Background
Chemotherapy-Induced Peripheral Neurotoxicity (CIPN) is a dose-limiting toxicity of many chemotherapeutic agents, often leading to numbness and tingling in the hands and feet, as well as pain. Treatment and quality of life are negatively affected by this condition.

Menthol is a compound derived from mint leaves that functions as an agonist of the transient receptor potential (TRP) family of ion channels. TRPM8 is distributed in peripheral nerves and has been shown to be associated with cold hypersensitivity, tissue cold and sensory disturbance. It is also related to the occurrence of CIPN. Menthol is endowed with analgesic properties mediated through a selective activation of kappa-opioid receptors.1,2

We previously reported that applying menthol reduced existing CIPN in 75% of patients in a phase II study. As the next step, we conducted a phase II study to address the preventive effect of CIPN.

Methods

Study design
Single-arm open-label phase II study. The primary endpoint was the frequency of Grade 2 CIPN at the cumulative Oxaliplatin dose of 500 mg/m².

Secondary endpoints: Safety of topical menthol, Compliance with chemotherapy with CIPN, 1.35% rate per month for application.

This study has been approved by the Institutional Review Board of Aizu Central Hospital based on ethical norms presented in the Helsinki Declaration of the World Medical Association as well as under the provisions of the Personal Information Protection Act in Japan.

Treatment method
Participants applied 1.35% topical menthol twice daily to their hands and feet from the start of Oxaliplatin treatment.

Assessment of CIPN
CIPN symptoms were assessed using the FACT-GOG-NTX and Visual Analog Scale (VAS).

Assessment of adverse events
Adverse events were graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Study drug (Mentholatum®) Over-the-counter drug

Ingredients
Active ingredients: Camphor 8%, Menthol natural 1.5%, Eucalyptus oil 1.5%

Menthol protects the surface of the skin and ease external irritation, also stimulates blood circulation, and relieves itching and cracking of skin.

Camphor, Menthol and Eucalyptus oil, especially ease cutaneous discomfort, and ease the unpleasantness by local stimulus.

Manufactured and sale of Rohto Pharmaceutical Co., Ltd.

The Mentholatum Company, Inc., founded in 1948 by Akitaro Hiyoshi, is an American maker of non-prescription health care products. It was bought out by Rohto Pharmaceutical Co., Ltd. in 1997. The Mentholatum Company is widely associated with its top three products, the Mentholatum Ointment, Mentholatum Deep Heating Rub, and Mentholatum Lip Cream.

Statistical analysis

A total of 32 patients were enrolled in the study, 24 of whom completed the study. Doses were generally well tolerated, and there were no unexpected safety events. The mean of the VAS scale was 2.5 (0-6).

In our targeted study, on the other hand, the results turned out to be quite different from what we expected, as it applies to the past 7 days. This was significantly lower than the expectation value at the cumulative Oxaliplatin dose of 500 mg/m².

Moreover, a beneficial effect on hand-foot syndrome is also suggested.

Conclusions
This phase II study showed preventive Mentholatum application significantly reduced Oxaliplatin-induced CIPN compared with other studies. A 1.35% concentration of menthol is sufficient to use for analgesic effect. Therefore, we can use topical menthol for the preventive effect of CIPN for everyday use.

References


