The role of genetic variants GSTA1 and CYP39A1 and ontogenesis on busulfan clearance in pediatric patients undergoing hematopoietic SCT

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Introduction
- Busulfan is used in preparative regimens prior to hematopoietic stem cell transplantation (HSCT) in pediatric patients.
- Busulfan has a narrow therapeutic index and exposure is related to outcome.
- There is significant interpatient variability in busulfan pharmacokinetics (PK).
- Glutathione-S-transferases are the main enzymes involved in busulfan conjugation and metabolism.
- To date, only polymorphisms in genes encoding for GSTs were studied, which could only explain a small portion of the variability in PK.
- We hypothesize that a set of genetic variants may be more important to explain interindividual differences in busulfan clearance than a single gene.

Objective
- To investigate the effect of 7 genetic markers (resulting from a explorative pharmacogenetic study in adults) on busulfan clearance in pediatric patients.
- In addition, we aimed to study the effect of ontogenesis on these genetic markers.

Conclusions
- GSTA1 and CYP39A1 haplotype are associated with busulfan PK in pediatric patients.
- An age-dependent effect of the role of GSTA1 in busulfan clearance is demonstrated.

Results

Table 1: Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (s.d.)</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>6.14 (5.4)</td>
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<tr>
<td>Weight (kg)</td>
<td>25.4 (17.3)</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>113 (32.9)</td>
</tr>
<tr>
<td>Sex (n and % male)</td>
<td>58 (69%)</td>
</tr>
</tbody>
</table>

Diagnosis for HSCT
- Patients (n) 4 (3)
- Immune deficiency 28
- Hematological malignancy 31
- Other 4
- Thalassemia 21

Graft type
- Patients (n) 62
- Bone marrow 62
- Peripheral blood stem cells 11
- Cord blood 11

Donor matching
- Matched unrelated donor 53
- Identical related donor 24
- Other related donor 7

**Table 1** Representative Figure 1: Association of the number of variant alleles in GSTA1 and CYP39A1 and busulfan clearance.

Discussion
- A new genetic marker (CYP39A1) was found to be associated with busulfan PK in children, the role of this marker is not clear yet.
- The role of GSTA1 genotype in pediatric busulfan metabolism is not always clear.
- In the positive studies on GSTA1 genotype and busulfan PK clearance was normalized for weight, which was not the case in the negative studies.
- When clearance is not corrected for body size variability is much larger and the effect of body size surpasses the probably smaller effect of the genetic variants.
- A larger effect of GSTA1 genotype in the youngest children was observed.
- This observation is the youngest children (< 2yr) could potentially be caused by an incomplete development of enzyme, resulting in a more pronounced effect of genetic variation on busulfan clearance in this subset of patients.

Methods
- In a previous explorative pharmacogenetic study in adults, applying DMET array containing 1,936 variants in 225 ADME genes, 7 genetic markers in GSTA1, CYP2C19, CYP39A1, ABCB4, SLC22A4 and SLC7A8 were significantly associated with busulfan clearance.
- In the current study, we explored association of the 7 markers with busulfan clearance in 84 pediatric patients.
- Busulfan clearance was estimated using a limited sampling (t=2.5, 4 hrs) PK model.