Original Article

Tetrodotoxin for Moderate to Severe Cancer Pain: A Randomized, Double Blind, Parallel Design Multicenter Study

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Abstract

Cancer pain is a serious public health issue and more effective treatments are needed. This study evaluates the analgesic activity of tetrodotoxin, a highly selective sodium channel blocker. This randomized, placebo-controlled, parallel design study of subcutaneous tetrodotoxin, in patients with moderate or severe unrelieved cancer pain persisting despite best available treatment, involved 22 centers across Canada. The design called for tetrodotoxin administered subcutaneously over Days 1–4 with a period of observation to Day 15 or longer. All patients could enroll into an open-label extension efficacy and safety trial. The primary endpoint was the proportion of analgesic responders in each treatment arm. Eighty-two patients were randomized, and results on 77 were available for analysis. There was a nonstatistically significant trend toward more responders in the active treatment arm based on the primary endpoint (pain intensity difference). However, analysis of secondary endpoints, and an exploratory post hoc analysis, suggested there may be a robust analgesic effect if a composite endpoint is used, including either fall in pain level, or fall in opioid dose, plus improvement in quality of life. Most patients described transient perioral tingling or other mild sensory phenomena within about an hour of each treatment. Nausea and other toxicities were generally mild, but one patient experienced a serious, adverse event, truncal and gait ataxia. This trial suggests tetrodotoxin may potentially relieve moderate to severe, treatment-resistant cancer pain in a large proportion of patients, and often for prolonged periods following treatment, but further study is warranted using a composite primary endpoint. J Pain

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Introduction

More than 10 million people in North America are diagnosed with cancer every year, and between 75% and 90% of patients with metastatic or advanced stage cancer will experience significant cancer-related pain.[1] In hospitalized patients, 79% experience pain, with 46% experiencing severe pain despite the fact that the majority of patients are adequately medicated with analgesics.[2] Moreover, treatment of cancer can cause pain. Chemotherapy-induced peripheral neuropathy occurs in about half of patients receiving some types of chemotherapy.[3] Over half of the patients undergoing surgery for breast cancer will develop chronic pain.[4] These data indicate that cancer-related pain is a prevalent and serious public health issue despite existing analgesic approaches.

Many valuable nondrug and drug interventions are available to help patients with cancer to experience relief of pain. However, these strategies are not always effective and can be associated with dose limiting toxicity. Contributing to the incidence of unrelieved pain is the high frequency of adverse effects produced by analgesics. For instance, 42% of patients with cancer receiving regular opioids develop clinically significant adverse effects, such as cognitive impairment and hallucinations, and most patients develop constipation or nausea and vomiting.[5,6]

Unrelieved pain often results in decreased quality of life, impaired function, and reduced productivity. Suffering from unrelieved pain may lead to suicide.[7,8] The personal, social, and economic impact of untreated pain is enormous.[9] Effective treatment of cancer-related pain remains both a high priority and an ongoing challenge in clinical practice.[10]

Tetrodotoxin (TTX) is a naturally occurring sodium channel blocker, which is found in several species of tetraodon pufferfish, notably of the Fugu genus. TTX is also found in a variety of other marine animals including the globefish, starfish, sunfish, stars, frogs, crabs, snails, and the Australian blue-ringed octopus. Animal studies have shown that TTX exhibits a strong analgesic effect.[11–13] Sodium channels are found on most nociceptive pain fibers; the mechanism by which TTX exerts its analgesic effect is thought to be related to its sodium channel blocking properties but the exact mechanism remains to be elucidated.[14]

A Phase 2, open-label, multicenter study of TTX in severe cancer-related pain was recently completed.[15] The study involved administration of TTX two or three times daily for four consecutive days followed by a period of observation. Seventeen of 31 treatments resulted in clinically meaningful reduction in pain intensity, and relief of pain persisted for up to two weeks or longer. Somatic, visceral, or neuropathic pain could all respond, and various dimensions of neuropathic pain as defined by the Neuropathic Pain Scale[16] also could respond. The dose of 30 μg intramuscularly twice daily was the highest well-tolerated dose within that study.

We further assessed the role of TTX in cancer-related pain in a large, multicenter, placebo-controlled clinical trial.

Methods

Trial Design

This multicenter, randomized, double-blind, placebo-controlled, parallel design trial evaluated the efficacy and safety of TTX in patients with stable but inadequately controlled moderate to severe pain associated with cancer.

The primary objective of the study was to compare the efficacy of subcutaneous (s.c.) TTX treatment vs. placebo in reducing the intensity of cancer-related pain. Secondary objectives were to (1) estimate the onset of analgesic response to s.c. TTX; (2) estimate the time to and period of peak analgesic response of s.c. TTX; (3) determine the duration of analgesic response associated with s.c. TTX treatment; (4) determine whether or not s.c. TTX reduces