Practical Aspects of Iron Chelation Therapy in HSCT

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When and how to start with iron depletion?
When to start with iron chelation?

disease-specific therapy

Graft

conditioning

Transfusions

Toxicity

Infections

GVHD

Early
VOD
Infection
Mucositis

Intermediate
Acute GVHD
Infection

Late
Chronic GVHD
Infection
Endocrine dysfunction
Cardiac disease

Tx

Here!
If you have time prior to HSCT

- Iron chelation as early as possible
- Alternatively, do a Tx before SIO occurs
- When to start: Ferritin >1000 or 20U of RBC
- **Goal:** Ferritin as low as possible prior to HSCT
How to start with iron chelation?

Deferoxamine  Deferiprone  Deferasirox
Deferasirox dosing by transfusion requirements and therapeutic goals

Standard dose

- 20 mg/kg/day
- 4 Units/months
- 30 mg/kg/day
- 2 Units/months

Starting doses may also be modified as follows:

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<th>Transfusions</th>
<th>Therapeutic goal</th>
<th>Deferasirox dose</th>
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<td>4 Units/ months</td>
<td>Reduction of body iron</td>
<td>30 mg/kg/day</td>
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<td>2 Units/ months</td>
<td>Maintenance of body iron</td>
<td>10 mg/kg/day</td>
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How to assess iron load?

Pts. with rather „low“ ferritin levels might have substantial SIO

MDS/AML n=83 prior to HSCT

Wermke et al. 2011
If you don`t have time prior to HSCT

disease-specific therapy
Graft
conditioning
Transfusions

Tx

Toxicity
Infections
GVHD

NTBI
Iron overload after HSCT

- Iron overload often continues due to ongoing RBC support
- Can mimic GVHD of the liver
- Ferritin often not a reliable marker – go for MRI to objectify SIO!
- In patients at risk - consider chelation as early as possible after HSCT

Iron overload after HSCT: chelation effective?

![Graph showing iron levels over time after HSCT, with baseline LIC and 6-month LIC values labeled.](image)
## Safety of deferasirox therapy

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<th>Frequency (% patients)</th>
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<td>Elevations &gt; 10 × ULN were uncommon (0.3%)</td>
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Deferasirox in non-HSCT patients

Interaction with renal function?

Studies 107 and 107E

Deferasirox 20 mg/kg/day (n = 84)  Deferasirox 30 mg/kg/day (n = 118)

-50
0
25
50
BL 8 16 24 32 40 48 56 64 72 80 88 96 104 112 120 128

Core
Extension

Median change in creatinine clearance (mL/min)

-25
-50

Initial decrease

No subsequent continuous decline

Note:
Dose adjustments were permitted from week 52 onwards

Decline in creatinine clearance was observed in the first 4 weeks with no subsequent decline
Deferasirox after HSCT
Interaction with renal function?

- Changes in serum creatinine observed in app. 30% of pts.

- Often slightly above the threshold and not further increase
Deferasirox in non-HSCT patients
Interaction with CsA?

<table>
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<th>n (%)</th>
<th>Two values Crea &gt; ULN, no. (%)</th>
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<tr>
<td>No cyclosporine</td>
<td>95 (82)</td>
<td>8 (8.4)</td>
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<tr>
<td>Concomitant cyclosporine</td>
<td>21 (18)</td>
<td>3 (14.3)</td>
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<td>Total</td>
<td>116 (100)</td>
<td>11 (9.5)</td>
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Patients with SAA in the EPIC trial
Deferasirox in HSCT patients

Interaction with other drugs?

**Metabolized by glucuronidation** and minimally (8%) by oxidative cytochrome P450 enzymes

Potential loss of effectiveness of deferasirox when administered with drugs that are potent UGT inducers (e.g., rifampicin, phenytoin, phenobarbital, ritonavir)

**Modest induction of CYP3A4/5**
Caution: cyclosporine, tacrolimus, simvastatin, contraceptive agents

**Inhibition of CYP2C8**
Caution: repaglinide

Skerjanec et al. J. of Clin Pharm 2010
Deferasirox after HSCT

Interaction with CsA?

- CsA level was measured thrice weekly

- no significant alterations could be found over time

- There was no influence of the dose of deferasirox

Al-Ali HK et al. ASH 2010
Practical guidance for managing renal toxicity in patients on deferasirox

Consider:
- Start with 10mg/kg/d, keep hydrated
- Regular measurement (at least once weekly) of renal function and CsA/TAC
- Stop and dose adjustment if creatinine increase by at least 33% of baseline
- Avoid or monitor other concomitant drugs with renal toxicity
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**Practical guidance for managing GI -toxicity in patients on deferasirox**

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<td>Abdominal pain</td>
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Skin rash during deferasirox therapy - GVHD?

Mild-to-moderate rash

Continue treatment without interruption
Deferasirox after HSCT

general considerations

Before you start, look for:

- Renal function
- CsA/TAC levels
- Skin, intestinal, liver GVHD involvement
- Diarrhea
- Other nephrotoxic drugs
Deferasirox after HSCT

general considerations

- Start with 10mg/kg/d
- 15mg/kg/d day 14 and 20mg/kg/d day 28
- Rather noon or in the evening
- ½ hour before a meal
- Allow for adequate hydration
- Discuss in advance potential side effects with the patient
Deferasirox after HSCT case report

AML after allo-HSCT

Liver enzymes normalized
No drug interaction with TAC
Iron chelation in the context of allgeneic HSCT

Prior to HSCT:
- as early and as long as possible in pts at risk
- target ferritin as low as possible

After HSCT:
- deferasirox effective in decreasing SIO
- renal and GI-side effects manageable
- no obvious interaction with CsA/TAC
- randomized trials warranted