Adenovirus Load Dynamics Are Consistently Correlated With Risk of Mortality in Pediatric Allogeneic Hematopoietic Cell Transplant Recipients: Findings From the Landmark AdVance Study

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Disclosures

- The AdVance study was funded by Chimerix, Inc.
- FG, RW, and PC took part in the AdVance study
- RW has also received benefits from consulting and a licensing agreement/royalty for Orchard Therapeutics, where he is a shareholder and advisor, and speaker support from Genzyme
- AC is an employee of Analytica Laser, and provided statistical support for the AdVance study, funded by Chimerix, Inc.
- EV, TB, EM, and GN are employees of Chimerix, Inc.
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Adenovirus infection can be a serious complication following allogeneic HCT

- AdV infection is a cause of mortality among allogeneic hematopoietic cell transplant (allo-HCT) recipients, with pediatric patients at highest risk\(^1\)-\(^4\).
- AdV viremia is an indicator of viral dissemination and an independent predictor for mortality post allo-HCT\(^5\)-\(^7\).
- There is limited understanding of the relative prognostic strength of different dynamic AdV viral load measures\(^8\)-\(^10\).

AdV, adenovirus

Characterized the current screening and treatment practices for AdV infection in allo-HCT recipients

- A multinational, multicenter study
- 50 European centers
- HCT performed between January 2013 and September 2015

Assessed association between AdV viral load and mortality in pediatric (<18 years) allo-HCT recipients under current standard of care
We focused on pediatric patients with AdV viremia ≥1000 copies/mL within 6 months of allo-HCT
  • Threshold commonly used for initiation of pre-emptive antiviral therapy¹,²

The relationship between six different dynamic AdV viral load measures and all-cause mortality in the six months after first AdV viremia ≥1000 copies/mL was examined in univariate and multivariate analyses
  • Multivariate Cox proportional hazard models controlled for factors including immune reconstitution

Dynamic AdV viral load measures

1 Peak AdV viremia:
Peak Log\(_{10}\) AdV viremia

All measures were over the 16 weeks following first AdV viremia ≥1000 copies/mL, except 2-week change in AdV viremia, and AdV viremia over time.
Dynamic AdV viral load measures

2 Days AdV viremia <1000 copies/mL:
Number of days AdV viremia <1000 c/mL

All measures were over the 16 weeks following first AdV viremia ≥1000 copies/mL, except 2-week change in AdV viremia, and AdV viremia over time.
Dynamic AdV viral load measures

3 Days undetectable AdV viremia:
Number of days AdV viremia < LOD

All measures were over the 16 weeks following first AdV viremia ≥1000 copies/mL, except 2-week change in AdV viremia, and AdV viremia over time

LOD, limit of detection
Dynamic AdV viral load measures

2-week change in AdV viremia:
Change in $\log_{10}$ AdV in 2 wks following first AdV viremia $\geq$1000 copies/mL

All measures were over the 16 weeks following first AdV viremia $\geq$1000 copies/mL, except 2-week change in AdV viremia, and AdV viremia over time.
Dynamic AdV viral load measures

5 AdV viremia over time:
Highest $\log_{10}$ AdV viremia in 15-day time windows over 6 months following allo-HCT as a time dependent covariate

All measures were over the 16 weeks following first AdV viremia $\geq 1000$ copies/mL, except 2-week change in AdV viremia, and AdV viremia over time
Dynamic AdV viral load measures

**AdV AAUC**<sub>0-16 weeks</sub>:
Log<sub>10</sub> of the time-averaged area under the curve (AdV AAUC) for 16 weeks following first AdV≥1000

All measures were over the 16 weeks following first AdV viremia ≥1000 copies/mL, except 2-week change in AdV viremia, and AdV viremia over time
**Dynamic AdV viral load measures**

1. **Peak AdV viremia:**
   Peak $\log_{10}$ AdV viremia

2. **Days AdV viremia <1000 copies/mL:**
   Number of days AdV viremia <1000 c/mL

3. **Days undetectable AdV viremia:**
   Number of days AdV viremia <LOD

4. **2-week change in AdV viremia:**
   Change in $\log_{10}$ AdV in 2 wks following first AdV viremia $\geq$1000 copies/mL

5. **AdV viremia over time:**
   Highest $\log_{10}$ AdV viremia in 15-day time windows over 6 months following allo-HCT as a time dependent covariate

6. **AdV AAUC$_{0-16}$ weeks:**
   $\log_{10}$ of the time-averaged area under the curve (AdV AAUC) for 16 weeks following first AdV $\geq$1000

All measures were over the 16 weeks following first AdV viremia $\geq$1000 copies/mL, except 2-week change in AdV viremia, and AdV viremia over time.
241/1736 pediatric patients developed AdV viremia \( \geq 1000 \) copies/mL within 6 months of transplant.

**Demographic characteristics**

<table>
<thead>
<tr>
<th>Pediatric patients n=241</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age in years</strong></td>
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<tr>
<td>Median (range)</td>
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<tr>
<td><strong>Gender</strong></td>
</tr>
<tr>
<td>Male</td>
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<tr>
<td><strong>Stem cell source</strong></td>
</tr>
<tr>
<td>BM</td>
</tr>
<tr>
<td>PBSC</td>
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<tr>
<td>Cord blood</td>
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</table>

BM, bone marrow; PBSC, peripheral blood stem cell.
A range of demographic and clinical factors were included in the multivariate analyses

Based on published data

Univariate prognostic factors with p ≤0.20 were entered into full multivariate model, with backward selection (p for exit of ≤0.10)

* = significant in one or more univariate analysis

### Factors evaluated in univariate analyses

<table>
<thead>
<tr>
<th>AdV dynamic measure*</th>
<th>Lymphocyte count*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cidofovir use</td>
<td>Country*</td>
</tr>
<tr>
<td>Gender*</td>
<td>Use of renal replacement therapy*</td>
</tr>
<tr>
<td>Graft vs Host Disease (maximum across organs)*</td>
<td>Underlying disease</td>
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<tr>
<td>Age at time of transplant</td>
<td>Type of donor</td>
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<tr>
<td>T-cell depletion / Serotherapy</td>
<td>Comorbidities</td>
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<tr>
<td>Time from allo-HCT to AdV infection</td>
<td>AdV disease*</td>
</tr>
<tr>
<td>Time from allo-HCT to AdV viremia ≥1000 copies/mL</td>
<td>Time from AdV infection to AdV viremia ≥1000 copies/mL</td>
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<tr>
<td>Co-infections (CMV/EBV/BKV)</td>
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</table>


CMV, cytomegalovirus; EBV, Epstein-Barr virus; BKV, BK virus
In multivariate analyses, all measures of AdV were significantly associated with all-cause mortality.

- In multivariate models, each 1 log_{10} increase in AdV AAUC_{0-16} ~doubles the risk of mortality.
- Lymphocyte count, gender, and renal replacement therapy were also significant.
- Findings were comparable for non-relapse mortality.
All measures of AdV viral load were independent predictors of all-cause mortality

<table>
<thead>
<tr>
<th>(95% CI)</th>
<th>Peak AdV viremia</th>
<th>Days AdV viremia &lt;1000 c/mL</th>
<th>Days with undetectable AdV viremia</th>
<th>2-week change in AdV viremia</th>
<th>AdV viremia over time</th>
<th>AdV AAUC&lt;sub&gt;0-16 weeks&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard for all-cause mortality</td>
<td>1.31 (1.13 - 1.53)</td>
<td>0.96 (0.95 - 0.97)</td>
<td>0.96 (0.95 - 0.97)</td>
<td>1.24 (1.04 - 1.47)</td>
<td>1.37 (1.22 - 1.55)</td>
<td>1.91 (1.57 - 2.32)</td>
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<tr>
<td>Lymphocyte count</td>
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<tr>
<td>≥ 900</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
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<tr>
<td>300-899</td>
<td>1.88 (0.47 - 7.53)</td>
<td>1.82 (0.45 - 7.35)</td>
<td>1.71 (0.43 - 6.89)</td>
<td>1.80 (0.45 - 7.18)</td>
<td>1.64 (0.41 - 6.50)</td>
<td>2.19 (0.54 - 8.86)</td>
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<tr>
<td>&lt;300</td>
<td>7.81 (2.22 - 27.46)</td>
<td>5.20 (1.48 - 18.32)</td>
<td>5.09 (1.44 - 17.96)</td>
<td>7.97 (2.27 - 27.95)</td>
<td>4.87 (1.35 - 17.52)</td>
<td>6.82 (1.92 - 24.22)</td>
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<td>Renal replacement therapy</td>
<td></td>
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<tr>
<td>No</td>
<td>1.00</td>
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<tr>
<td>Yes</td>
<td>13.10 (5.54 - 30.97)</td>
<td>5.09 (1.85 - 14.02)</td>
<td>6.12 (2.21 - 16.98)</td>
<td>14.56 (6.30 - 33.67)</td>
<td>6.90 (2.74 - 17.39)</td>
<td>5.91 (2.38 - 14.72)</td>
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<tr>
<td>AdV disease</td>
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<tr>
<td>No</td>
<td>1.00</td>
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<td>1.00</td>
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<tr>
<td>Yes</td>
<td>1.79 (0.92 - 3.48)</td>
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<td></td>
<td>1.90 (1.00 - 3.63)</td>
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<td>Maximum GvHD stage</td>
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<td>0</td>
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<tr>
<td>1,2</td>
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<td>0.89 (0.34 - 2.33)</td>
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<tr>
<td>3,4</td>
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<td></td>
<td>2.31 (1.08 - 4.92)</td>
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</tr>
</tbody>
</table>

- Associations were independent of lymphocyte immune reconstitution in all models
- Renal replacement therapy (possible side effect of IV cidofovir) was also highly correlated with mortality

All models also adjusted for country and patient gender
AdV peak and persistence are associated with stepwise increases in mortality

Lymphocyte count, sex, and renal replacement therapy were significant (p<0.05) prognostic factors in each of the final models. Viremia over time could not be divided by quartiles.
AdV AAUC$_{0-16w}$ incorporates peak and persistence; Higher AdV AAUC$_{0-16w}$ is associated with mortality

- 79% (34/43) of patients who died still had AdV viremia before death (median 2.5 days test to death)
- This includes 97% (30/31) of patients who died in the 4$^{th}$ quartile
Conclusions

- Several measures of AdV viral load are strongly and independently associated with mortality after pediatric allo-HCT.
- Both the peak and persistence of AdV viremia contribute to mortality risk, even after adjusting for immune reconstitution.
  - AdV AAUC incorporates both viral peak and persistence, with each log_{10} increase in AdV AAUC associated with a ~doubling of mortality risk.
  - Higher viral burden likely reflects higher tissue damage for this lytic infection.
  - Interventions that further reduce AdV viral load/burden should reduce mortality.
- AdV AAUC$_{0-16w}$ is a clinically useful indicator for AdV infection outcome.
  - Currently the primary endpoint in the ongoing AdAPT clinical trial (NCT03339401).
    - This trial is assessing the safety and efficacy of pre-emptive oral brincidofovir treatment vs. current standard of care in pediatric allo-HCT recipients.

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