Population pharmacokinetics of anti-thymocyte globulin (ATG) in children receiving allogeneic-hematopoietic cell transplantation: towards individualized dosing to improve survival

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Introduction: Challenges in pediatric HCT

- Reducing the toxicity of HCT:
  - Short term toxicity
  - Long term toxicity
- Improving efficacy
  - Better disease control

Balancing optimal disease control and reduced toxicity

Introduction: ATG (Thymoglobulin®)

- In vivo lymphodepletion
- Thymoglobulin® (anti-thymocyte globulin, ATG)
  - Different brands ATG; horse or rabbit derived
- Polyclonal rabbit derived IgG antibody
- Very broad range of targets
  - T-lymphocytes
  - Other lymphocytes
  - Epithelium etc.
- ~9% of ATG directed against human targets (active ATG)
Introduction: ATG (Thymoglobulin®)

- Critical therapeutic window:
  - Underdosing
    - GvHD
    - Rejection
  - Overdosing
    - Delayed immune reconstitution, infection
    - More relapse (Graft vs Leukemia)

Introduction: outcome

Pediatric UCB transplants
- No ATG
- Early ATG (day -9 to -5)
- Late ATG (day -5 to 0)

Comparable EFS/OS

Introduction: PK/PD

Dose is often a poor descriptor of response
Project aim

- Describing the pharmacokinetics of active Thymoglobulin in pediatric HCT
- Explore the influence of weight and other factors on PK
- First step in development of individualized dosing regimen
- Evaluate current dosing regimen of Thymoglobulin®

Learning Objective

Describe the effect of weight on the pharmacokinetics of active Thymoglobulin®

Methods

- Patients treated from 2004 to 2012 at two pediatric SCT-units in the Netherlands
- Serum active Thymoglobulin® concentrations quantified by flow cytometry
- Population pharmacokinetic (PK) modelling (NONMEM)
  - Population mean
  - Between patient variability
- Covariates influencing variability
- Model validation with advanced methods (bootstrap, NPDE)
- Simulations
Results: patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Leiden</th>
<th>Utrecht</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>153</td>
<td>114</td>
<td>267</td>
</tr>
<tr>
<td>Number of HCTs</td>
<td>159</td>
<td>121</td>
<td>280</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>67</td>
<td>57</td>
<td>62</td>
</tr>
<tr>
<td>Age (years)</td>
<td>6.5 (2.7–12)</td>
<td>5.6 (2.3–13)</td>
<td>6.0 (2.9–12)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>21.3 (13–38)</td>
<td>20.3 (12–46)</td>
<td>21.3 (13–45)</td>
</tr>
<tr>
<td>Number of samples (n) (mean per patient)</td>
<td>20.00 (16)</td>
<td>11.0 (8)</td>
<td>20.5 (12)</td>
</tr>
<tr>
<td>Starting day (d) (day before transplantation)</td>
<td>5 (4–6)</td>
<td>5 (4–7)</td>
<td>5 (4–6)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>50</td>
<td>42</td>
<td>46</td>
</tr>
<tr>
<td>Immune-deficiency</td>
<td>16</td>
<td>24</td>
<td>19</td>
</tr>
<tr>
<td>Bone-marrow-failure</td>
<td>4</td>
<td>10</td>
<td>6</td>
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<tr>
<td>Metabolic-disease</td>
<td>0</td>
<td>21</td>
<td>9</td>
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<tr>
<td>Benign hematology</td>
<td>0</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Auto-immune disease</td>
<td>0</td>
<td>2</td>
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<tr>
<td>Stem cell source (%)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Bone marrow</td>
<td>63</td>
<td>29</td>
<td>48</td>
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<tr>
<td>Peripheral blood stem cells</td>
<td>23</td>
<td>5</td>
<td>15</td>
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<tr>
<td>Cordblood</td>
<td>14</td>
<td>60</td>
<td>34</td>
</tr>
<tr>
<td>Cordblood plus haplo or 2nd cordblood</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Leukocyte count before conditioning (x 10^9)</td>
<td>0.84 (0.29–1.19)</td>
<td>0.87 (0.26–2.71)</td>
<td>0.87 (0.26–2.71)</td>
</tr>
</tbody>
</table>

Shown as median (interquartile range) unless otherwise specified.

Results: PK-model 1

Dose

Central volume of distribution

Body weight

Peripheral volume of distribution

Body weight

Baseline lymphocytes

MAX

Results: PK-model 2

Tm (Intercompartmental distribution)

Km (Clearance)
Results: Model performance 1

Body weight = 9kg

Cumulative 10 mg/kg

Results: Model performance 2

1.5-2.5 years old

2.5-5 years old

Simulations

- Current dosing regimen
  - Cumulative 10 mg/kg Thymoglobulin® over 4 days
- Higher exposure with higher weight
Audience Response Question

A cumulative dose of 10mg/kg Thymoglobulin® over 4 days, the current dosing regimen, leads to a constant exposure in all age groups

A) True  
B) False

Conclusions

- A model was developed and validated, describing active Thymoglobulin® pharmacokinetics, yielding accurate predictions
- Weight and baseline lymphocytes important factors influencing the PK
- Current dosing regimen results in increasing exposure with higher weight
- First step in developing an individualized dosing regimen

Perspectives

- Pharmacokinetic-pharmacodynamic (concentration-effect) relationship needs to be explored
- Development of a dosing regimen to reach optimal exposure

Multivariate predictors for worse overall survival:
- Post-HCT AUC >20, p=0.024
- Mismatched donor, p=0.01
- Malignancy, p=0.007

Log-rank p=0.026
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