements are not always available and therefore serum ferritin assessments may be required

Slide courtesy of Dr. Taher.
Serum Ferritin Level Underestimates LIC in NTDT

Relying solely on serum ferritin level can delay monitoring of iron and initiation of therapy in NTDT

Without Iron Chelation Therapy, Serum Ferritin Level Increases with Time

Study of 52 patients with beta-thalassaemia intermedia followed from 2000 through 2010
SF level increased on average by 9% per year and by 67% over the entire follow-up period

SF Level ≥800 ng/mL Associated with Occurrence of Morbidity

At least 1 morbidity

<table>
<thead>
<tr>
<th></th>
<th>SF ≤300 ng/mL</th>
<th>SF &gt;300 to &lt;800 ng/mL</th>
<th>SF ≥800 ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>100%</td>
<td>47.1%</td>
<td>0%</td>
</tr>
<tr>
<td>Yes</td>
<td>0%</td>
<td>52.9%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Multiple morbidity

<table>
<thead>
<tr>
<th></th>
<th>SF ≤300 ng/mL</th>
<th>SF &gt;300 to &lt;800 ng/mL</th>
<th>SF ≥800 ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>100%</td>
<td>94.1%</td>
<td>40.7%</td>
</tr>
<tr>
<td>Yes</td>
<td>0%</td>
<td>5.9%</td>
<td>59.3%</td>
</tr>
</tbody>
</table>

Pearson Chi-square, $P = .001$
Fisher’s exact, $P = .001$

Slide courtesy of Dr. Taher.
Iron Chelation Studies in NTDT

<table>
<thead>
<tr>
<th>Drug</th>
<th>Disease Type</th>
<th>Doses Tested</th>
<th>Study Types</th>
<th>Largest N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deferasirox</td>
<td>Beta-thalassaemia intermedia</td>
<td>10 or 20 mg/kg/d</td>
<td>Prospective, single-arm, open-label</td>
<td>11</td>
</tr>
<tr>
<td>Deferiprone</td>
<td>Beta-thalassaemia intermedia</td>
<td>25, 50, or 75 mg/kg/d</td>
<td>Prospective, single-arm or control-matched, open-label</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>HbE/beta-thalassaemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HbH disease</td>
<td></td>
<td>Case study</td>
<td></td>
</tr>
<tr>
<td>Desferrioxamine</td>
<td>Beta-thalassaemia intermedia</td>
<td>150 mg/kg over 24 hours</td>
<td>Prospective, placebo-controlled, crossover</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 days each at 20, 50, 60, 80, and 100 mg/kg/d</td>
<td>Prospective, single-arm, open-label</td>
<td></td>
</tr>
</tbody>
</table>

Until recently, iron chelation therapy was usually overlooked in NTDT; studies were small

Iron Chelation Therapy

• Subcutaneous desferrioxamine
  – 1st iron chelator studied in patients with NTDT
  – Optimal dosage, duration, and administration interval not clear
  – Adherence limited because of pain and inconvenience

• Oral deferiprone
  – Limited study, mixed results on serum ferritin level and liver iron concentration

THALASSA—Deferasirox in NTDT

- Multinational, prospective, randomized, placebo-controlled study
- Primary objective: absolute change in LIC

**Screening**
28 days

**Randomization**
(2:1 deferasirox/placebo)

- Deferasirox 5 mg/kg/day
- Placebo 5 mg/kg/day
- Deferasirox 10 mg/kg/day
- Placebo 10 mg/kg/day

**CORE**
24 weeks

**EXTENSION**
52 weeks

**LIC**

- LIC <3: Interrupt
- LIC 3–15: ≤10 mg/kg/day
- LIC >15: ≤20 mg/kg/day

**LIC was measured by MRI every 6 months**

**SF was measured monthly**

**Patients (N)**

<table>
<thead>
<tr>
<th></th>
<th>Screening</th>
<th>Randomization</th>
<th>Completed Core Study (Week 52)</th>
<th>Completed Extension Study (Week 104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>339</td>
<td>166</td>
<td>148</td>
<td>130</td>
<td></td>
</tr>
</tbody>
</table>


Study scheme graphic courtesy of Dr. Taher.
• Rate of adverse events similar between deferasirox and placebo groups\textsuperscript{1}
• Deferasirox 5 mg or 10 mg better than placebo in beta-thalassaemia intermedia, HbE/beta-thalassaemia, and HbH disease\textsuperscript{3}

LIC and SF Thresholds for DFX

- Good correlation between SF and LIC across treatment groups in THALASSA
- Corresponding SF thresholds identified through (ROC) analysis

<table>
<thead>
<tr>
<th></th>
<th>LIC</th>
<th>SF Level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initiation</strong>&lt;sup&gt;1, 2&lt;/sup&gt;</td>
<td>5 mg Fe/g dry weight</td>
<td>800 ng/mL</td>
</tr>
<tr>
<td><strong>Discontinuation</strong>&lt;sup&gt;1, 2&lt;/sup&gt;</td>
<td>3 mg Fe/g dry weight</td>
<td>300 ng/mL</td>
</tr>
<tr>
<td><strong>Dose escalation</strong>&lt;sup&gt;2&lt;/sup&gt;</td>
<td>7 mg Fe/g dry weight</td>
<td>2000 ng/mL*</td>
</tr>
</tbody>
</table>

* A conservative threshold proposed on the drug label; ROC analysis found that using SF levels between 1700 and 2000 ng/mL results in 100% appropriate dose escalation and 0% risk for over-chelation.

Abbreviations: DFX, deferasirox; LIC, liver iron concentration; ROC, Receiver Operating Characteristics; SF, serum ferritin.

Deferasirox

• Approved by the FDA on January 23, 2013 as first-line therapy for iron overload in patients age ≥10 years with NTDT syndromes

• Approved by European Medicines Agency on November 16, 2012 for chronic iron overload requiring chelation therapy when desferrioxamine is contraindicated or inadequate in patients 10 years and older with NTDT syndromes

Thalassaemia International Federation (TIF) developed separate guidelines for NTDT to increase global awareness of the monitoring and management requirements of NTDT overall.

TIF Recommendations—
Iron Overload Assessment in NTDT

• Assessment in all NTDT patients age ≥10 years (age threshold of 15 years used in patients with deletional HbH disease)

• Assessment of LIC every 1–2 years, preferably by MRI

• Assessment of SF level every 3 months; primary measure when LIC not available

• LIC supersedes SF level when both measures available

TIF Recommendations—Treatment

- Iron chelation therapy with deferasirox in patients age ≥10 years

<table>
<thead>
<tr>
<th>Measure</th>
<th>Initiation Threshold</th>
<th>Discontinuation Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIC</td>
<td>≥5 mg Fe/g dry weight</td>
<td>3 mg Fe/g dry weight</td>
</tr>
<tr>
<td>SF level</td>
<td>≥800 ng/mL</td>
<td>300 ng/mL</td>
</tr>
</tbody>
</table>

- LIC supersedes SF level when both measures are available

TIF Recommendations—Dosing and Monitoring

- Starting dose: 10 mg/kg/day
- LIC assessments 6 months after initiation, every 6–12 months thereafter
- Concomitant SF measurements every 3 months
- Dose escalation to 20 mg/kg/day after 6 months if
  - LIC >7 mg Fe/g dry weight (or SF level reaches 1500–2000 ng/mL) AND
  - LIC reduction <15%
- LIC supersedes SF level when both measurements available

TIF Recommendations—
Safety, Monitoring, and Other Considerations

• Safety and related dose modifications follow standard guidelines for transfusion-dependent beta-thalassaemia major

• Encourage tea consumption, which might decrease absorption of iron from the gut

• When frequent blood transfusions required for sustained durations of time, manage iron overload as you would for transfusion-dependent beta-thalassaemia major

Conclusions

• NTDT describes several distinct thalassaemia syndromes that do not require regular transfusions for survival

• Iron overload in NTDT arises from inefficient erythropoiesis and intestinal absorption, and iron accumulates in the liver

• TIF recommends regular iron assessments in patients age ≥10 years

• Patients should begin iron chelation therapy with deferasirox, at a starting dose of 10 mg/kg/day, when LIC reaches 5 mg Fe/g dry weight or SF level reaches 800 ng/mL or higher

• Dose escalation to 20 mg/kg/day should occur after the first 6 months if:
  – LIC >7 mg Fe/g dry weight (or SF level reaches 1500–2000 ng/mL) AND
  – LIC reduction <15%
Thank you for participating in this activity

Please remember to take the posttest