Tetrodotoxin (TTX) for Chemotherapy Induced Neuropathic Pain (CINP): A Randomized, Double-Blind, Dose-Finding, Placebo Controlled, Multicenter Study

Goldlust SA, Kavoosi M, Korz WK, Deck K
• Tetrodotoxin (TTX)
  – Produced by symbiotic bacteria
    • Tetraodontiformes (e.g. pufferfish)
  – Inhibits voltage gated Na+ channel (VGSC)
    • Action potential initiation & propagation
  – Nocioceptive fibers
    • Promote healing of damaged tissues
    • Unique profile of VGSC subtypes
    • Lower threshold of TTX for inactivation
BACKGROUND - CINP

- Neuropathy - variable presentation
  - Loss of function: ataxia, ‘numbness,’ weakness
  - Gain of function: pain, allodynia, paresthesia

- Chemotherapy induced neuropathic pain (CINP)
  - Taxanes (e.g. docetaxel)
  - Platinum compounds (e.g. oxaliplatin)
  - Vinca alkaloids (e.g. vincristine)
  - Proteosome inhibitors (e.g. bortezomib)
BACKGROUND - CINP

- Considerable unmet need
  - Solid tumors: breast, lung, GI
  - Liquid tumors: multiple myeloma, lymphoma
- Limited available options
  - Opiates, anti-depressants, NSAIDs, anti-convulsants
    - Toxicity (e.g. bleeding, constipation, sedation)
    - Drug – drug interactions (e.g. MAOI + SNRI)
METHODS

• Objectives
  – Identify dosing regimen for phase III
  – Safety and tolerability

• Primary endpoint
  – Mean change from baseline in average NPRS days 22-28 (week 4)
METHODS

• Key inclusion criteria
  – Taxane or platinum induced CINP
  – ECOG 0-1
  – Moderate to severe pain (≥ 4/10, NPRS*)
  – Stable NPRS for one week prior to randomization
  – Chemotherapy complete (30 day washout)
  – Stable cancer

*Numeric pain rating scale
METHODS

• Key exclusion criteria
  – Long acting opiates, tricyclic antidepressants, anti-convulsants, sodium channel blockers
    • Stable dose of SSRI*, SNRI** permissible
  – Peripheral neuropathy of alternative etiology (e.g. diabetes)
  – Bone metastases
  – Significant medical co-morbidity (e.g. cardiac arrhythmia)

*SSRI = selective serotonin reuptake inhibitor
**SNRI = selective norepinephrine reuptake inhibitor
METHODS

- Treatment – 4 consecutive days
- Safety and efficacy follow-up – weekly x 4
RESULTS

• 125 patients (77 women) randomized
  – Intent to treat: 125
  – Per protocol: 107
• Mean age 60
• Only 4 patients < 80% compliant with TTX
RESULTS – PRIMARY ENDPOINT

- Mean change from baseline in average NPRS days 22-28 (week 4)
- Placebo – shorter time to peak pain relief

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1 (7.5 µg BID)</th>
<th>Cohort 2 (15 µg BID)</th>
<th>Cohort 3 (30 µg QD)</th>
<th>Cohort 4 (30 µg BID)</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>-0.836 (0.9553)</td>
<td>-0.891 (0.8396)</td>
<td>-1.006 (1.6116)</td>
<td>-1.244 (1.5911)</td>
<td>-0.906 (1.1193)</td>
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<tr>
<td>Week 2</td>
<td>-1.164 (1.3583)</td>
<td>-1.218 (1.1188)</td>
<td>-1.508 (1.8307)</td>
<td>-1.433 (1.7853)</td>
<td>-1.423 (1.7218)</td>
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<tr>
<td>Week 3</td>
<td>-1.197 (1.4770)</td>
<td>-1.277 (1.6375)</td>
<td>-1.670 (2.0198)</td>
<td>-1.555 (1.5565)</td>
<td>-1.365 (1.8792)</td>
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<tr>
<td>Week 4</td>
<td>-1.269 (1.3959)</td>
<td>-1.052 (1.5742)</td>
<td>-1.682 (2.3231)</td>
<td>-1.529 (1.8203)</td>
<td>-1.339 (2.0681)</td>
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</tbody>
</table>
RESULTS – SECONDARY ENDPOINT

- Responder analysis - 30% reduction in average NPRS from baseline to any week
RESULTS – ADVERSE EVENTS

- Most grade I/II and nervous system related

<table>
<thead>
<tr>
<th>System Organ Class Preferred Term</th>
<th>Cohort 1 (N=25)</th>
<th>Cohort 2 (N=24)</th>
<th>Cohort 3 (N=25)</th>
<th>Cohort 4 (N=26)</th>
<th>Placebo (N=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td>13 (52.0%)</td>
<td>16 (66.7%)</td>
<td>17 (68.0%)</td>
<td>20 (76.9%)</td>
<td>11 (44.0%)</td>
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<tr>
<td>Paresthesia oral</td>
<td>4 (16.0%)</td>
<td>9 (37.5%)</td>
<td>10 (40.0%)</td>
<td>11 (42.3%)</td>
<td>3 (12.0%)</td>
</tr>
<tr>
<td>Hypoesthesia oral</td>
<td>5 (20.0%)</td>
<td>7 (29.2%)</td>
<td>6 (24.0%)</td>
<td>10 (38.5%)</td>
<td>3 (12.0%)</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>5 (20.0%)</td>
<td>7 (29.2%)</td>
<td>5 (20.0%)</td>
<td>7 (26.9%)</td>
<td>6 (24.0%)</td>
</tr>
<tr>
<td>Headache</td>
<td>6 (24.0%)</td>
<td>3 (12.5%)</td>
<td>1 (4.0%)</td>
<td>9 (34.6%)</td>
<td>5 (20.0%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3 (12.0%)</td>
<td>4 (16.7%)</td>
<td>3 (12.0%)</td>
<td>8 (30.8%)</td>
<td>5 (20.0%)</td>
</tr>
<tr>
<td>Hypoesthesia</td>
<td>2 (8.0%)</td>
<td>1 (4.2%)</td>
<td>2 (8.0%)</td>
<td>1 (3.8%)</td>
<td>2 (8.0%)</td>
</tr>
</tbody>
</table>
RESULTS – ADVERSE EVENTS

- Seven grade III AE
  - Paresthesia, burning sensation, pain (3), hypertension, viral URI
- No grade IV AE
- Notable absence of grade III/IV cardiopulmonary AE
- Three SAE
  - Two unrelated, one unlikely related to TTX
CONCLUSIONS

• CINP unmet need in oncology
• TTX well tolerated across cohorts
• TTX 30 µg b.i.d. (cohort 4) – promising early efficacy, response rate
• Phase III development underway