BACKGROUND

- Cytomegalovirus (CMV) is a major cause of morbidity and mortality in orthotopic heart transplantation (OHT).
- CMV donor seropositive, recipient seronegative (D+/R−) status is a major risk factor.
- Antiviral prophylaxis with ganciclovir/vancomycin is the most widely used prevention strategy in the US, with few studies on optimal duration.
- Current guidelines suggest 3 months for R−, 3-6 months in D+/R−.
- Controlled trials evaluating duration of prophylaxis were done in other populations but not in OHT.
- Whether longer durations are better than 3 months for CMV disease is not known in OHT specifically.
- Only a single observational study has assessed the impact of length of antiviral prophylaxis on CMV disease in OHT.
- Longer duration did not show beneficial impact.
- That study used non-guideline durations of prophylaxis.
- Thus, optimal duration of antiviral prophylaxis is uncertain.

Study Objective: to assess whether 6 months of prophylaxis reduces CMV disease incidence compared to 3 months in D+/R− OHT recipients.

METHODS

- Study design: Retrospective cohort
  - All first OHT ≤ 18 years transplanted 7/5/2005 – 12/30/2016 at UWMC with follow up >1 year or until death, whichever occurred earlier.
  - Prospected clinical and laboratory variables were extracted from electronic databases.
- Standard practices:
  - Standard immunosuppression: ATG induction, maintenance with tacrolimus, mycophenolate, and prednisone.
  - Ganciclovir (VCGR) for 3 months for R+ and 3 to 6 months for D+/R−, at clinical discretion.
  - All R+ and D+ patients received IV ganciclovir initially. 5mg/kg/day, then oral ganciclovir at 900mg once daily.
  - CMV syndrome and end-organ disease were assessed independently by 2 separate reviewers using consensus definitions, with discordant cases reviewed & assigned a consensus diagnosis by senior reviewer (APL).
- Statistical Analysis:
  - Chi-square and Mann-Whitney tests were used to compare categorical and continuous variables
  - p < 0.05 considered significant
  - Multivariable logistic model used to evaluate risk factors for CMV disease.
  - Inverse propensity weighting analysis evaluated to adjust for factors associated with prophylaxis duration

RESULTS

Table 1. Demographics of the study cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Cohort n = 310 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient age (years)</td>
<td>Mean: 52.2, IQR: 44.8-62.3</td>
</tr>
<tr>
<td>Follow up time (in months)</td>
<td>Mean: 44.1, IQR: 21.8-87.4</td>
</tr>
<tr>
<td>Acute rejection a OR by end of follow up</td>
<td>23 (7.4)</td>
</tr>
<tr>
<td>Re-transplantation</td>
<td>0</td>
</tr>
<tr>
<td>Year Survival</td>
<td>285 (91.9)</td>
</tr>
</tbody>
</table>

Table 2. Incidence and characteristics of proven CMV disease.

<table>
<thead>
<tr>
<th>Variable</th>
<th>All n = 310 (%)</th>
<th>D+/R− n=83 (%)</th>
<th>D+/R− n=47 (%)</th>
<th>D+/R− n=180 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proven CMV disease</td>
<td>27 (8.7)</td>
<td>22 (26.5)</td>
<td>0</td>
<td>5 (2.8)</td>
</tr>
<tr>
<td>Ganciclovir Resistant</td>
<td>3 (11.1)</td>
<td>3 (13.6)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Time of diagnosis after transplant, median months (IQR)</td>
<td>10.22 (6.3-15.9)</td>
<td>9.8 (6.5-14.4)</td>
<td>NA</td>
<td>16.7 (6.4-20.5)</td>
</tr>
<tr>
<td>CMV Disease type among identified cases</td>
<td>6 (22.2)</td>
<td>5 (22.7)</td>
<td>0</td>
<td>1 (20.0)</td>
</tr>
<tr>
<td>CMV Syndrome</td>
<td>21 (77.8)</td>
<td>17 (37.7)</td>
<td>0</td>
<td>4 (3.3)</td>
</tr>
<tr>
<td>Tissue Invasive Disease</td>
<td>18 (66.7)</td>
<td>15 (68.2)</td>
<td>0</td>
<td>3 (60.0)</td>
</tr>
<tr>
<td>GI disease</td>
<td>3 (11.1)</td>
<td>1 (4.5)</td>
<td>0</td>
<td>2 (40.0)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1 (3.7)</td>
<td>1 (4.5)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*One R+ patient with both GI and Pneumonia

CONCLUSIONS

1. CMV disease remains a major clinical problem in D+/R− OHT recipients despite current antiviral prophylaxis strategies.
2. 6 months of antiviral prophylaxis was not associated with a lower incidence of CMV disease compared to 3 months of ganciclovir prophylaxis in D+/R− OHT recipients.
3. Prophylaxis duration should be studied specifically in D+/R− OHT, and novel strategies to prevent CMV disease in D+/R− OHT are warranted.

REFERENCES