A Phase I Study of the Intrathecal Administration of Resiniferatoxin for Treating Severe Refractory Pain Associated with Advanced Cancer

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ABSTRACT

Previous studies in animal pain models demonstrated profound pain relief and improved mobility after intrathecal resiniferatoxin (RTX). We are conducting a phase I clinical trial of intrathecal administration of RTX in advanced cancer patients with severe, medically-refractory pain. RTX is a small organic compound that acts on the vanilloid receptor-1 (TRPV1) of pain-sensing primary afferent spinal and dorsal root ganglia neurons, deleting them by elevating their intracellular calcium to induce apoptosis. We administer intrathecal RTX under propofol sedation to prevent the acute pain that accompanies the excitotoxic destruction of TRPV1 neurons. Ten patients have been treated. Initially, 4 received 3-13 micrograms of RTX in a pilot safety study. The current, more comprehensive dose-escalating study obtains measurements of pre- and post-injection NRS (numerical rating scale), quality of life, quantitative thermal sensation, and safety data. The next 3 patients received 13 micrograms RTX and the subsequent 3 patients 26 micrograms RTX. Patients in the initial 4 patient pilot study experienced variable amounts of pain relief. Patients in subsequent cohorts also reported less pain and improved mobility after RTX injection. NRS trended lower compared to pretreatment, although the NRS change was statistically insignificant at these doses. Thermal perception reduction was consistent with cell death of the TRPV1 neurons. There were no other sensory or motor changes post-treatment. These preliminary findings suggest that intrathecal injection of RTX can selectively and irreversibly delete neurons that transmit pain. We plan to test the safety and efficacy of higher doses of RTX to determine if this targeted therapy can reduce severe, refractory pain while improving quality of life in patients with advanced cancer.

Figure 1. Euphorbia Resinifera

INTRODUCTION

In a systematic meta-analysis (1966-2005), van den Beuken et al. noted that early reports on the prevalence of moderate to severe pain in cancer patients ranged from 52% to 77% (Twycross 1983), however more recent studies reported ranges from 24% to 60% in patients undergoing active anticancer treatment and 62% to 86% in patients with advanced cancer (van den Beuken 2007). To patients with cancer, pain is both feared and burdensome, and the opioid analgesics typically used for treatment (Jadad 1995) come with baggage that presents patients with the Hobson's choice of pain or unwanted side effects.

Other than new routes of administration for opioids, there has been no true innovation in cancer pain treatment. Resiniferatoxin (RTX), an ultrapotent and specific TRPV1 receptor agonist obtained from a cactus-like plant (Figure 1), may represent such an innovation. TRPV1 modulates a calcium channel which is important for calcium signaling and thermal sensitivity responses. In addition to several non CNS locations, TRPV1 is expressed on the cell body, axon and central and peripheral terminals of specific primary afferents (C and A-delta) and in interneurons in the superficial dorsal horn. In chronic pain states, TRPV1 is upregulated. Preclinical studies have demonstrated that when injected in sufficient doses centrally, RTX produces a selective ablation of the neuron expressing TRPV1 through calcium influx-induced apoptosis. Deleting the TRPV1 portion of nociceptive pathways is hypothesized to provide pain relief without affecting vital somatosensory and motor activities. The potential efficacy of RTX is supported by published considerable preclinical data, including companion canine and nonhuman primate studies. A single intrathecal (IT) RTX dose in companion dogs with cancer-induced bone pain (e.g., osteosarcoma) demonstrated what appeared to be permanent and profound pain relief resulting in improved mobility and behavior (Brown 2005).

The current study is designed to assess the pain treatment response to IT RTX in a first-in-human study designed to identify the maximum tolerated dose and characterize its dose limiting toxicity (DLT). This is a preliminary report from this ongoing study.

MATERIALS AND METHODS

This is an open-label, single-site clinical trial of ascending IT RTX doses in adult patients with cancer reporting severe, medically-refractory pain. Eligible patients must have histologically confirmed cancer with progressive disease after standard therapies and no effective palliative therapy to alleviate pain, and must not be seeking curative therapies. Patients must have inadequate pain relief with maximally tolerated opioids and adjuvants, and other treatment methodologies have been of limited benefit. The targeted pain area must be below the mid chest region and its severity determined using a 7-day worst average NRS score must be 6 or greater. DLT is defined as the development of a grade 3 or higher RTX-related toxicity or two or more grade 2 RTX-related toxicities, with severity (grade) determined by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.

Patients were placed under propofol general anesthesia for 2 hours to prevent awareness of any acute pain that might accompany the RTX injection delivery in a 2 mL volume with 0.5 mL flush via a spinal catheter placed in the lumbar region (standard epidural catheter kit). Afterwards, the patients were awakened and observed overnight. Outcome measures included NRS scores, BPI pain interference items, thermal sensitivity, opioid use, spontaneous adverse reactions, and pre- and post-RTX ECGs, MRI scans with gadolinium enhancement, neurological examinations by an independent neurologist with quantitative sensory and position sense testing, ophthalmological examinations by an independent ophthalmologist. Various study assessments were repeated at approximately 2 weeks after RTX administration and at various study time points thereafter.

Table 1. Baseline Characteristics

Demographics at Study Entry	Cancer Diagnosis	Target Pain Area
49 yowf	Metastatic breast cancer	Low back and bilateral leg pain 2º bone mets
56 yobm	Metastatic supraglottic squamous cell cancer	Low back and bilateral hip pain 2º bone mets
57 yobm	Metastatic pancreatic cancer	Bilateral abdominal (visceral) pain
68 yowm	Lymphoma, small fiber monoclonal gammopathy	Bilateral hip and buttocks (neuropathic) pain
55 yowm	Metastatic small cell lung cancer	Left hip pain 2º bone mets
61 yowf	Metastatic endometrial cancer	Low back and left hip/groin pain 2º bone mets

RESULTS

Six patients ranging in age between 49-68 with advanced cancer and severe, medically-refractory pain at or below the T5 dermatome received one IT RTX injection of either 13 mcg (first 3 patients in Table 1) or 26 mcg (last 3 patients in Table 1). Post RTX average worst NRS scores demonstrated a mean 19.5% decrease in pain intensity (range 3.6 - 54.0%) at end of week 2 and 24.7% decrease from baseline to the last NRS score obtained (Table 2). The average improvement across the 7 BPI pain interference items was 1.6 at the end of week 2 after the injection (Table 3). Two patients reported dramatic improvements in mobility (wheelchair or bed bound to walking) after the RTX injection. Patient #2 remained in the hospital for nearly 2 weeks after his RTX injection due to his pneumonia and other medical problems related to his cancer, and as a result, daily current pain intensity scores and detailed opioid consumption data was available rather than retrospective data from diary collections (Figure 2).

Safety Summary: No SAEs related to RTX were observed. Most AEs were mild to moderate and deemed unrelated to RTX. Four of 6 patients died as a result of their cancer progression or due to illness related to their cancer. No dose limiting toxicity was identified. Independent neurological (including quantitative sensory testing) and ophthalmological examinations revealed no changes from baseline. MRIs with gadolinium enhancement similarly showed no changes from baseline. It was anticipated that RTX might affect urinary retention transiently based upon prior preclinical studies, 2 cases were mild (one in each dose group) and resolved within days without sequelae or treatment and 2 cases were moderate (also one in each group) and similarly were transient. Two of these patients also had UTIs which may have precipitated or worsened the retention. Observed reduced thermal sensitivity above the mid thoracic level, while not anticipated, was consistent with the TRPV1 mechanism and apparent cephalad spread of RTX in the CSF column. Two patients experienced second degree burns on their fingers from holding hot beverages. All the cases of reduced thermal sensitivity were mild, not associated with other sensory changes, and were treated with education regarding safety precautions. Similarly, the second degree burns were mild and resolved without treatment or sequelae over a few days. Despite the persistence of the reduced thermal sensitivity (described as a delayed response in noting heat), no further burn episodes occurred.

Table 2. Changes in Worst Average NRS Pain Intensity (PI) Score from Baseline Post IT RTX Administration

Patient	Pre RTX	Injection Date	D8-14 average	Last NRS score	% Improvement	Details
1	7.3	5/9/11	6.7	6.1 (6 mo)	15.5	Bedridden to walking; nearly Y3 post RTX; cancer has progressed
2	8.3	5/10/12	3.8	3.8 (2 wk)	54.0	Died D35 of pneumonia 2º cancer
3	8.4	8/3/12	5.9	6.0 (1 mo)	28.8	Died just past D30 of cancer
4	8.0	10/23/12	7.7	5.4 (6 mo)	32.1	Wheelchair-bound to walking; Y1.5 post RTX; cancer has progressed
5	9.0	2/13/13	7.7	8.1 (1 mo)	9.6	Died W6 of cancer
6	8.6	9/23/13	8.0	7.9 (1 mo)	8.3	Break-through pain meds reduced by half by Month 1; ET from study due to cancer progression; died just after M3
	Baseline average NRS = 8.27			Average NRS PI reduction = 2.05 (24.7% improvement)		

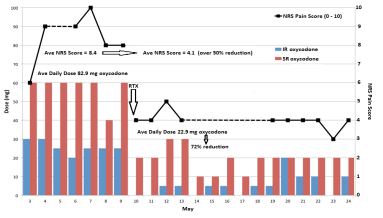
Table 3. Changes in Average Score Across the 7 Brief Pain Inventory Pain Interference Items from Baseline to Day 15 Post IT RTX Administration

	Baseline	D15	Difference	% Improvement
1	8.9	7.1	1.8	20.2%
2	6.6	2.3	4.3	65.2%
3	5.7	1.1	4.6	80.7%
4	5.6	3.6	2	35.7%
5	5.6	6.7	- 1.1	- 19.6%
6	5.3	7.6	- 2.3	- 43.4%
Ave	6.3	4.7	1.6	23.1%

The BPI Pain Interference Items: Circle the one number that describes how, during the past week (0=does not interfere; 10=completely interferes), pain has interfered with your:

General activity; Mood; Walking ability; Normal work (includes housework); Relations with others; Sleep; Enjoyment of life

Figure 2. Patient #2 Details Pre and Post RTX Injection



DISCUSSION

Resiniferatoxin selectively targets and ablates neurons with TRPV1 receptors, a vastly different mechanism than that of pharmacologic agents used to treat cancer pain. Its action has not interfered with the actions of opioids or other agents. The research study of intrathecal resiniferatoxin in patients with advanced cancer pain is actively recruiting new patients. Dose escalation will continue in subsequent cohorts of 3 subjects until the maximum tolerated dose (MTD) is determined.

CONCLUSIONS

- While the patient numbers are limited, intrathecal resiniferatoxin represents a promising approach to the treatment of intractable chronic pain in patients with cancer.
- Pain intensity changes showed only a moderate improvement, but considering the baseline average of 8.3/10, a 24.7% improvement (or a 2.05 point reduction) is clinically meaningful.
- The 1.6 average improvement across the 7 BPI pain interference items also represents a clinically meaningful improvement.
- To date, an IT RTX dose up to 26 mcg has not yielded any DLT or unexpected adverse reactions.
- IT RTX has been reasonably well tolerated under the conditions studied.
- Additional cohorts at a higher RTX dose are planned.
- Modifications to the formulation and method of administration are planned to reduce the cephalad spread of IT RTX in order to avoid inadvertent reduced thermal sensitivity involving the hands.

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