Protective Effects of Statins on Cisplatin-Related Hearing Loss

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James Madison University
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Overview

• Cisplatin Ototoxicity

• Animal Model of Ototoxicity

• Therapeutic Intervention
  • Animal Model
  • Clinical Study
Ototoxicity: oto=ear, toxicity = poisoning

- Two major classes of ototoxic drugs
  - Aminoglycoside antibiotics
  - Platinum-based anti-cancer drugs (cisplatin)
- Aminoglycosides and cisplatin are toxic to sensory hair cells

**Basic Science:** Ototoxic drugs represent a major stressor to hair cells

**Clinical:** These drugs cause permanent hearing loss for ~500,000 Americans every year
Cisplatin ototoxicity

- Among the most widely-used and effective anti-cancer drugs
- Used to treat testicular, bladder, lung, stomach, head & neck, ovarian, and other cancers
- The most ototoxic drug in clinical use
- Incidence of hearing loss varies widely (20-90%)
- Cisplatin-induced hearing loss is sensorineural, bilateral, progressive and irreversible
Cisplatin has no substitute
Preconditioning can be oto-protective

- Sound pre-conditioning
  - Measure baseline hearing
  - Expose to 90 dB OBN
  - Wait 6 hours
  - Administer cisplatin
  - Measure change in hearing (ABR)

Roy et al., 2013
Preconditioning can be oto-protective

- Sound pre-conditioning
- Heat stress
  - Measure baseline hearing
  - Raise body temp 4.5° for 15 min
  - Expose to 100 dB SPL OBN for 2 hr
  - Measure change in hearing threshold (CAP)

Yoshida et al., 2000
Preconditioning can be oto-protective

- Sound pre-conditioning
- Heat stress
  - Whole organ cultures
  - Heat Shock to 43° for 30 min
  - Expose to aminoglycosides
  - Compare hair cell survival

Taleb et al., 2008
Stress can activate both cell-survival and cell-death pathways in a cell
Clinical limitations of preconditioning
Are there already drugs that induce HSPs?
HSP induction via statins inhibits ototoxicity

- Statins induce HSP32 (Ali et al., 2009)
- Simvastatin reduces gentamicin-induced hair cell death in mice (Brand et al., 2011)
- Pravastatin reduces NIHL in mice (Park et al., 2012)
- Atorvastatin reduces ARHL in mice (Syka et al., 2007)

- Statins could be potential candidates for reducing ototoxicity
An animal model of cisplatin ototoxicity

Fernandez et al., in prep
Cisplatin ototoxicity is progressive

Fernandez et al., *in prep*
Cisplatin causes hair cell death

Fernandez et al., in prep
Summary

• An ear under stress induces pro-life and pro-death signals to its cells
• Heat shock proteins (HSPs) are induced by stress and offer protection
• HSPs can be induced pharmacologically by statins
• Statins are protective against other forms of acoustic stress
• Cisplatin ototoxicity can be modeled in mice
Lovastatin reduces ototoxicity in mice

Female Mice

Male Mice

Fernandez et al., in prep
Can statins protect in humans, too?

<table>
<thead>
<tr>
<th>Age</th>
<th>Total N=118</th>
<th>Statin Users N=50</th>
<th>Non-Statin Users N=68</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (years)</td>
<td>62.4</td>
<td>55.8</td>
<td></td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>7.8</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Minimum</td>
<td>44</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Maximum</td>
<td>78</td>
<td>76</td>
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</table>

<table>
<thead>
<tr>
<th>Sex</th>
<th>Total N=118</th>
<th>Statin Users N=50</th>
<th>Non-Statin Users N=68</th>
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<tbody>
<tr>
<td>Male</td>
<td>102 (86%)</td>
<td>45 (90%)</td>
<td>57 (84%)</td>
</tr>
<tr>
<td>Female</td>
<td>16 (14%)</td>
<td>5 (5%)</td>
<td>11 (16%)</td>
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</table>

<table>
<thead>
<tr>
<th>Pre-existing Hearing Loss</th>
<th>Total N=118</th>
<th>Statin Users N=50</th>
<th>Non-Statin Users N=68</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>68 (58%)</td>
<td>29 (58%)</td>
<td>39 (57%)</td>
</tr>
<tr>
<td>No</td>
<td>50 (42%)</td>
<td>21 (42%)</td>
<td>29 (43%)</td>
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<table>
<thead>
<tr>
<th>Cisplatin Cumulative Dose</th>
<th>Total N=118</th>
<th>Statin Users N=50</th>
<th>Non-Statin Users N=68</th>
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</thead>
<tbody>
<tr>
<td>Mean (mg/m²)</td>
<td>252.6</td>
<td>242.6</td>
<td>257.9</td>
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<tr>
<td>Standard Deviation</td>
<td>105</td>
<td>100.2</td>
<td>108.7</td>
</tr>
<tr>
<td>Minimum</td>
<td>75</td>
<td>100</td>
<td>75</td>
</tr>
<tr>
<td>Maximum</td>
<td>525</td>
<td>450</td>
<td>525</td>
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</table>

<table>
<thead>
<tr>
<th>Initial Cisplatin Dose</th>
<th>Total N=118</th>
<th>Statin Users N=50</th>
<th>Non-Statin Users N=68</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low, &lt;75 mg/m²</td>
<td>36 (31%)</td>
<td>18 (26%)</td>
<td></td>
</tr>
<tr>
<td>High, ≥75 mg/m²</td>
<td>83 (69%)</td>
<td>32 (64%)</td>
<td>51 (74%)</td>
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</table>

<table>
<thead>
<tr>
<th>Radiation</th>
<th>Total N=118</th>
<th>Statin Users N=50</th>
<th>Non-Statin Users N=68</th>
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<tbody>
<tr>
<td>Yes</td>
<td>80 (68%)</td>
<td>41 (82%)</td>
<td>39 (57%)</td>
</tr>
<tr>
<td>No</td>
<td>38 (32%)</td>
<td>9 (18%)</td>
<td>29 (43%)</td>
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</tbody>
</table>

Retrospective Cohorts

- University of Rochester Medical Center
- National Institutes of Health, Audiology Unit
- Walter Reed National Military Medical Center
Retrospective cohorts reinforce statin protective effects against cisplatin
Ototoxicity monitoring scales

- American Speech Language Hearing Association (ASHA)
- Common Terminology Criteria for Adverse Events (CTCAE)
- Society for Industrial and Organizational Psychology (SIOP)
- TUNE
- Brock Ototoxicity Grades
- Chang Scale
Statins reduce the incidence of cisplatin-induced ototoxicity

**ASHA Criteria**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>No</td>
<td>No hearing loss</td>
</tr>
<tr>
<td>Yes</td>
<td>Threshold shift ≥20dB shift at any frequency OR threshold shift ≥10dB shift at 2 consecutive frequencies</td>
</tr>
</tbody>
</table>

\[ * p=0.02 \]
Statins reduce the incidence of cisplatin-induced ototoxicity.

**TUNE Criteria**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No hearing loss</td>
</tr>
<tr>
<td>1</td>
<td>Threshold shift &gt; 10dB at 1-4kHz PTA or 8-12.5kHz PTA</td>
</tr>
<tr>
<td>2</td>
<td>Threshold shift ≥ 20dB at 1-4kHz PTA or 8-12.5kHz PTA</td>
</tr>
<tr>
<td>3</td>
<td>Threshold Shift ≥ 35dB at 1-4kHz PTA or 8-12.5kHz PTA</td>
</tr>
<tr>
<td>4</td>
<td>Threshold Shift ≥ 50dB at 1-4kHz PTA or 8-12.5kHz PTA</td>
</tr>
</tbody>
</table>

* p=0.02, ASHA  
* p=0.03, TUNE  

Fernandez et al., unpublished
Statins reduce the severity of cisplatin-induced ototoxicity

**TUNE Criteria**

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<tr>
<th>Grade</th>
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<tr>
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</tbody>
</table>

Fernandez et al., unpublished
Statins are protective against cisplatin-induced ototoxicity

**Chi Square Analysis**

<table>
<thead>
<tr>
<th>Statins x HL</th>
<th>P-Value</th>
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<tbody>
<tr>
<td>ASHA</td>
<td>0.0210</td>
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<tr>
<td>TUNE</td>
<td>0.0533</td>
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<tr>
<td>Either Scale</td>
<td>0.0324</td>
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</table>
Prospective study to determine if statins protect against cisplatin-induced ototoxicity

Clinicaltrials.gov: NCT03225157
ShoeBox: Self-administered hearing test
Clinical study inclusion criteria

- Adult patients >18 years old
- Patients with head and neck cancer
- Patients prescribed cisplatin
- Subject willing to self-administer their hearing test via the iPad
- Subjects with hearing thresholds better than 80 dB SPL at 1, 2, 4 kHz
- Subjects must have a Type A tympanogram
- Subjects must be able to provide their own consent
Clinical study overview

TIME (weeks)

0 1 2 3 4 5 6 7 8 9 10 11 12 13 33

Hearing test

Cisplatin

Enrollment

Tinnitus questionnaire
Noise questionnaire

Target N of 334
Summary

• Cisplatin is a highly effective but very ototoxic drug causing significant hearing loss in both children and adults

• Clinically relevant animal models of cisplatin ototoxicity are critical to determining therapeutic strategies that address hearing loss

• Statin drugs may reduce the incidence and severity of cisplatin-induced hearing loss
  • Data collection is ongoing
Future directions

Screen for molecules that reduce cisplatin uptake

Test “hits” in mice receiving cisplatin

Test in humans receiving cisplatin
Cisplatin is localized to stria vascularis and spiral ganglion neurons in human cochlea.

Breglio et al. 2017 Nature Communications
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