Treatment of MDR-TB in high HIV-prevalence settings

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PIH-Lesotho
October 20, 2008
Early outcomes of MDR-TB treatment

- Retrospective cohort analysis
- Registered between July 21, 2007 and December 21, 2007
- Included all patients starting treatment with second-line TB drugs for confirmed or presumptive MDR-TB
## Baseline characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>N (%)</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>15 (37.5%)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td>36.1 (10.1)</td>
</tr>
<tr>
<td>Previously worked in South Africa</td>
<td>15 (37.5%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical</th>
<th>N (%)</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV seropositive</td>
<td>27 (67.5%)</td>
<td></td>
</tr>
<tr>
<td>Body mass index</td>
<td></td>
<td>18.9 (3.8)</td>
</tr>
<tr>
<td>Serum albumin (g/L)</td>
<td></td>
<td>31.3 (8.8)</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td></td>
<td>11.4 (2.5)</td>
</tr>
<tr>
<td>Bilateral disease on CXR</td>
<td>16 (40%)</td>
<td></td>
</tr>
<tr>
<td>Cavitory disease on CXR</td>
<td>23 (57.5%)</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Previous treatment</th>
<th>N (%)</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of previous treatment regimens</td>
<td>2 (0.93)</td>
<td></td>
</tr>
<tr>
<td>Treatment with second-line drugs</td>
<td>6 (15%)</td>
<td></td>
</tr>
<tr>
<td>Previous treatment in South Africa</td>
<td>8 (20%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Household contacts</th>
<th>N (%)</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of household contacts</td>
<td>3.5 (2.3)</td>
<td></td>
</tr>
</tbody>
</table>
Bacteriology

- Thirty-nine (97.5%) patients were sputum AFB positive at the beginning of treatment.
- Twenty-four (60%) patients had laboratory-confirmed MDR-TB; the remainder of the patients had negative or contaminated cultures.
- Fourteen isolates were tested by MRC in South Africa for resistance to first- and second-line drugs. Of these, two (14.3%) had resistance to second-line drugs, one of whom met criteria for XDR-TB.
Empiric MDR-TB treatment

- In 27 (67.5%) patients, MDR-TB treatment was started empirically, meaning that MDR-TB treatment was started before receiving laboratory confirmation of resistance to isoniazid and rifampicin.
HIV co-infection and ART co-treatment

- Twenty-seven (67.5%) patients were infected with HIV
- Mean CD4 cell count was 259 cells/μl (SD 222).
- Of the HIV-infected patients, 9 patients were already receiving ART before starting MDR-TB therapy, and 10 patients were started on ART a mean of 36 days (SD 10 days) after starting MDR-TB therapy. The remaining 8 patients died without starting ART.
Survival

- Eleven patients (27.5%) had died.
- 29 patients (72.5%) were alive and in treatment. No patients had defaulted or transferred.
- In those who did not survive, death occurred after a mean of 54 days in treatment (SD 26 days).
- In univariate analyses, hemoglobin < 10 g/dL, serum albumin < 30 g/L, and a history of three or more previous TB treatments were associated with death.
Survival

Logrank p=0.2578

<table>
<thead>
<tr>
<th></th>
<th>No. of Subjects</th>
<th>Event</th>
<th>Censored</th>
<th>Median Survival (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-negative</td>
<td>13</td>
<td>15% (2)</td>
<td>85% (11)</td>
<td>NA ( NA NA NA )</td>
</tr>
<tr>
<td>HIV-positive</td>
<td>27</td>
<td>33% (9)</td>
<td>67% (18)</td>
<td>NA ( 95.00 NA )</td>
</tr>
</tbody>
</table>
Side effects

- Hypothyroidism
- Hypokalemia
- Severe anemia
- Neuropathy
- Nausea and vomiting
- Psychosis
- Seizures
- Depression
- Otoxicity
- Hematemesis
- Pneumothorax
Lesotho vs. rest of the world†


* Tomsk, Latvia, Estonia, Peru, Philippines
Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Lesotho (N=40)</th>
<th>Peru (N=75)</th>
<th>Tomsk (N=244)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-positive</td>
<td>67.5%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Body mass index</td>
<td>18.9</td>
<td>19.9</td>
<td>20.5</td>
</tr>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>11.4</td>
<td>12.2</td>
<td>-</td>
</tr>
<tr>
<td>Serum albumin (g/L)</td>
<td>31.3</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Tomsk (N=244)

- Nausea and vomiting
- Arthralgias
- Diarrhea
- Hypokalemia
- Hypothyroidism
- Hepatotoxicity
- Rash
- Otoxicity
- Psychosis
- Seizure
- Nephrotoxicity
- Depression
- Neuropathy
Case 1

• 42 y.o. man who previously failed two courses of TB treatment in South Africa, most recently with Rimstar, KM, CPX, ETO.
• Started empirically MDR-TB treatment: CM-MFX-ETO-CS-PAS.
• HIV-positive, CD4 106. Started on AZT-3TC-EFV on day 48.
• BMI 18.5; bilateral lesions on CXR.
Case 1 (cont.)

• 15 Oct: Cr 88, K 2.8*
• 19 Oct: Cr 85, K 3.0, Mg < 1.5
• 22 Oct: Cr 69, K 3.2
• 12 Nov: Cr 69, K 3.8

* 11 days after starting ART
Table 1—Patient Characteristics Among 115 Patients Receiving MDR-TB Therapy*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>With Hypokalemia (n = 36)</th>
<th>Without Hypokalemia (n = 79)</th>
<th>p Value</th>
<th>Crude Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>31.7 ± 10.0</td>
<td>29.3 ± 9.6</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td>18 (50.0)</td>
<td>47 (59.5)</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td>No. of drugs to which strain resistant</td>
<td>5.6 ± 1.6</td>
<td>5.8 ± 1.7</td>
<td>0.58</td>
<td></td>
</tr>
<tr>
<td>No. of previous treatments</td>
<td>3.5 ± 1.6</td>
<td>3.5 ± 1.3</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>Initial weight, kg</td>
<td>52.2 ± 11.2</td>
<td>58.2 ± 12.1</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Body mass index</td>
<td>20.2 ± 3.9</td>
<td>21.7 ± 3.8</td>
<td>0.059</td>
<td></td>
</tr>
<tr>
<td>Injectable drug</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amikacin</td>
<td>2 (5.6)</td>
<td>1 (1.3)</td>
<td>0.23</td>
<td>2.09 (0.42–10.40)</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>30 (83.3)</td>
<td>14 (17.7)</td>
<td>&lt; 0.0001</td>
<td>2.88 (1.86–4.46)</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>3 (8.3)</td>
<td>26 (32.9)</td>
<td>0.005</td>
<td>0.69 (0.56–0.85)</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>1 (2.8)</td>
<td>38 (48.1)</td>
<td>&lt; 0.0001</td>
<td>0.55 (0.45–0.69)</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>14 (38.9)</td>
<td>4 (5.1)</td>
<td>&lt; 0.0001</td>
<td>3.45 (1.46–8.31)</td>
</tr>
<tr>
<td>Comorbid conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0 (0)</td>
<td>2 (2.5)</td>
<td>1.0</td>
<td>0.68 (0.60–0.77)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>16 (44.4)</td>
<td>17 (21.5)</td>
<td>0.015</td>
<td>1.47 (1.03–2.09)</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>2 (5.6)</td>
<td>1 (1.3)</td>
<td>0.23</td>
<td>2.09 (0.42–10.40)</td>
</tr>
<tr>
<td>Treatment outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favorable outcome</td>
<td>25 (69.4)</td>
<td>62 (78.5)</td>
<td>0.35</td>
<td>0.85 (0.61–1.18)</td>
</tr>
<tr>
<td>Death</td>
<td>8 (22.2)</td>
<td>8 (10.1)</td>
<td>0.14</td>
<td>1.43 (0.57–2.38)</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD or No. (%).
Figure 1. Serum and urine electrolytes after recognition of magnesium, calcium and potassium abnormalities which developed after seven weeks of viomycin-PZA administration. Admission serum electrolyte values are listed in the text. Serum calcium and magnesium normalized concurrently by day 75 and required no further supplementation (amounts of magnesium sulfate and calcium chloride cited in the Figure represent nondietary supplementation; calcium gluconate was also administered on days 53 and 54). Serum K stabilized at 3.5 mEq/L by day 110 when supplementary KCl was discontinued. The intake of potassium (bottom panel) includes supplemental and estimated dietary K. Urinary potassium excretion shows inability to conserve K appropriately until day 80, and significant K retention only after day 100.
Hypokalemia in hospitalized patients

• K < 3.6 in 20% of hospitalized patients; K < 3.0 in 5% of hospitalized patients.†

• There are multiple causes of hypokalemia in MDR-TB/HIV co-infected patients:
  - Vomiting
  - Diarrhoea
  - Renal wasting

Hypokalemia protocol

• Slow-K 3600 mg (6 tabs = 48 mEq) daily. Give in 2-3 divided doses.
• Mg gluconate 2 g (4 tabs) daily. Give in 2-3 divided doses.
• Recheck K within one week. Increase dosing of Slow-K and Mg gluconate if K is not within normal limits.
Case 2

• 48 y.o. woman previously treated twice for TB and started on MDR-TB treatment in August 2007: 1800 / KM 1000 / OFX 800 / ETO 750 / CS 750 / PAS 8 gm. HIV+, CD4 678

• 1 month clinic visit: Cough, blood-stained sputum, night sweats, nausea, rash, symptoms of neuropathy.

• Wt 49.8 kg. BP 90/60, Pulse 90/min, Temp 36, RR 28. Lungs with crackles on right side. Fine skin rash on knees.

• Labs: ALT 15, T. bili 8; Cr/K: requested, but not done
Case 2

• 2 month home visit: for 2 days of hemoptysis.

• Patient reported a large amount of blood on the first day (~1 liter!), but said that on the second day, her sputum was blood-stained only, without frank blood. She looked pale.

• Labs (Leribe Hospital): Hb 9.2; Urea 4.8 (nl); Total protein 89; GGT 40; ALT 77 (nl)

• AZT switched to d4T.
Causes of anemia

- AZT
- Massive GI bleeding
- Chronic disease

- Admitted to the hospital one week later. Weak, vomiting dehydrated. Labs: Hb 7.2; Cr 79 (nl); Urea 4.7; Na 128; K 3.1; GGT 59; ALT 6; AST 65
Case 3

• 45 y.o. man with history of multiple treatments for TB in South Africa, including second-line TB drugs (AMK-TRD-ETO-CLR).

• Bilateral lesions on CXR; purulent draining cervical lesions; Hb 6.

• Started empirically on Z-CM-MFX-ETO-CS-PAS

• Known HIV-positive; CD4 9.

• Witnessed tonic-clonic seizure in hospital bed one month after starting treatment.
Case 3 (cont.)

- CSF: glucose 3.3; protein 0.33
- WBC/RBC not done
- India ink negative
- CrAg negative
Cycloserine-related side effects

Psychosis: 10% (Lesotho), 12% (Tomsk)
Fits: 8% (Lesotho), 10% (Tomsk)
Depression: 6% (Lesotho), 8% (Tomsk)
Seizure protocol

- Uncomplicated fits: start phenytoin (with or without loading dose), continue CS at same dose.
- Complicated fits: start phenytoin, suspend or reduce dose of CS, consider other causes.
Case 4

- 53 y.o. man previously treated twice with first-line regimens, but sputum AFB positive.
- Started Z-KM-OFX-ETO-CS-PAS.
- Rapid HIV test negative at initiation of MDR-TB therapy.
- Three weeks after initiation, awoke and brushed his teeth. His wife found him convulsing on the floor, incontinent of feces and urine.
- He was brought urgently to the hospital. He responded to voice, but was drowsy and was unable to sit up.
Lab tests

- Urea 14
- Creatinine 223
- Potassium normal
Renal protocol

• Hold injectable immediately.
• Check Creatinine frequently.
• Renally dose medications if CrCl < 30.
• In this patient, Cr 182 two days after seizure; Cr 120 three days after seizure; Cr back to baseline within one week; patient was discharged home on original dose of Kanamycin, with close follow-up.
Conclusion

- Side effects are more common and more early in Africa compared to other countries
- Don’t forget about HIV
- Seizures are good
- “If you don’t take a temperature, you can’t find a fever”