Model-based characterization of neutrophil dynamics in children receiving busulfan or treosulfan for haematopoietic stem cell transplant conditioning

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Stem cells extracted from blood

Chemotherapy ablates immune system

Stem cells treated and stored

Stem cells (re)introduced

Isolation and follow up

• Replace the haematopoietic system in total or in part
• Curative potential for a wide variety of conditions
Chemotherapy ablates immune system

- Severely immunocompromised and liable to infections
  Main cause of transplant-related death
- Different depending on diagnosis, age, clinical conditions, donor type and source of cells

Debate surrounding the relative methods of **Busulfan (Bu)** and **Treasulfan (Treo)**
Background

Chemotherapy ablates immune system

TIME??

Stem cells (re)introduced

C

T

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Background

Neutrophil count over time with chemotherapy treatment.
Objectives

Establish a PKPD model for the **treatment** and **engraftment effects** on neutrophil counts comparing busulfan and treosulfan

Optimise **PK sampling schedules** for therapeutic drug monitoring of busulfan

Evaluate the **dosing schedules** of busulfan and treosulfan with respect to time to HSCT

Establish the relationship between **neutropenia and overall survival**
<table>
<thead>
<tr>
<th>Patient Population</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Busulfan</strong></td>
<td><strong>Treosulfan</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>72 children</td>
<td>54 children</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.1 – 47.0 Kg</td>
<td>3.8 – 35.8 Kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 months – 18 years</td>
<td>4 months – 17 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DIAGNOSIS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Solid tumours</td>
<td>30</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Non-malignancies</td>
<td>42</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td><strong>TRANSPLANT TYPE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autologous</td>
<td>12</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Allogeneic</td>
<td>60</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td><strong>CONDITIONING GROUPS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Different combinations</td>
<td>8</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>
Response data

Baseline values

<table>
<thead>
<tr>
<th></th>
<th>Busulfan</th>
<th>Treosulfan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>5.10</td>
<td>2.95</td>
</tr>
<tr>
<td>Median</td>
<td>3.42</td>
<td>2.49</td>
</tr>
</tbody>
</table>

Neutrophil counts

Overall Survival

- Non-malignant diseases
- Malignant diseases

Probability of survival

Time [years]

Probability of survival

Time [years]
Pharmacokinetics

Allometric scaling
Maturation function affecting elimination
IOV on CL

Busulfan

Treosulfan

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Busulfan

Allometric scaling
Maturation function affecting elimination*
IOV on CL and V1

\[
AGEF = \frac{1}{\left(1 + \left(\frac{PM50}{PMAW}\right)^{HILL}\right)}
\]

PMAW – Post-menstrual age in weeks

* In this case fixed from Clin Cancer Res 2014;20:754-6
PKPD Model Development

PKPD - treatment and engraftment effects

Stem cells infused 
HSCT

Myeloablation 
Bu / Treo

Rebuilding of the 
immune system

Myeloablation

Immune reconstitution

3/4 days

-15

Kprol = Ktr = Kcirc

Feedback = (Circeq/Circ)'

MTT = 4/Ktr

Ktr

Kprol

Edrug

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OVERALL MODEL PERFORMANCE

BUSULFAN

TREOSULFAN

BUSULFAN AND ALEMTUZUMAB

TREOSULFAN AND ALEMTUZUMAB

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CLINICALLY RELEVANT METRICS

- **Nadir Grade**
  - Busulfan
  - Treosulfan

- **Time to Nadir**
  - Busulfan
  - Treosulfan

- **Time to Recovery**
  - Busulfan
  - Treosulfan
Model Evaluation

**SYSTEM PARAMETERS**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate (RSE%)</th>
<th>IIV [CV%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circ0</td>
<td>0.79 (18.91)</td>
<td>75.90</td>
</tr>
<tr>
<td>MTT [h]*</td>
<td>94.8 (12.04)</td>
<td>35.41</td>
</tr>
<tr>
<td>γ*</td>
<td>0.11 (13.93)</td>
<td>77.10</td>
</tr>
</tbody>
</table>

* After transplant effect

- High IIV
- Multiple factors
  - Not initially at steady state

PKPD Model of Neutropenia in Patients with Myeloma receiving high-dose melphalan for Autologous Stem Cell Transplant

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Final model</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASE (K/μL)</td>
<td>Estimate: 5.61, RSE: 4.7, IIV: 34.4 (59.6)</td>
</tr>
<tr>
<td>SLOPE (mL/μg)</td>
<td>Estimate: 7.46, RSE: 7.4, IIV: 25.1 (18.3)</td>
</tr>
<tr>
<td>MTT (hours)</td>
<td>Estimate: 97, RSE: 2.5, IIV: 6.6 (22.7)</td>
</tr>
<tr>
<td>γ</td>
<td>Estimate: 0.218, RSE: 2.3, IIV: 0.218 (0.206–0.230)</td>
</tr>
</tbody>
</table>

## Model Evaluation

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* After transplant effect

### SYSTEM PARAMETERS

**TABLE 1**  
Population pharmacodynamic parameter estimates corresponding to the reference model for neutropenia (Friberg et al., 2002)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Estimate</th>
<th>Shrinkage (%)</th>
<th>Bootstrap (n = 500)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circ0 (× 10⁹/l)</td>
<td>4.70</td>
<td>4.65</td>
<td>Median: 3.9–5.4</td>
</tr>
<tr>
<td>MTT (d)</td>
<td>4.81</td>
<td>4.75</td>
<td>3.9–6.0</td>
</tr>
<tr>
<td>θslope (ml/ng)</td>
<td>1.49</td>
<td>1.51</td>
<td>0.6–3.2</td>
</tr>
<tr>
<td>Emax</td>
<td>4.02</td>
<td>3.96</td>
<td>2.1–11.2</td>
</tr>
<tr>
<td>γ</td>
<td>0.14</td>
<td>0.14</td>
<td>0.08–0.2</td>
</tr>
</tbody>
</table>

Parameters are listed together with the coefficient of variation (CV[%]) in parentheses. CL, total plasma clearance; V₁, volume of distribution in the central compartment; V₂, and V₃, volume of distribution in the peripheral compartments; Q₀ and Q₁, intracompartmental clearances; Circₒ, basal ANC; MTT, maturation mean transit time; γ, feedback parameter; IPV, inter-patient variability expressed as CV [%]; Na, not estimated; No, not applicable

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Mangas-Sanjuan et al. J Pharmacol Exp Ther. 2015 Jul;354(1):55-64

Summary PKPD Model

First time, to our knowledge, that the HSCT effect is introduced in a neutropenia model in children

- Different value at baseline and at steady state
- Transplant effect
  - Enhancing Proliferation
  - Enhancing Feedback
  - Decreasing MTT
- Alemtuzumab effect
  - Decreasing MTT
- Drug effect
  - Eliminating cells

Same transplant effect regardless type of transplant

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Model Applicability

PKPD MODEL

Clinical Applications
Evaluation of the dosing schedules
Model Applicability

Evaluation of the **dosing schedules**
Evaluation of the dosing schedules
Optimization of the PK sampling schedules

Protocol sample times

Software used: PopED

*Foraccia, Hooker, Vicini and Ruggeri 2004
Optimization of the PK sampling schedules

Protocol sample times

Software used: PopED

*Foraccia, Hooker, Vicini and Ruggeri 2004

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Optimization of the PK sampling schedules

![Graph showing busulfan concentration over time, with a peak at 2 hours and a decline thereafter.]

Software used: PopED
*Foraccia, Hooker, Vicini and Ruggeri 2004
Model Applicability

Bias = $\frac{\theta_{\text{Real}} - \theta_{\text{Est}}}{\theta_{\text{Real}}}$
Model Applicability

Neutropenia and overall survival

AUC stratification
- > 141 [10^9 cells·days/L]
- ≤141 [10^9 cells·days/L]

Malignancies

P = 0.013
HR = 0.26 (0.09 – 0.81)
Neutropenia and overall survival

AUC stratification

- > 141 [10^9 cells·days/L]
- ≤141 [10^9 cells·days/L]

Non-Malignancies

\[ P = 0.31 \]
\[ HR = 0.10 (0.01 - 1.25) \]
Conclusions

1. New **dosing schedules** are proposed
2. PKPD model developed predicts **neutrophil reconstitution trajectories** after HSCT
3. Differences between patients with **malignant** and non-malignant **diseases** are found
4. Different **sampling schedules** are found to be more informative
Conclusions

1. New dosing schedules are proposed.
2. PKPD model developed predicts neutrophil reconstitution trajectories after HSCT.
3. Differences between patients with malignant and non-malignant diseases are found.
4. Different sampling schedules are found to be more informative.

Useful tool to improve the clinical management of children receiving HSCT.
THANK YOU