Contemporary Clinical Trials 41 (2015) 146–151

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

Rationale and design of a randomized double-blind clinical trial in breast cancer: Dextromethorphan in chemotherapy-induced peripheral neuropathy

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ARTICLE INFO

Article history:
Received 19 November 2014
Received in revised form 18 January 2015
Accepted 20 January 2015
Available online 28 January 2015

Keywords:
Breast cancer
Dextromethorphan
Cognition
Quality of life
Genetic polymorphism

ABSTRACT

Background: Anti-cancer chemotherapy often induces peripheral neuropathy and consequent cognitive and quality of life impairment. Guidelines recommend antiepileptics or antidepressants but their efficacy is limited.Dextromethorphan, a *N*-methyl-D-aspartate receptor antagonist, has shown its efficacy in painful diabetic neuropathy and in post-operative pain but has not been studied in chemotherapy-induced peripheral neuropathy. This clinical trial evaluates the effect of dextromethorphan on pain, cognition and quality of life in patients who suffer from neuropathic pain induced by chemotherapy for breast cancer. It also assesses the impact of dextromethorphan genetic polymorphism on analgesia.

Methods and design: This trial is a randomized, placebo-controlled, double-blind clinical study in two parallel groups (NCT02271893). It includes 40 breast cancer patients suffering from chemotherapy-induced peripheral neuropathy. They are randomly allocated to dextromethorphan (maximal dose 90 mg/day) or placebo for 4 weeks. The primary endpoint is pain intensity measured after 4 weeks of treatment on a (0–10) Numeric Pain Rating Scale. Secondary outcomes include assessment of neuropathic pain, cognitive function, anxiety/depression, sleep and quality of life. Data analysis is performed using mixed models and the tests are two-sided, with a type I error set at $\alpha = 0.05$.

Discussion: Considering the poor efficacy of available drugs in chemotherapy-induced neuropathic pain, dextromethorphan may be a valuable therapeutic option. Pharmacogenetics may provide predictive factors of dextromethorphan response in patients suffering from breast cancer.

1. Introduction

Abbreviations: BC, Breast cancer; CIPN, Chemotherapy-induced peripheral neuropathy; CYP2D6, Cytochrome P450 2D6; CYP3A4, Cytochrome P450 3A4; DN4, Neuropathic pain in 4 questions; DSST, Digit Symbol Substitution Test; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items; FACT-COG, Functional Assessment of Cancer Therapy—Cognitive Function; HAD, Hospital Anxiety and Depression scale; MR, Metabolic ratio; NMDAR, *N*-Methyl-D-aspartate receptor; NMDAR, *N*-Methyl-D-Aspartate receptor; NP, Neuropathic pain; NS, Numeric Pain Rating Scale; PGIC, Patient global impression of change; PSQI, Pittsburgh Sleep Quality Index; TMT, Trail Making Test.

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http://dx.doi.org/10.1016/j.cct.2015.01.012
1551-7144/

Breast cancer (BC) is the most frequent cancer affecting women and the most common cause of cancer deaths [1]. Chemotherapy-induced peripheral neuropathy (CIPN) is a common neurological complication whose prevalence varies from 10% to 100% depending on the anticancer drug, the drug combination and the dosing regimen [2]. CIPN is characterized by a dysfunction of peripheral neurons affecting patients in a "stocking-glove" distribution reaching the longest axons and inducing sensory changes in feet and fingers [3]. Sensory symptoms reported by the patients include loss of proprioception, of touch and temperature discrimination, burning, shooting or electric-shock-like pain, allodynia and hyperalgesia [3,4]. Another common and distressing adverse event of chemotherapy is cognitive impairment called "chemobrain" with a prevalence ranging from 10% to 75% [5–7] and symptoms such as memory loss, inability to concentrate and impaired processing speed. A diminished quality of life of the patients is largely reported in the literature [8].

Despite international recommendations for neuropathic pain (NP) management, antiepileptics, local anesthetics, antidepressants and opioids are not fully effective in CIPN [9]. To the best of our knowledge, only one large phase III trial [10] has shown duloxetine efficacy, a serotonin-norepinephrine reuptake inhibitor, on CIPN. Other adjuvant drugs need to be further explored in order to offer BC patients new therapeutic options after neurotoxic chemotherapy. *N*-Methyl-D-aspartate receptors (NMDAR) are present at peripheral and central level and play an important role not only in central sensitization leading to NP [11] but also in cognitive function and memorization [12]. Non-competitive NMDAR antagonists like ketamine, memantine and dextromethorphan have been shown to inhibit the hyperexcitability of spinal cord nociceptive neurons and may decrease NP intensity [11,13].

Dextromethorphan an over-the-counter antitussive drug in many countries does alleviate NP induced by diabetes [14–17] and trauma [18–22]. Recently, a preclinical study showed that dextromethorphan, administered after spinal nerve ligation reversed NP symptoms and restored spatial memory [23]. Another NMDAR antagonist, memantine, diminished chemotherapy NP in BC patients [24]. The analgesic potential of dextromethorphan has however not been studied so far in BC patients suffering from CIPN. Recent studies on dextromethorphan metabolism have underlined that the polymorphism of the metabolizing enzymes, cytochrome P450 2D6 (CYP2D6) and to a lesser extent cytochrome P450 3A4 (CYP3A4) may modulate the analgesic efficacy of dextromethorphan [18,19]. Moreover, preclinical data [25–27] have shown that dextromethorphan is a P-glycoprotein substrate suggesting that the polymorphism of ABCB1 gene (encoding for P-glycoprotein, a protein able to influence transport in the gut and at brain-blood barrier) modulates the bioavailability of dextromethorphan.

This clinical trial aims to assess the analgesic efficacy of dextromethorphan on CIPN and its modulation by pharmacogenetic factors. It also assesses the effect of dextromethorphan on the cognitive-emotional status and the quality of life of BC women, in order to optimize the management of CIPN treatment.

2. Materials and methods

2.1. Study design

This is a prospective, randomized, placebo-controlled, double-blind, clinical trial with a parallel design including a dextromethorphan group and a placebo group. The French Research Ethics Committee gave a positive approval on May 2, 2014 (Ethics committee number AU 1119). The trial is registered in ClinicalTrials.gov (trial number NCT02271893).

Women meeting inclusion criteria sign a consent form after receiving oral and written information about the study. At baseline they complete tests assessing: 1) pain with a Numeric Pain Rating Scale (NS), Neuropathic pain in 4 questions (DN4) [28] and the McGill pain questionnaire [29,30]; 2) cognition with the Trail Making Test (TMT) [31,32], Digit Symbol Substitution Test (DSST) [33,34] and Functional Assessment of Cancer Therapy—Cognitive Function (FACT-COG) [35]; 3) fine fingertip dexterity with the Purdue Pegboard test [36]; 4) anxiety and depression with the Hospital Anxiety and Depression scale (HAD) [37]; 5) quality of life with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items (EORTC QLQ-C30) [38] and 6) sleep with the Pittsburgh Sleep Quality Index (PSQI) [39]. After inclusion, patients are then randomly assigned to dextromethorphan ($n = 20$) or placebo ($n = 20$) and complete a daily pain questionnaire (mean daily pain and maximum pain using NS, concomitant analgesic treatment). Urine collection to measure urinary metabolites is programmed to start on the morning before the second visit 4 weeks after randomization. Dextromethorphan or placebo (lactose) is given orally for 4 weeks. Dextromethorphan is given in increasing doses: week 1: 30 mg/day (1 tablet); week 2: 60 mg/day (2 tablets); and weeks 3 and 4: 90 mg/day (3 tablets). In order to respect double-blind, placebo is also given in increasing doses: week 1: 1 tablet; week 2: 2 tablets; weeks 3 and 4: 3 tablets. After 4 week treatment, patients come back for a second medical visit (V2). Tests are repeated and a supplementary questionnaire the Patient Global Impression of Change (PGIC) is added [40]. Blood and urine samples are obtained for dextromethorphan and dextrorphan (a dextromethorphan metabolite, also NMDAR antagonist with potential analgesic properties [19]) quantification. Genotyping of CYP2D6, CYP3A4 and ABCB1 is also performed. Patients will be called by phone once a week in order to maintain a good compliance, to verify that they do not develop adverse events and to detect signs or symptoms suggesting dextromethorphan abuse. Concerning the monitoring of adverse events, the patients will be asked an open-ended question about how they are feeling and then guided to specific adverse events such as dizziness, drowsiness, nausea, vomiting, or gastro-intestinal disturbance.

2.2. Objectives

The primary objective of this study is to assess if oral dextromethorphan administered during 4 weeks may induce a decrease of pain intensity in BC patients suffering from CIPN when compared to placebo.

The secondary objectives are to estimate at 4 weeks pain intensity, analgesic concomitant medication and the impact of treatment (dextromethorphan or placebo) on cognitive