Linezolid-containing regimens for the treatment of drug-resistant tuberculosis in South African children*

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Background (1)

• Increasing recognition of the importance of MDR-TB in children
  – 2007-2009 – 8.9% of children with culture-confirmed TB - MDR\(^1\)

• Good treatment outcomes
  – 81.7% favorable

• Limited options for treatment of XDR-TB
  – Less experience in children

Background (2)

- Linezolid – oxazolidinone antibiotic
  - Adult data increasingly showing efficacy in MDR- and XDR-TB treatment regimens
  - Substantial rates of adverse events
- Linezolid in paediatric MDR- or XDR-TB
  - 4 case reports of 7 children (1 HIV pos) \(^2,^3,^4,^5\)
  - 7/7 favorable outcome - cure or clinical response
  - 3/7 adverse events
    - 1 child – lactic acidosis - linezolid stopped
    - 1 child - anaemia and neuropathy – linezolid dose reduced
    - 1 child - urticarial rash – linezolid dose reduced

Methods

• Objective - To describe additional experience with linezolid in children with MDR- or XDR-TB
• Study Design – Retrospective chart audit
• Patient Population
  – <15 years of age
  – treated with linezolid for drug-resistant TB
  – Feb 2007 and Mar 2012
  – Brooklyn Hospital for Chest Disease, Cape Town, and Pelonomi Hospital, Bloemfontein
• Patient management
  – Optimized background treatment regimen based on DST
  – Routine clinical monitoring for side-effects
  – Lab monitoring every 2 months and if clinically indicated (full blood picture, thyroid function tests, liver enzymes)
## Results (1) – Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Age at XDR- or MDR-TB diagnosis</th>
<th>Gender</th>
<th>Previous TB episode</th>
<th>Comorbid conditions at diagnosis</th>
<th>Chest radiographic findings at diagnosis</th>
<th>Resistance Profile of TB Strain</th>
<th>TB Source Case</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 year</td>
<td>Female</td>
<td>No</td>
<td>None, non-HIV-infected</td>
<td>Expansile RUL pneumonia with bronchial compression and perihilar lymphadenopathy</td>
<td>HREAmkOfx</td>
<td>MDR-TB, no second-line drugs tested (mother; died)</td>
</tr>
<tr>
<td>2</td>
<td>13 years 8 months</td>
<td>Male</td>
<td>No</td>
<td>None, non-HIV-infected</td>
<td>Left upper lobe cavity with bronchopneumonic picture in left lung</td>
<td>HRAmk</td>
<td>XDR-TB (mother; died)</td>
</tr>
<tr>
<td>3</td>
<td>10 years 4 months</td>
<td>Male</td>
<td>Yes – 5 years earlier</td>
<td>HIV-infected, deaf mute, epilepsy</td>
<td>Bilateral extensive upper lobe cavitation</td>
<td>HREAmkOfx</td>
<td>MDR-TB, no second-line DST performed (caregiver; died)</td>
</tr>
<tr>
<td>4</td>
<td>13 years 6 months</td>
<td>Female</td>
<td>No</td>
<td>None, non-HIV-infected</td>
<td>Bilateral upper lobe opacification with left upper lobe cavitation</td>
<td>HREAmkEthOfx</td>
<td>XDR-TB (mother, 3 adult siblings; all died)</td>
</tr>
<tr>
<td>5</td>
<td>7 months</td>
<td>Male</td>
<td>No</td>
<td>Ex-premature, very low birth weight; ventilated for severe pneumonia at age 3 months; chronic lung diseases; non-HIV-infected</td>
<td>Expansile RML pneumonia with hilar and paratracheal lymphadenopathy and bilateral broncho-pneumonic infiltrates</td>
<td>HREAmkOfx</td>
<td>Unknown, multiple chronic defaulters (1 died, no DST)</td>
</tr>
<tr>
<td>6</td>
<td>10 years</td>
<td>Female</td>
<td>No</td>
<td>HIV-infected, unilateral chronic suppurative otitis media</td>
<td>Bilateral cavitations</td>
<td>HREEthKmS</td>
<td>None identified</td>
</tr>
<tr>
<td>7</td>
<td>5 years 11 months</td>
<td>Female</td>
<td>Yes – 2 years earlier</td>
<td>HIV infected, bronchiectasis, chronic suppurative otitis media with hearing loss</td>
<td>Miliary pattern with extensive bronchiectasis</td>
<td>HREKmSOFx</td>
<td>None identified</td>
</tr>
</tbody>
</table>
## Results (2) – Outcomes and Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Previous TB Treatment during this TB episode</th>
<th>Linezolid-containing TB Regimen</th>
<th>Time to Culture Conversion (from start of Linezolid)</th>
<th>Treatment Outcome</th>
<th>Linezolid Dosage</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Failed 4 months HR prophylaxis, and 7 months MDR-TB regimen</td>
<td>HEZEthCpmTrdClmAmx/ClvLzd</td>
<td>23 days</td>
<td>Cured</td>
<td>10 mg/kg twice daily</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>Failed 6 months first-line treatment and 12 months MDR-TB treatment</td>
<td>HESMfxEthTrdPASClmAmx/ClvLzoCfz</td>
<td>3 months, 5 days</td>
<td>Cured</td>
<td>300 mg daily</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>Failed 6 months first-line treatment and received 1 month MDR-TB treatment</td>
<td>HZCpmEthTrdPASClrAmx/ClvLzd</td>
<td>4 months</td>
<td>Cured</td>
<td>300 mg daily</td>
<td>Pancreatitis (8 months)</td>
</tr>
<tr>
<td>4</td>
<td>Started XDR-TB treatment as known contact</td>
<td>HZCpmEthOfxTrdPASClmAmx/ClvLzd</td>
<td>2 months, 20 days</td>
<td>Cured</td>
<td>300 mg daily</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>Started MDR-TB treatment, switched to XDR-TB treatment after 1 month</td>
<td>HZCpmEthOfxTrdPASLzd</td>
<td>3 months</td>
<td>Treatment ongoing, but culture converted</td>
<td>10 mg/kg twice daily</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>Failed 6 months first-line treatment, 6 months MDR-TB treatment</td>
<td>HZCpmOfxTrdAmx/ClvClrPASLzd</td>
<td>18 months (9 months after adherence treatment)</td>
<td>Treatment ongoing, but culture converted</td>
<td>300 mg/kg twice daily (reduced to 200 mg/kg twice daily)</td>
<td>Peripheral neuropathy (24 months); anaemia (25 months)</td>
</tr>
<tr>
<td>7</td>
<td>Failed 6 months first-line treatment and 9 months MDR-TB treatment</td>
<td>CpmMfxPASTrdClmAmx/ClvLzdCfz</td>
<td>Already negative prior to commencing</td>
<td>Treatment ongoing, but culture converted</td>
<td>300 mg daily (discontinued)</td>
<td>Pancreatitis and lactic acidosis (7 months)</td>
</tr>
</tbody>
</table>
### Results (3) – Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Antiretrovirals</th>
<th>Adverse Event</th>
<th>Time after starting linezolid</th>
<th>Cause</th>
<th>Action and Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>d4T, 3TC EFV</td>
<td>Pancreatitis</td>
<td>8 months</td>
<td>Attributed to combination of d4T, 3TC, anticonvulsants, linezolid, and high fat diet</td>
<td>No drugs were stopped; pancreatitis resolved</td>
</tr>
<tr>
<td>6</td>
<td>d4T, 3TC, EFV</td>
<td>Peripheral neuropathy</td>
<td>Mild anaemia and leucopaenia</td>
<td>Peripheral neuropathy - attributed to multiple causes</td>
<td>Linezolid dose reduced, d4T changed to ABC, terizidone dose reduced, pyridoxine increased – symptoms resolved</td>
</tr>
<tr>
<td>7</td>
<td>ABC, 3TC, EFV</td>
<td>Neutropaenia, asymptomatic</td>
<td>Elevated transaminases, asymptomatic (ALT 2x ULN; AST 6x ULN)</td>
<td>Pancreatitis, lactic acidosis – attributed to linezolid</td>
<td>All meds discontinued, recovered, restarted all medications other than linezolid</td>
</tr>
</tbody>
</table>
Discussion

• Linezolid efficacy
  – Culture conversion – 7/7
  – Favorable outcome – 7/7
  – Efficacious in very difficult cases

• Dosing of linezolid
  – PK differs in children – age-related
  – 10 mg/kg twice daily if <30 kg, if >30 kg 10 mg/kg once daily OR 300 mg once daily

• Adverse events
  – 3/7 with adverse events, including serious events
  – Similar to published adult data
  – Association of HIV and ART with AEs may need further evaluation
    • Few HIV-positive patients described in the literature
    • Close monitoring in HIV-infected patients
Conclusion

• Linezolid-containing regimens can be effective for children with XDR-TB and refractory MDR-TB
• Serious adverse events are frequent, requiring close monitoring
• Forthcoming adult data will help inform paediatric practice
• Children need to be considered in plans for evaluation of existing and novel drugs for DS- and DR-TB