Evaluation of Tacrolimus Levels and Risk of Graft-Versus-Host Disease, Relapse and Non-Relapse Mortality after Haploidentical Transplantation with Post-Transplant Cyclophosphamid

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Disclosures

• No relevant conflicts of interest to disclose

• Non-FDA approved use of tacrolimus will be discussed in this presentation
Learning Objective

• Discuss the impact of early post-transplant tacrolimus levels following haploidentical (haplo) hematopoietic stem cell transplantation (HCT) on the incidence of graft-versus-host disease (GVHD) and other post-transplant outcomes
Background

• Following haplo-HCT with post-transplant cyclophosphamide (PTCy), the range of target tacrolimus blood levels is wide (5 – 15 ng/mL)

• This fact, combined with pharmacogenomic variation and effects of drug interactions, leads to significant variability in tacrolimus serum concentrations

• We hypothesized that early post-transplant tacrolimus levels following haplo-HCT might impact the incidence of GVHD and other post-transplant endpoints and that more precise tacrolimus level targeting may improve post-transplant outcomes
Tacrolimus Levels and Acute GVHD in Matched Related and Unrelated Allogeneic Transplants

- In the setting of matched related or unrelated donor transplantation using conventional GVHD prophylaxis, several published studies have correlated higher post-transplant tacrolimus levels with a lower risk of acute GVHD (aGVHD).

  - Higher tacrolimus levels in the first 2 weeks post-transplant correlated with decreased incidence of aGVHD
    - 37% reduction in unrelated donors and 44% reduction in related donors
    - Suggest targeting tacrolimus levels of 14 – 15 ng/mL in the first 2 weeks post-transplant to reduce risk of aGVHD

Study Design and Objectives

• Retrospective electronic medical record review
• Objectives:
  — Primary objective:
    • To analyze the impact of early serum tacrolimus concentrations on the incidence of acute and chronic GVHD
  — Secondary objective:
    • To evaluate the effect of early serum tacrolimus concentrations on relapse, non-relapse mortality (NRM) and survival
Patient Criteria

• Inclusion Criteria
  — Haplo-HCT (5/10 – 8/10 human leukocyte antigen (HLA)-matched related donor)
  — Between 2013 – 2018
  — Hematologic malignancy
  — Using conventional GVHD prophylaxis with PTCy, tacrolimus, and mycophenolate mofetil (MMF)

• Exclusion Criteria
  — Tacrolimus start delayed beyond day +5, (n = 1)
  — Received less than 2 weeks of tacrolimus, (n = 1)
  — Received ATG (antithymocyte globulin) (n = 1)
  — 9/10 HLA-match (n = 3)
  — Death prior to day +28, (n = 2)
GVHD Prophylaxis

• All patients received the same GVHD prophylaxis schedule:
  — PTCy 50 mg/kg IV day +3 and day +4
  — Tacrolimus (target serum level of 5 – 15 ng/mL) day +5 to day +180
  — MMF 15mg/kg PO TID (max 3 gm/day) day +5 to day +35

• Tacrolimus dosing schedule
  — 0.03 mg/kg/day continuous IV infusion
  — Tacrolimus given IV through day +21, then converted to PO

• Tacrolimus monitoring
  — 3x weekly until at least day +21, then weekly
Methods

• Tacrolimus levels
  — Mean weekly tacrolimus levels
    • Calculated each week for the first 4 weeks
    • Starting day +7 and ending day +35 post-transplant
  — Aggregate mean tacrolimus levels for 2- and 4- week intervals

• Transplant endpoints
  — GVHD
    • Grade 2 – 4 and grade 3 – 4 aGVHD
    • All grade and moderate-to-severe cGVHD
  — Post-transplant outcomes
    • Relapse, NRM and overall survival (OS)

aGVHD graded by Glucksberg criteria

cGVHD graded by National Institutes of Health criteria

cGVHD: chronic graft-versus-host disease
## Patient Characteristics

### Patient Demographics (n = 158)

| Age | 51 (19 – 75) |
| Males | 89 (56%) |

### Transplant Details (n = 158)

<table>
<thead>
<tr>
<th>Stem cell source</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral blood</td>
<td>142 (90%)</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>16 (10%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regimen intensity</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myeloablative</td>
<td>90 (57%)</td>
</tr>
<tr>
<td>Non-myeloablative</td>
<td>46 (29%)</td>
</tr>
<tr>
<td>Reduced intensity</td>
<td>22 (14%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comorbidity index</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 3</td>
<td>97 (61%)</td>
</tr>
<tr>
<td>&lt; 3</td>
<td>61 (39%)</td>
</tr>
</tbody>
</table>

### Hematologic Malignancy (n = 158)

<table>
<thead>
<tr>
<th>Malignancy Type</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute myeloid leukemia</td>
<td>64</td>
</tr>
<tr>
<td>Acute lymphoblastic leukemia</td>
<td>36</td>
</tr>
<tr>
<td>Myelodysplastic syndrome</td>
<td>15</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>13</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia</td>
<td>7</td>
</tr>
<tr>
<td>Hodgkin’s lymphoma</td>
<td>6</td>
</tr>
<tr>
<td>Myeloproliferative syndromes</td>
<td>6</td>
</tr>
<tr>
<td>Acute leukemia</td>
<td>3</td>
</tr>
<tr>
<td>Chronic myeloid leukemia</td>
<td>3</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>3</td>
</tr>
<tr>
<td>Plasma cell disorder</td>
<td>1</td>
</tr>
<tr>
<td>Waldenstrom’s macroglobulinemia</td>
<td>1</td>
</tr>
</tbody>
</table>
## Results – Weekly Mean Tacrolimus Levels

Table 1.

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean tacrolimus level week 1</td>
<td>158</td>
<td>14.21 ± 2.80</td>
</tr>
<tr>
<td>Mean tacrolimus level week 2</td>
<td>158</td>
<td>11.30 ± 2.99</td>
</tr>
<tr>
<td>Mean tacrolimus level week 3</td>
<td>157</td>
<td>10.97 ± 3.80</td>
</tr>
<tr>
<td>Mean tacrolimus level week 4</td>
<td>153</td>
<td>11.58 ± 4.06</td>
</tr>
</tbody>
</table>

n = number of patients with levels
Results – Weekly Mean Tacrolimus Levels and Grade 2 – 4 aGVHD

Figure 1.

Mean Week 1 Tacro Level
- <13 (N=50)
- 13-15.5 (N=56)
- >=15.5 (N=52)

13-15.5 vs. <13 P = 0.63
>=15.5 vs. <13 P = 0.70

Figure 2.

Mean Week 1-4 Tacro Level
- <10.9 (N=53)
- 10.9-13 (N=51)
- >=13 (N=53)

10.9-13 vs. <10.9 P = 0.45
>=13 vs. <10.9 P = 0.88
Results – Weekly Mean Tacrolimus Levels and Grade 3 – 4 aGVHD

Figure 3.

Mean Week 1 Tacrolimus Level
- <13 (N=50)
- 13-15.5 (N=56)
- >=15.5 (N=52)

cumulative incidence of grade III-IV acute GVHD (%)

Days since transplant

13-15.5 vs. <13 P = 0.98
>=15.5 vs. <13 P = 0.34

Figure 4.

Mean Week 1-4 Tacrolimus Level
- <10.9 (N=53)
- 10.9-13 (N=51)
- >=13 (N=53)

cumulative incidence of grade III-IV acute GVHD (%)

Days since transplant

10.9-13 vs. <10.9 P = 0.99
>=13 vs. <10.9 P = 0.83
Results – Weekly Mean Tacrolimus Levels and All Grade cGVHD

Figure 5.

Figure 6.
Results – Weekly Mean Tacrolimus Levels and Moderate – Severe cGVHD

Figure 7.

Figure 8.
Results – Weekly Mean Tacrolimus Levels and GVHD

Table 1. Univariate analysis to assess association of weekly mean tacrolimus level with GVHD

<table>
<thead>
<tr>
<th>Mean Tacrolimus Level</th>
<th>Grade 2 – 4 aGVHD</th>
<th>All Grade cGVHD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>P</td>
</tr>
<tr>
<td>Week 1</td>
<td>1.04</td>
<td>0.38</td>
</tr>
<tr>
<td>Week 2</td>
<td>1.04</td>
<td>0.31</td>
</tr>
<tr>
<td>Week 3</td>
<td>0.99</td>
<td>0.83</td>
</tr>
<tr>
<td>Week 4</td>
<td>0.97</td>
<td>0.22</td>
</tr>
<tr>
<td>Week 1 – 2</td>
<td>1.07</td>
<td>0.20</td>
</tr>
<tr>
<td>Week 3 – 4</td>
<td>0.98</td>
<td>0.46</td>
</tr>
<tr>
<td>Weeks 1 – 4</td>
<td>1.01</td>
<td>0.90</td>
</tr>
</tbody>
</table>

HR is for each 1 ng/mL unit increment in mean tacrolimus level
Note: Only mean tacrolimus level was evaluated for different endpoints.
Results – Weekly Mean Tacrolimus Levels and NRM

Figure 9.

Mean Week 1 Tacrolimus Level

- <13 (N=50)
- 13-15.5 (N=56)
- >15.5 (N=52)

13-15.5 vs. <13 P = 0.88
>15.5 vs. <13 P = 0.79

Figure 10.

Mean Week 1-4 Tacrolimus Level

- <10.9 (N=53)
- 10.9-13 (N=51)
- >13 (N=53)

10.9-13 vs. <10.9 P = 0.59
>13 vs. <10.9 P = 0.57
Results – Weekly Mean Tacrolimus Levels and Relapse/Progression

Figure 11. Mean Week 1 Tacrolimus Level
- <13 (N=50)
- 13-15.5 (N=56)
- >=15.5 (N=52)

13-15.5 vs. <13 P = 0.59
>=15.5 vs. <13 P = 0.54

Year since transplant

Figure 12. Mean Week 1-4 Tacrolimus Level
- <10.9 (N=53)
- 10.9-13 (N=51)
- >=13 (N=53)

10.9-13 vs. <10.9 P = 0.72
>=13 vs. <10.9 P = 0.27

Month since transplant
### Results – Weekly Mean Tacrolimus Levels and Other Post-Transplant Endpoints

Table 2. Univariate analysis to assess association of weekly mean tacrolimus level with survival

<table>
<thead>
<tr>
<th>Mean Tacrolimus Level</th>
<th>OS</th>
<th>DFS</th>
<th>NRM</th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>P</td>
<td>HR</td>
<td>P</td>
</tr>
<tr>
<td>Week 1</td>
<td>0.97</td>
<td>0.47</td>
<td>0.98</td>
<td>0.69</td>
</tr>
<tr>
<td>Week 2</td>
<td>1.04</td>
<td>0.45</td>
<td>1.04</td>
<td>0.39</td>
</tr>
<tr>
<td>Week 3</td>
<td>1.04</td>
<td>0.24</td>
<td>1.03</td>
<td>0.33</td>
</tr>
<tr>
<td>Week 4</td>
<td>1.02</td>
<td>0.57</td>
<td>1.01</td>
<td>0.68</td>
</tr>
<tr>
<td>Week 1 – 2</td>
<td>1.00</td>
<td>0.98</td>
<td>1.02</td>
<td>0.74</td>
</tr>
<tr>
<td>Week 3 – 4</td>
<td>1.04</td>
<td>0.35</td>
<td>1.02</td>
<td>0.53</td>
</tr>
<tr>
<td>Weeks 1 – 4</td>
<td>1.05</td>
<td>0.45</td>
<td>1.04</td>
<td>0.51</td>
</tr>
</tbody>
</table>

HR is for each 1 ng/mL unit increment in mean tacrolimus level
Note: Only mean tacrolimus level was evaluated for different endpoints.
Limitations of Analysis

• Limited sample size

• Subject heterogeneity (e.g. age, disease and regimen intensity)

• As most of our patients received posaconazole or other strong CYP3A4 inhibitor for antifungal prophylaxis, our current IV dosing strategy results in relatively high initial tacrolimus serum concentrations (mean 14 ng/mL during week 1), limiting the power of our analysis to study the effect of low tacrolimus levels on transplant outcomes
Conclusions

• In contrast to matched related or unrelated donor HCT, no protective benefit of higher early serum tacrolimus concentrations was seen in regard to aGVHD incidence.

• No associations of early post-transplant tacrolimus levels on the incidence of cGVHD or other post-transplant outcomes following haplo-HCT with PTCy were found.

• Given the 1) lack of significant detrimental effects of lower tacrolimus levels, combined with the 2) known toxicities associated with tacrolimus use (i.e. renal, neurologic, cardiovascular, diabetes mellitus):
  — We propose that lower target tacrolimus serum concentrations (i.e. 5 – 11 vs. 12 – 15 ng/mL) may be preferable following PTCy-based haplo-HCT.
Audience Response Question

Following haplo-HCT with PTCy, early serum tacrolimus concentrations were found to be associated with which of the following?

A. Lower early serum tacrolimus levels and increased risk for aGVHD
B. Lower early serum tacrolimus levels and decreased risk for relapse
C. Higher early serum tacrolimus levels and decreased risk for aGVHD
D. There was no significant association between early serum tacrolimus levels and risk for aGVHD
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