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Pain and Quality of Life Assessments in Cancer Patients Pre and Post Intrathecal Resiniferatoxin Injection

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ABSTRACT

Introduction: More than 70% of cancer patients develop cancer related pain during the course of their illness and, in many of those cases, pain remains unsuccessfully treated. Ferrell, et al suggested that pain and pain relief are related to perceived quality of life. By looking at both self-reported pain and quality of life measures in patients treated with resiniferatoxin (RTX), we hoped to gain a better overall impression of pain treatment response.

Materials and Methods: RTX is a small organic compound that acts as a potent agonist on the vanilloid receptor-1 (TRPV1) a pain-sensing ion channel expressed by dorsal root ganglion Aδ and C-fiber neurons. Prolonged ion channel opening causes neuronal deletion by elevating their intracellular calcium to cytotoxic levels. This is a preliminary report of an ongoing Phase 1b, dose escalation, study to assess the safety and efficacy of one intrathecal injection of RTX. Six patients ranged in age from 49-68 with advanced cancer and severe, medically-refractory pain at or below the T5 dermatome received one injection of either 13 or 26 mcg of RTX. In addition to intolerance or resistance to available narcotic agents and other pain remedies, patient eligibility was determined using a numerical rating score (NRS) to calculate a 7 day average worst pain score. Patients were placed under general anesthesia using propofol to prevent the acute pain that accompanies the excitotoxic destruction of TRPV1 neurons. Patients were administered several questionnaires including the Functional Assessment of Cancer Therapy-General (FACT-G) and were asked to report daily worst pain for seven days during the pre-treatment screening period. The same assessments were repeated approximately 2 weeks after study drug administration.

Results: Post RTX worst NRS scores demonstrated a mean 19.5% decrease in pain (range 3.6 - 54.0%). Changes in FACT-G responses demonstrated a comparable improvement.

Discussion: Patients who have improvements in pain may increase activity levels until maximum tolerable pain threshold is reached. Therefore, pain scores alone are not necessarily the most accurate or best representation of effective pain management. By utilizing a combination of assessment tools, a better understanding and measure of treatment efficacy should help the clinician better meet the pain needs of the cancer patient. We plan to extend this methodology in a larger patient group and continue to escalate the dose until the maximum effect is seen.

Figure 1. Euphorbia Resinifera

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INTRODUCTION

In a systematic meta-analysis (1966-2005) by van den Beuken et al., the authors 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 p-resents 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 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 preclinical data in cellular preparations, rodent models, companion canine clinical trials 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).

Pain experienced by patients with cancer is directly related to perceived quality of life and the patient's ability to perform activities of daily living (Ferrell 1994). By looking at both self-reported pain and quality of life measures in a population with advanced cancer, we hoped to gain a better overall impression of 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. 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 in adult patients with cancer reporting severe, medically-refractory pain. Eligible patients must have histological documentation of 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. Patients were placed under propofol general anesthesia for an hour to prevent awareness of any acute pain that might accompany the RTX injection. Afterwards, the patients are awakened and observed overnight. Outcome measures included NRS scores, BPI pain interference items, thermal sensitivity, opioid use and spontaneous adverse reactions are among the outcome measures. Additionally, patients were administered the validated Functional Assessment of Cancer Therapy-General (FACT-G), a 27 question assessment (grouped into 4 subscales: physical well-being, social/family well-being, emotional well-being, and functional well-being) graded on a five-point (0=not at all to 4=very much) scale (www.facit.org; Cella 1993). Assessments were repeated approximately 2 weeks after RTX administration.

RESULTS

Six patients ranged in age from 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).

Table 1. Baseline Characteristics

Age	Cancer Diagnosis	Targeted Pain Area
49 yowf	Metastatic (bone) Breast cancer	Low back and bilat leg pain
56 yowm	Metastatic (bone) supraglottic cancer	Low back and bilat hip pain
57 yobm	Metastatic (liver) pancreatic cancer	Bilateral abdominal pain
68 yowm	Lymphoma, small fiber monoclonal gammopathy	Bilat hip and buttocks pain (peripheral neuropathy)
55 yowm	Metastatic (bone) non small cell lung cancer	Left hip pain
61 yowf	Metastatic (liver, lung, skin) endometrial cancer	Low back and left hip/groin pain

Post RTX average worst NRS scores demonstrated a mean 19.5% decrease in pain intensity (range 3.6 - 54.0%) (Table 2) and 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.

Table 2. Changes in Worst Average NRS Pain Intensity Score from Baseline to Days 8-14 Post IT RTX Administration

Worst Average NRS Score				
Patient	**Pre**	**D8-14**	**Diff**	**% improvement**
1	7.29	6.71	0.58	8.0%
2	8.33	3.83	4.50	54.0%
3	8.43	5.86	2.57	30.5%
4	8.00	7.71	0.29	3.6%
5	9.00	7.71	1.29	14.3%
6	8.58	8.00	0.58	6.8%
				Ave: 19.5%

Table 3. Changes in Brief Pain Inventory Pain Interference Items from Baseline to Day 15 Post IT RTX Administration

Ave BPI Pain Interference Item Score				
Patient	**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%**

RESULTS (Cont.)

Changes in FACT-G responses demonstrated a comparable improvement. The average overall improvement in the FACT-G during the two weeks after the IT RTX injection was 6.5 points (individual overall values -1, -8, +7, +10, +14, +17; positive scores equal improvement).

Safety: Observed reduced thermal sensitivity was consistent with the TRPV1 mechanism. Two patients experienced second degree burns on their fingers from holding hot beverages, apparently as a result of cephalad CSF spread of the RTX. No dose limiting toxicity was identified and there were no other sensory or motor changes noted post-treatment.

DISCUSSION

Patients who have improvements in pain may increase activity levels until maximum tolerable pain threshold is reached. Therefore, pain intensity scores alone are not the most accurate or best representation of effective pain management. The results from the first two cohorts seems to exemplify this premise as the pain intensity NRS data shows only a moderate (20%) improvement, whereas the BPI pain interference items and FACT-G shows improvements that are clinically meaningful. By utilizing a combination of assessment tools, such as the FACT-G and BPI pain interference items, a better understanding and measure of treatment efficacy should help the clinician better meet the pain needs of the cancer patient. We plan to extend this methodology in a larger patient group and continue to escalate the dose until the maximum effect is seen.

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, however the 1.6 average improvement across the BPI pain interference items 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 in the near future.
- 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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