Defining a Neuroinflammatory Signature of Chemotherapy-Induced Peripheral Neuropathy

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Background

- **Chemotherapy-induced peripheral neuropathy (CIPN)** affects more than half of breast cancer patients treated with **taxane or epothilone therapy**.
- Symptoms often persist and can lead to **dose reductions, treatment delays, or early discontinuation**, compromising therapeutic outcomes and quality of life.
- **No FDA-approved preventive strategies** exist, and effective treatments remain limited to symptom management.
- The **biological mechanisms** driving CIPN are not fully understood, but growing evidence supports a key role for **neuroinflammation**.
- **Cryotherapy**, one of the few interventions shown to mitigate symptoms, may act by altering this inflammatory microenvironment, although its mechanism has not been defined.
- This study sought to **define the neuroinflammatory signature** associated with severe CIPN by **profiling serum cytokines** from participants in a completed prospective trial, with the goal of identifying potential biomarkers and mechanistic targets for prevention.

Objective

To define the **neuroinflammatory cytokine signature** associated with severe chemotherapy-induced peripheral neuropathy (CIPN) by profiling serum biomarkers from participants in a completed prospective ixabepilone trial.

Methods and Materials

Cohort:

- 14 patients with metastatic breast cancer from a completed **phase II ixabepilone trial**.
- Neuropathy assessed every 3 weeks using **Total Neuropathy Score–Clinical (TNSc)**.
- Severe CIPN defined as:
  - TNSc ≥10
  - TNSc increase ≥4
  - Dose modification due to CIPN.

Samples:

- 5 patients with severe CIPN; 3 without.
- 18 vs 10 longitudinal serum samples.

Assay:

Luminex 48-plex + custom discovery panel (80 analytes).

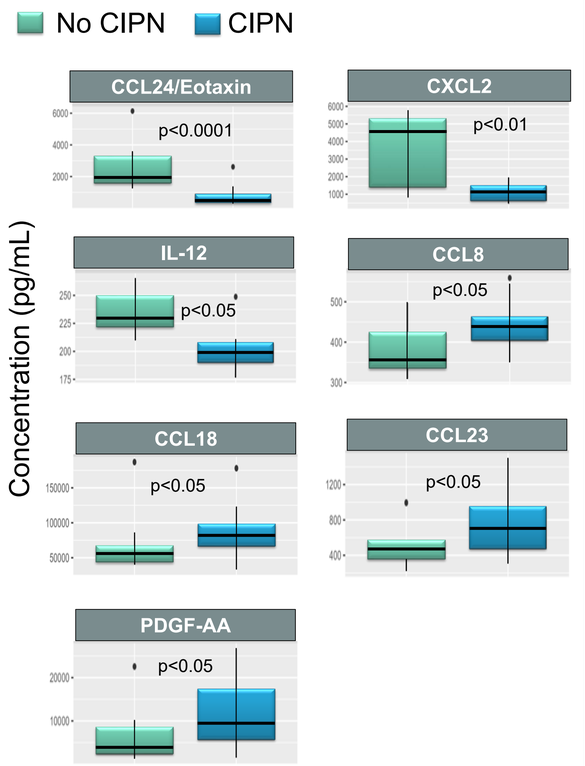
Duplicates analyzed; **MFI → pg/mL** via standard curve.

Analysis:

Average biomarker concentration was compared between groups with severe CIPN and those without.

Results

Table 1. Seven biomarkers were significantly different between groups:



Discussion

Our findings suggest that **chemotherapy-induced peripheral neuropathy (CIPN)** arises not only from direct axonal toxicity but also from a **neuroinflammatory and immune-fibrotic cascade**. Elevated **CCL18** and **PDGF-AA** in patients with severe neuropathy indicate activation of **pro-fibrotic macrophages**, previously implicated in chronic neuropathic pain and fibrotic nerve remodeling. These immune responses may perpetuate injury to peripheral sensory neurons long after chemotherapy exposure.

Conversely, decreased **CCL24**, **CXCL2**, and **IL-12** suggest suppression of Th1 and neutrophil-recruiting pathways. The opposite regulation of **CCL18** and **CCL24**, both ligands for **CCR3**, points to a potential feedback mechanism in which sustained CCR3 activation downregulates CCL24 expression—an unsuccessful attempt to control chronic inflammation in susceptible individuals.

Conclusions

Conclusions:

- A distinct **neuroinflammatory cytokine signature** differentiates severe CIPN.
- Elevated **CCL18** and **PDGF-AA** suggest **macrophage-driven fibrosis**.
- **CCL24 downregulation** may indicate feedback suppression of CCR3 signaling—a novel finding.
- Ongoing work will validate this signature in a prospective mechanistic trial.

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