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

John Theurer Cancer Center
at Hackensack University Medical Center

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BACKGROUND - TTX

- 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

Cohort	n	Drug Dose (TTX/Placebo)	Dosing Schedule		Dosing Duration	Cumulative Dose
			TTX	Placebo		
1	25	Placebo	NA	BID	4 days	NA
2	25	7.5 µg	BID	NA	4 days	60 µg
3	25	15 µg	BID	NA	4 days	120 µg
4	25	30 µg	QD	QD	4 days	120 µg
5	25	30 µg	BID	NA	4 days	240 µg

- 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

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

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

RESULTS – SECONDARY ENDPOINT

	Cohort 1 (7.5 µg BID)	Cohort 2 (15 µg BID)	Cohort 3 (30 µg QD)	Cohort 4 (30 µg BID)	Placebo
Yes	9 (36.0%)	11 (45.8%)	10 (40.0%)	15 (57.7%)	8 (32.0%)
No	16 (64.0%)	13 (54.2%)	15 (60.0%)	11 (42.3%)	17 (68.0%)
P-value	0.333	0.0657	0.992	0.072	

	Cohort 1 (7.5 µg BID)	Cohort 2 (15 µg BID)	Cohort 3 (30 µg QD)	Cohort 4 (30 µg BID)
Odds Ratio (vs. placebo)	1.12	1.99	1.65	3.39
95% CI for Odds Ratio	(0.32, 3.96)	(0.56, 7.13)	(0.46, 5.90)	(0.96, 11.97)

- Responder analysis - 30% reduction in average NPRS from baseline to any week

RESULTS – ADVERSE EVENTS

- Most grade I/II and nervous system related

System Organ Class Preferred Term	Cohort1 (N=25)	Cohort2 (N=24)	Cohort3 (N=25)	Cohort4 (N=26)	Placebo (N=25)
Nervous system disorders	13 (52.0%)	16 (66.7%)	17 (68.0%)	20 (76.9%)	11 (44.0%)
Paresthesia oral	4 (16.0%)	9 (37.5%)	10 (40.0%)	11 (42.3%)	3 (12.0%)
Hypesthesia oral	5 (20.0%)	7 (29.2%)	6 (24.0%)	10 (38.5%)	3 (12.0%)
Paresthesia	5 (20.0%)	7 (29.2%)	5 (20.0%)	7 (26.9%)	6 (24.0%)
Headache	6 (24.0%)	3 (12.5%)	1 (4.0%)	9 (34.6%)	5 (20.0%)
Dizziness	3 (12.0%)	4 (16.7%)	3 (12.0%)	8 (30.8%)	5 (20.0%)
Hypesthesia	2 (8.0%)	1 (4.2%)	2 (8.0%)	1 (3.8%)	2 (8.0%)

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