ADENOVIRUS VIRAL BURDEN IS ASSOCIATED WITH MORTALITY IN PEDIATRIC ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANT RECIPIENTS: RESULTS FROM THE ADVANCE STUDY

Marco Zecca,1 Kanchan Rao,2 Antonio Pérez-Martínez,3 Cécile Pochon,4 Sebastian Voigt,5 Enrikas Vainorius,6 Tom Brundage,6 Aastha Chandak,7 Essy Mozaffari,6 Garrett Nichols6

1Fondazione IRCCS Policlinico San Matteo, Pediatric Hematology/Oncology, Pavia, Italy;  
2Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom;  
3Hospital Universidad Autónoma de Madrid, Madrid, Spain;  
4University Hospital of Nancy, Allogeneic Hematopoietic Stem Cell Transplantation Unit, Department of Hematology, Vandoeuvre-lès-Nancy, France;  
5Charité-Universitätsmedizin Berlin, Department of Pediatric Oncology/Hematology/Stem Cell Transplantation, Berlin, Germany;  
6Chimerix, Durham, NC, United States;  
7Analytica-Laser, New York, NY, United States
Disclosures

MZ, KR, APM, CP, and SV are investigators in the AdVance study sponsored by Chimerix

EV, TB, EM, and GN are employees of the study sponsor, Chimerix

AC is an employee of Analytica-Laser, a research consultancy who conducted the study on behalf of the sponsor, Chimerix
Rationale for the AdVance study

There is a lack of detailed, multicenter data collected using consistent methodology on standards of care, disease course, and outcomes in patients with adenovirus (AdV) post-allogeneic HCT.

Despite published data on the high risk of morbidity and mortality with AdV infection (most from the single-center experience),\(^1\)\(^-\)\(^3\) the literature is difficult to interpret due to the lack of clear definitions regarding various stages of infection.

No clear correlation between virology parameters, response to antiviral therapy, and comorbidities/outcomes has been established.


The AdVance study

AdVance is a retrospective, multicenter, multinational study of the incidence, management, and clinical outcomes of AdV infection in allo-HCT recipients

• Data were from transplants between January 2013 and September 2015 at participating centers

• Quantitative and qualitative data were extracted for AdV infection, AdV viremia, and AdV viremia ≥1000 copies/mL within 6 months of transplant

  o Results were stratified by age (pediatric [<18 years] vs adult)
Objectives of this analysis

- To assess mortality within 6 months of AdV diagnosis in pediatric allo-HCT recipients with AdV viremia ≥1000 copies/mL
- To investigate any correlation between viral burden and mortality (overall and non-relapse related)
Baseline characteristics in patients with AdV viremia ≥1000 copies/mL

<table>
<thead>
<tr>
<th>Demographic characteristics</th>
<th>Pediatric patients n=241</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>5.0 (0.1-17.0)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>159 (66%)</td>
</tr>
<tr>
<td>Graft type</td>
<td></td>
</tr>
<tr>
<td>BM</td>
<td>116 (48%)</td>
</tr>
<tr>
<td>PBSC</td>
<td>92 (38%)</td>
</tr>
<tr>
<td>Cord blood</td>
<td>33 (14%)</td>
</tr>
</tbody>
</table>

Pediatric allo-HCT recipients n=1738

Any AdV infection¹
n=558 (32%)

AdV viremia¹
n=395 (23%)

AdV viremia ≥1000 copies/mL¹
n=241 (14%)

¹Within 6 months of transplant

BM, bone marrow; PBSC, peripheral blood stem cell
AdV AAUC as a potential surrogate for mortality

- AdV viral burden was assessed as time-averaged area under the curve (AAUC) over 16 weeks from the time of viremia ≥1000 copies/mL.

- AdV AAUC is a virologic endpoint that quantifies the course and severity of disease in acute lytic viral infections such as AdV\(^1,2\).

- AdV AAUC is a clinically relevant measure of viral burden that controls for variability in follow-up duration and has been used as a primary endpoint in Phase 2 and 3 studies of investigational antivirals\(^3-5\).

- We assessed the correlation between viral load measured by AdV AAUC and mortality in allo-HCT recipients.

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Calculating AdV average viral burden

AdV viremia (copies/mL)

Day 0

AdV AUC

Week 16

1000

Undetectable

AdV AUC

AdV AAUC

Wk 1 + Wk 2 + Wk 3 + Wk 4 + Wk 5 + Wk 6 + Wk 7 + Wk 8 + Wk 9 + Wk 10 + Wk 11

16
Peak and persistence of AdV viremia over time are higher in upper AdV AAUC quartiles

Days from AdV viremia ≥1000 copies/mL

AAUC 1st quartile  AAUC 2nd quartile  AAUC 3rd quartile  AAUC 4th quartile
3rd & 4th quartiles reflect higher, more prolonged AdV viremia
Increasing mortality was associated with AdV viral burden

All-cause mortality 6 months after first AdV viremia ≥1000 copies/mL

Mortality rate (%)

1st 2nd 3rd 4th

Mortality rate:
- 1st: 3% (2/60)
- 2nd: 7% (4/61)
- 3rd: 10% (6/60)
- 4th: 52% (31/60)

Comparable findings in non-relapse related mortality
40% of patients in the 4th quartile die within 2 months

All-cause mortality 6 months after first AdV viremia ≥1000 copies/mL

Survival probability

Days from first AdV viremia ≥1000 copies/mL

AdV AAUC quartiles

- 1st
- 2nd
- 3rd
- 4th
40% of patients in the 4th quartile die within 2 months

Non-relapse related mortality 6 months after first AdV viremia $\geq 1000$ copies/mL

AdV AAUC quartiles
- 1st
- 2nd
- 3rd
- 4th
**AdV viral burden and lymphocyte count significantly impact mortality risk**

Pediatric allo-HCT recipients with AdV viremia ≥1000 copies/mL

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lower risk</th>
<th>Higher risk</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AdV AAUC</strong></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
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<tr>
<td>( \log_{10} \text{AAUC}_{0-16w} ) continuous</td>
<td></td>
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<td></td>
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<tr>
<td>100-199</td>
<td>0.650</td>
<td></td>
<td></td>
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<tr>
<td>200-299</td>
<td>0.349</td>
<td></td>
<td></td>
</tr>
<tr>
<td>300-899</td>
<td>0.017</td>
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<td></td>
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<tr>
<td>≥900</td>
<td>0.005</td>
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<tr>
<td><strong>Immune Reconstitution</strong></td>
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<tr>
<td>Lymphocyte counts (vs &lt;100)</td>
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<td></td>
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<tr>
<td>100-199</td>
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<td></td>
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<td>200-299</td>
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<tr>
<td>≥900</td>
<td></td>
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</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td>0.018</td>
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<tr>
<td>Female (vs male)</td>
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<tr>
<td><strong>Dialysis</strong></td>
<td></td>
<td></td>
<td>0.0004</td>
</tr>
<tr>
<td>Renal replacement (vs no renal replacement)</td>
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</tbody>
</table>

Country was also included in the model \( (p=0.075) \)
AdV viral burden and lymphocyte count significantly impact mortality risk

Higher AdV AAUC\textsubscript{0-16w} increases the hazard of mortality

Decreasing hazard of mortality with increasing lymphocyte count

<table>
<thead>
<tr>
<th>AdV AAUC\textsubscript{0-16w}</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median of 4th Quartile</td>
<td>11.7 [7.6-24.0]</td>
</tr>
<tr>
<td>Median of 3rd Quartile</td>
<td>2.7 [2.3-3.6]</td>
</tr>
<tr>
<td>Median of 2nd Quartile</td>
<td>1.5 [1.4-1.6]</td>
</tr>
<tr>
<td>Median of 1st Quartile</td>
<td>1.0 (ref)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lymphocyte count</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td>1.0</td>
</tr>
<tr>
<td>100-199</td>
<td>1.2 [0.5-2.9]</td>
</tr>
<tr>
<td>200-299</td>
<td>0.6 [0.2-1.8]</td>
</tr>
<tr>
<td>300-899</td>
<td>0.3 [0.1-0.8]</td>
</tr>
<tr>
<td>≥900</td>
<td>0.1 [0.0-0.5]</td>
</tr>
</tbody>
</table>
Conclusions

- Over half of the pediatric allo-HCT recipients who developed AdV viremia surpassed the threshold of ≥1000 copies/mL, shown to be associated with high levels of short-term mortality.

- AdV AAUC was strongly correlated with both all-cause and non-relapse related mortality.

- AdV AAUC\(_{0-16\text{weeks}}\) and lymphocyte counts are independent prognostic survival factors.

- AdV AAUC represents an appropriate measure of AdV viral burden to assess the potential benefits of antiviral therapies.

- New treatment approaches that can decrease AdV viral burden may improve outcomes.
The AdVance centers

FRANCE (10)
- Robert Debré Hospital, Paris
- CHU Angers
- Institut of Hematology, Lyon
- CHU Nancy
- CHU Montpellier
- CHU Bordeaux
- CHU Lyon
- CHU Nantes
- Saint Louis Hospital, Paris
- CHU Nice

SPAIN (12)
- Hospital Universitario y Politécnico La Fe (2)
- Hospital Universitario 12 de Octubre
- Hospital Universitario La Paz
- Hospital Universitario de Salamanca
- Hospital Universitario Vall d’Hebrón
- Hospital de la Santa Creu i Sant Pau (2)
- Hospital Universitario Reina Sofía
- Hospital Regional Universitario de Málaga
- Hospital Infantil Universitario Niño Jesús Meseguer
- Hospital General Universitario Morales Meseguer

ITALY (9)
- Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico Centro Trapianti Midollo Osseo, Milano
- Hospital Casa Sollievo Sofferenza, San Giovanni Rotondo
- Azienda Ospedale ‘Riuniti e Morelli’ Bianchi-Melacrino Centro Unico Regionale Trapianti Cellule Staminali e Terapia Cellulare, Reggio Calabria
- Pediatric Hematology/Oncology Department Policlinico San Matteo, Pavia
- Ospedale Civile Centro Trapianti Midollo Osseo Dip. Ematologia Medicina Trasfusionale e Biotecnologie, Pescara
- Pediatric Hematology/Oncology Department San Gerardo Hospital, Monza
- S.C. Oncoematologia Pediatrica e Centro Trapianti Regina Margherita, Torino
- Oncoematologia e TMO, Ospedale ‘La Maddalena’ Palermo
- Ospedale Bambin Gesù-Dip. Oncoematologia Pediatrica e Medicina Transfusionale, Roma

GERMANY (7)
- Charité Campus Virchow Klinikum
- J. W. Goethe Universität
- Medizinische Hochschule Hannover
- Universitätsklinikum Jena
- Universitätsklinikum Köln
- Universitätsklinik Tübingen
- Klinikum der Universität München (LMU)

UK (10)
- Royal Manchester Children’s Hospital
- Bristol Royal Children’s Hospital
- Sheffield Children’s Hospital
- St. James’s University Hospital and The General Infirmary, Leeds
- Great North Children’s Hospital, Newcastle
- Great Ormond Street Hospital, London
- University College London Hospitals,
- University Hospital of Wales Cardiff
- The Royal Marsden Hospital, London
- Birmingham Children’s Hospital

The NETHERLANDS (1)
- UMC Utrecht

CZECH REPUBLIC (1)
- Hospital Motol, Praha