Utilizing Intravenous Busulfan Pharmacokinetics for Dosing Busulfan And Fludarabine Conditioning Regimens In Institutions Where The Capability Of Doing Pharmacokinetics Is Not Present

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Disclosure

• The speaker has no actual or potential conflict of interest in relation to this presentation.

Learning Objective

• Describe a method by which pharmacokinetically guided IV busulfan-based conditioning regimens may be implemented in institutions where the ability to perform in-house pharmacokinetics is not present.
Question 1

At your institution how are busulfan pharmacokinetics (PK) addressed?

A. PK is not routinely performed
B. PK on samples performed in-house
C. PK on samples sent to outside laboratory for analysis

Overview

• Background
• Study rationale
• Methods
• Results
• Conclusions

Busulfan

• Busulfan has been effectively used for hematopoietic stem cell transplant for decades[1-4]
• Safety and efficacy of busulfan appears to be influenced by the PK parameters of the patient[5]
• IV busulfan reduces PK variability and improved outcomes have been linked with precise targeting of busulfan systemic exposure with PK based dose adjustment[6-10]
• Toxicities commonly associated with busulfan:
  – Myelosuppression
  – Gastrointestinal
  – Hepatic sinusoidal obstruction syndrome
Pharmacokinetics

- Busulfan pharmacokinetics are described by a 1-compartment model[11]
- Aim to achieve a constant AUC
  - Clearance = Dose/ AUC
  - Established AUC target levels are based on mg/m² daily dosing schedule
  - At our institution:
    - Myeloablative AUC target ~ 5000 - 6000 µM*min
    - Reduced intensity AUC target ~ 4000 µM*min

Question 2

Q - Which of the following is a well described non-hematologic dose limiting toxicity of busulfan?
A: Sinusoidal Obstruction Syndrome (SOS)
B: Cardiomyopathy
C: Encephalopathy
D: Progressive Multifocal leucoencephalopathy (PML)

Study Rationale and Hypothesis

- Rationale: Lack of data describing the use of IV busulfan in institutions where the ability to perform in-house PK is not present
- Hypothesis: We propose that IV busulfan may be safely and effectively used in institutions where in-house busulfan assay is not available
Study Design

Retrospective study

- Adult allogenic stem cell transplants performed at University of Kentucky Markey Cancer Center between November 2012 - September 2013
- Patients who received a conditioning regimen comprising of IV busulfan and IV fludarabine
  - Actual body weight used to calculate BSA
  - Corrected body weight used if weight >125% of actual body weight
- Busulfan PK calculations performed by the Seattle Cancer Care Alliance Pharmacokinetics Laboratory, Seattle, WA

Dosing Strategy

- 1st dose of IV Busulfan and collection of levels
- IV Busulfan levels drawn at:
  - End of busulfan infusion
  - 15 minutes after completion of busulfan infusion
  - 4 hours after START of busulfan infusion
  - 5 hours after START of busulfan infusion
  - 6 hours after START of busulfan infusion
  - 8 hours after START of busulfan infusion

- 2nd dose of IV Busulfan

Data Analysis
### Patient Characteristics

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Number of patients</strong></td>
<td>14</td>
</tr>
<tr>
<td><strong>Age at the time of transplant (years)</strong></td>
<td>48.5 (range: 23-61)</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td>8</td>
</tr>
<tr>
<td>MDS</td>
<td>3</td>
</tr>
<tr>
<td>ALL</td>
<td>2</td>
</tr>
<tr>
<td><strong>Disease Status</strong></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>11</td>
</tr>
<tr>
<td>N/A</td>
<td>3</td>
</tr>
<tr>
<td><strong>Regimen</strong></td>
<td></td>
</tr>
<tr>
<td>IV Busulfan/ IV Fludarabine</td>
<td>9</td>
</tr>
<tr>
<td>IV Busulfan/ IV Fludarabine + Thymoglobulin</td>
<td>5</td>
</tr>
<tr>
<td><strong>CD34 Cells Infused (10^6 cells/kg)</strong></td>
<td>7 (range: 2.7-15)</td>
</tr>
</tbody>
</table>

AML - Acute myeloid leukemia; HLH - Hemophagocytic lymphohistiocytosis; ALL - Acute lymphoblastic leukemia; CR - Complete remission.

Data are represented as median (range).

### Donors

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>Related</strong></td>
<td>5</td>
</tr>
<tr>
<td><strong>Unrelated</strong></td>
<td>9</td>
</tr>
<tr>
<td><strong>HLA Match</strong></td>
<td></td>
</tr>
<tr>
<td>9/10</td>
<td>2</td>
</tr>
<tr>
<td>10/10</td>
<td>12</td>
</tr>
</tbody>
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Regimen Intensity:
- AUC 6000 µM*min: 8
- AUC 4500 µM*min: 1
- AUC 4000 µM*min: 5

Body Surface Area (m²): 1.825 (range: 1.5 – 2.1)

**PK - Pharmacokinetics; AUC - Area under the curve. Data are represented as median (range).**

### Results

<table>
<thead>
<tr>
<th></th>
<th>For patients with target of 6000µM*min</th>
<th>For patients with target of 4000µM*min</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC Achieved prior to PK adjustment</td>
<td>4822.5 (range: 3852 - 5772)</td>
<td>3221 (range: 2516 - 4079)</td>
</tr>
<tr>
<td>Daily AUC Estimate</td>
<td>5380.5 (range: 4821 - 5978)</td>
<td>4004 (range: 3752 - 4252)</td>
</tr>
<tr>
<td>Dose Adjustment (mg/m²)</td>
<td>53.3 (range: 5 - 95)</td>
<td>47.9 (range: 15 - 85)</td>
</tr>
</tbody>
</table>

AUC - Area under the curve. Data are represented as median (range).
Results

<table>
<thead>
<tr>
<th>Incidence of acute GVHD</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Acute grade I</td>
<td>2 (14.3%)</td>
</tr>
<tr>
<td>Acute grade II – IV</td>
<td>4 (28.6%)</td>
</tr>
</tbody>
</table>

| Incidence of chronic GVHD  | 2 (14.3%) |

<table>
<thead>
<tr>
<th>Median time to achieve engraftment (days)</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>ANC &gt; 100/uL</td>
<td>15</td>
</tr>
<tr>
<td>(range: 10 - 19)</td>
<td></td>
</tr>
<tr>
<td>Platelets &gt; 20,000/uL</td>
<td>17</td>
</tr>
<tr>
<td>(range: 11 - 25)</td>
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</table>

| Cytomegalovirus viremia | 2 (14.3%) |

| Relapse                  | 1 patient |
| (Day + 88 post-transplant)|        |

| Median follow-up period | 6 months |

Conclusion

• PK guided IV busulfan-based conditioning regimens may be implemented at institutions where the ability to perform in-house PK is not present
• Larger sample size and longer follow-up period are necessary to definitively determine the effect of our strategy on patient outcomes

Limitations

• Retrospective study
• Single center data
  – Small group of patients
• Limited follow-up period
• Post dose PK levels were not collected
  – Data based on projected AUC
Thank you

Questions?

Research Advisors:
Zartash Gul, MD
Amber Lawson, PharmD, BCOP
Heidi Weiss, PhD

References