Marie Curie Research Grants Scheme

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A phase II RCT of topical menthol gel versus placebo in cancer chemotherapy-related peripheral neuropathic pain.

Start date: 1st September 2018
End date: 31st August 2020

Costs to Marie Curie: £60,329.09
Costs to Chief Scientist Office: £60,329.09

Total funding awarded: £120,658.17

Research abstract

Background

Cancer-related pain is the commonest reason for out of hours emergency contact with cancer patients. Neuropathic pain is a common cause for poorly controlled cancer pain. It is becoming more complex and difficult to manage, because of chemotherapy-induced peripheral neuropathy (CIPN). CIPN has emerged over the last decade as a major clinical challenge. CIPN is painful and predominantly sensory, affecting up to 90% of patients and persisting in about 50% of all patients who have received neurotoxic chemotherapy (120,000 per year in UK). There are no effective preventive treatments nor predictable management strategies. The sequelae which evolve as patients reach the terminal phase are underpinned by an exacerbation of all other pains by this neuropathy

We have been working on this challenge for 10 years and identified in a laboratory model of neuropathic pain a novel yet simple way to manage this problem, using the topical transient receptor potential melastatin (TRPM8) channel agonist; menthol. We translated this to the clinic and have several publications reflecting our work, including a successful phase 1/Proof of Concept study with topical levomenthol cream (1%). We have refined the treatment since the PoC, with identification of optimum and safe menthol dose (at 5% rather than 1%), frequency (twice daily) and formulation (gel is easier to use than cream). We have also developed a robust placebo gel, which looks, smells and has the same texture as menthol gel and does not have any measurable activity at the TRPM8 receptor.

We are now ready to conduct an exploratory randomised, double blind placebo-controlled phase 2 study. Embedded fMRI analysis will enable correlation to effects on central nervous system regions activated during pain processing.

In neuropathic pain in particular, assessment of new analgesics in RCTs is compromised by both poor characterisation of pain and increased active placebo response. Such analgesic RCTs often describe small effect sizes, difficult to interpret clinically. This contributes to the current situation of often poorly controlled neuropathic pain in cancer patients.

The advent of fMRI as a research tool, with its ability to objectively detect pain-associated changes in specific brain regions, has greatly aided in elucidating neuropathic pain perception. In particular the subjective non-standardised nature of pain has become more readily understood using fMRI. Over the last decade fMRI has also been implemented in drug discovery and drug efficacy assessment.

We have completed successful studies using fMRI in peripheral neuropathic pain. To overcome barriers with neuropathic pain trials, we will embed fMRI in the proposed phase 2 double-blind placebo controlled RCT of topical menthol gel, in patients with chronic CIPN for independent corroboration. Using established understanding of central mechanisms of analgesia and of the placebo response, fMRI will facilitate the assessment of a potentially centrally-mediated analgesic effect of menthol and distinguish this from a placebo response.

We will recruit oncology patients with chronic stable CIPN, as this is a major problem, both in itself and in its impact on accentuating other cancer related pain(s). Consenting patients fulfilling inclusion/exclusion criteria, would (following baseline assessments) apply a gel themselves to the affected areas twice daily.

Primary outcome

4 weeks

Clinically significant reduction in pain (at least a 30% decrease in BPI SF as relates to index neuropathic pain)

Secondary outcomes

4 weeks

BPI SF

Combined sensory and motor scales for CIPN (CIPN-20)

Functional interference (BPI scale)

Anxiety and depression (HADS)

Side-effects

Psychophysical testing (QST)

(fMRI analysis related tests DSST,GCOS,NART)

fMRI baseline and 4 weeks

Patients will have a 12 week follow-up to assess ongoing analgesic response (BPI-SF).

Methods and analysis