CHEMOTHERAPY INDUCED
PERIPHERAL NEUROPATHY
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Chemotherapy-induced peripheral neuropathy (CIPN) is a disabling side effect of several commonly used antineoplastic agents. The development of CIPN may require chemotherapy dose reduction or cessation, which can increase cancer-related morbidity and mortality. CIPN is a predominantly sensory neuropathy that may be accompanied by motor and autonomic changes.
CLINICAL MANIFESTATIONS OF CIPN

Peripheral Neuropathy

- Tingling
- Stabbing
- Numbness
- I feel like I am wearing gloves
- Muscle pain
- Weakness

Peripheral Neuropathy Symptoms

- Ulcers or slow healing wound
- Shooting or burning pain
- Sensitivity to touch
- Lack of sensation
- Increased falls
- Tingly or numb feet
- Difficulty walking

6 Areas Affected When Autonomic Nerves Are Damaged

**EYES**
- Difficulty adjusting from light to dark

**BLADDER**
- Loss of bladder control
- Urinary retention
- Urinary tract infections

**DIGESTIVE SYSTEM**
- Indigestion or heartburn
- Nausea or vomiting
- Diarrhea or constipation
- Bloating
- Loss of appetite

**HEART & BLOOD VESSELS**
- Dizziness or fainting
- Difficulty breathing
- Abnormal blood pressure
- High heart rate
- Heart attack (without warning signs)

**SEX ORGANS**
- Erectile dysfunction
- Difficulty achieving orgasm during sex (women)
- Vaginal dryness

**SWEAT GLANDS**
- Lack of sweat
- Excessive sweat
- Dry skin on feet

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In a meta-analysis of 4179 patients, 1960 developed CIPN (aggregate prevalence 48%).

CIPN prevalence was 68.1% (95% CI = 57.7–78.4) within the first month of the end of chemotherapy.

- 60.0% (36.4–81.6) at 3 months
- 30.0% (6.4–53.5) at 6 months or later
• Underlying neuropathy (e.g., Diabetic neuropathy)
• B12 or folate deficiency
• Tumor related nerve compression
• Surgical trauma
• High doses of chemotherapy
## Nervous system disorders

<table>
<thead>
<tr>
<th>CTCAE Term</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>Asymptomatic</td>
<td>Moderate symptoms; limiting instrumental ADL</td>
<td>Severe symptoms; limiting self care ADL</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>-</td>
</tr>
<tr>
<td>Phantom pain</td>
<td>Mild pain</td>
<td>Moderate pain; limiting instrumental ADL</td>
<td>Severe pain; limiting self care ADL</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Presyncope</td>
<td>-</td>
<td>Present (e.g., near fainting)</td>
<td>-</td>
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</tr>
<tr>
<td>Pyramidal tract syndrome</td>
<td>Asymptomatic; clinical or diagnostic observations only; intervention not indicated</td>
<td>Moderate symptoms; limiting instrumental ADL</td>
<td>Severe symptoms; limiting self care ADL</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Death</td>
</tr>
<tr>
<td>Radiculitis</td>
<td>Mild symptoms</td>
<td>Moderate symptoms; medical intervention indicated; limiting instrumental ADL</td>
<td>Severe symptoms; limiting self care ADL</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Death</td>
</tr>
<tr>
<td>Recurrent laryngeal nerve palsy</td>
<td>Asymptomatic; clinical or diagnostic observations only; intervention not indicated</td>
<td>Moderate symptoms</td>
<td>Severe symptoms; medical intervention indicated (e.g., thyroplasty, vocal cord injection)</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Death</td>
</tr>
<tr>
<td>Reversible posterior leukoencephalopathy syndrome</td>
<td>-</td>
<td>Moderate symptoms; limiting instrumental ADL</td>
<td>Severe symptoms; limiting self care ADL; hospitalization</td>
<td>Life-threatening consequences</td>
<td>Death</td>
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</table>

**Definition:** A disorder characterized by damage or dysfunction of the peripheral sensory nerves.

**Navigational Note:** -

**Definition:** A disorder characterized by a sensation of marked discomfort related to a limb or an organ that is removed from or is not physically part of the body.

**Navigational Note:** -

**Definition:** A disorder characterized by an episode of lightheadedness and dizziness which may precede an episode of syncope.

**Navigational Note:** -

**Definition:** A disorder characterized by dysfunction of the corticospinal (pyramidal) tracts of the spinal cord. Symptoms include an increase in the muscle tone in the lower extremities, hyperreflexia, positive Babinski and a decrease in fine motor coordination.

**Navigational Note:** -

**Definition:** A disorder characterized by inflammation involving a nerve root. Patients experience marked discomfort radiating along a nerve path because of spinal pressure on the connecting nerve root.

**Navigational Note:** -

**Definition:** A disorder characterized by paralysis of the recurrent laryngeal nerve.

**Navigational Note:** -

**Definition:** A disorder characterized by headaches, mental status changes, visual disturbances, and/or seizures associated with imaging findings of posterior leukoencephalopathy. It has been observed in association with hypertensive encephalopathy, eclampsia, and immunosuppressive and cytotoxic drug treatment. It is an acute or subacute reversible condition. Also known as posterior reversible encephalopathy syndrome (PRES).

**Navigational Note:** -
Problems with measuring neuropathy:

- Patient difficulty with describing the uncomfortable sensations, unless they are painful
- CIPN not always been considered a pertinent side effect—usually considered a minor problem that would eventually resolve
  - Easy, simple, and usefully comprehensive tool has yet to be developed
  - Limited because toxicity is determined subjectively by healthcare provider
ASSESSMENT OF PN

- **Subjective assessment:** Symptoms related to PN
  - Evaluate sensory, motor and autonomic symptoms

- **Objective assessment:**
  - Touch, Pinprick, vibration, & proprioception
  - Reflexes, muscle strength, Gait and balance.
  - Autonomic: assess bowel sounds, orthostatic blood pressures, pulse regularity
  - Difficulty with fine motor skills: opening jars, buttoning
MORE ABOUT CIPN

- CIPN is typically dose-dependent and cumulative.
- CIPN typically has a symmetric, distal, "stocking and glove" distribution.
- In many cases, gradual improvement over time after chemotherapy is stopped, although it may continue to worsen over a few months with some drugs (most notably cisplatin and oxaliplatin) before it starts to improve.
- Cisplatin-related CIPN continues to worsen for several months in 30 percent of patients; neuropathy may even begin after therapy is discontinued. It eventually improves in most patients, although recovery is often incomplete.
- Oxaliplatin neurotoxicity may also continue to worsen for a few months after treatment is discontinued. Neuropathy is at least partially reversible in approximately 80 percent of patients; one-half of these patients report complete resolution within eight months after treatment discontinuation. Some studies report persistence of neuropathy in a substantial number of patients five to six years after treatment cessation.
- With paclitaxel, after completing treatment, approximately one-half of patients improve over a period of four to six months. However, severe neuropathy can persist. In one study, up to 80 percent of patients still had neuropathic symptoms up to two years after completing treatment; approximately 25 percent reported severe symptoms of numbness and/or discomfort in their hands and feet.
- Vincristine neuropathy is usually reversible but improvement is gradual and may take up to several months.
- Symptoms of bortezomib neuropathy usually improve or completely resolve after three to four months following discontinuation of treatment; in one study, 64 percent with grade 2 or worse neuropathy experienced improvement or resolution of symptoms compared with baseline at a median of 110 days.
WHAT IS THE PATHOPHYSIOLOGY OF CIPN?

- Disrupted microtubule-mediated axonal transport
- Axonal degeneration
- Direct damage to the dorsal root ganglion
- Mitochondrial dysfunction

1. Chemotherapy-induced peripheral neuropathy: an update on the current understanding
## CHARACTERISTICS OF CIPN BASED ON SPECIFIC AGENTS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clinical manifestations</th>
<th>Recovery</th>
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</thead>
<tbody>
<tr>
<td><strong>Platirinum</strong></td>
<td>Distal, symmetric loss of sensation to all modalities; standing glove distribution; painful paresthesia or numbness</td>
<td>In proportion to sensory loss</td>
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<tr>
<td><strong>Cytoxan</strong></td>
<td>Similar but less severe than with cisplatin</td>
<td>Normal</td>
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<tr>
<td><strong>Gelclairin</strong></td>
<td>Cold-induced diaphoresis in mouth, throat, and upper limbs</td>
<td>Cramps and/or muscle spasms in throat muscles</td>
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<tr>
<td><strong>Vincristine</strong></td>
<td>Similar to cisplatin; symptoms worse in upper extremities during initial therapy, but upper extremity neuropathy improves faster than lower extremity neuropathy after treatment completion. One year after treatment completion, there is more neuropathy in lower extremities.</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Docetaxel</strong></td>
<td>Distal sensory loss, worse in lower extremities, rarely affects upper extremities; vincristine and vinorelbine are less hemorrhagic; vinorelbine more commonly causes nausea</td>
<td>Less common; distal symmetric weakness in lower limbs progressing to foot drop</td>
</tr>
<tr>
<td><strong>Paclitaxel</strong></td>
<td>Mild distal loss of sensation to all modalities; feet greater than hands, painful paresthesias</td>
<td>Occasional mild weakness in foot muscles; numbness; paresthesias</td>
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<tr>
<td><strong>Folotrexol</strong></td>
<td>Distal symmetric loss of sensation to all modalities in distal extremities; painful paresthesias</td>
<td>Occasional mild distal weakness in lower limbs; rare severe distal weakness; muscle cramps and fasciculations rare</td>
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<tr>
<td><strong>Gemcitabine</strong></td>
<td>Painful paresthesias; distal loss of sensation</td>
<td>10 to 15 percent have weakness</td>
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<tr>
<td><strong>Taxol</strong></td>
<td>Symmetric mild to moderate distal loss to all sensory modalities</td>
<td>Weakness and atrophy in 20 to 40 percent; muscle cramps and fasciculations common</td>
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<tr>
<td><strong>Epirubicin</strong></td>
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<td><strong>Doxorubicin</strong></td>
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<tr>
<td><strong>Mitoxantrone</strong></td>
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<tr>
<td><strong>Paclitaxel</strong></td>
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<td><strong>Docetaxel</strong></td>
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<tr>
<td><strong>Vinorelbine</strong></td>
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<tr>
<td><strong>Vincristine</strong></td>
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<tr>
<td><strong>Cisplatin</strong></td>
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<td><strong>Cytoxan</strong></td>
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<tr>
<td><strong>Platirinum</strong></td>
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</table>
DRUG MECHANISM OF ACTION

A. Microtubules:
- Vincristine: inhibition of microtubule aggregation
- Paclitaxel: inhibition of microtubule disaggregation

B. Nucleus:
- Oxaliplatin, cisplatin: inhibition of DNA replication/mRNA transcription
- DNA/RNA polymerase
- Cell arrest and cell death

C. Mitochondria:
- Oxaliplatin, cisplatin: activation of apoptosis
- Altered mitochondrial function
- ROS

D. Activation of immune system:
- Macrophages, T-cells, Monocytes
- Release of pro-inflammatory cytokines and activation of apoptotic pathways
- Cell death

Cancer cell
PLATINUM-INDUCED NEUROPATHY

Oxaliplatin

- Immune system
  - Activation of immune cells
  - Altered function of immune cell ion channels
  - Release of pro-inflammatory cytokines
  - Release of interleukins, activation of innate immune system and inflammation

- Microglia
  - Release of TNFα
  - Attraction and activation of immune cells

Cisplatin

- Peripheral neurons
  - Axon morphology
  - Axon degeneration
  - Loss of peripheral sensory fibers
  - Intra-epidermal fiber loss
  - Sensory-motor axon degeneration
  - Altered Na⁺ conductance, threshold potential and membrane resistance
  - Alteration of neuronal cell membrane remodelling

- Chelation of extracellular calcium?
  - Altered calcium homeostasis
  - Binding to mitochondrial DNA
  - Altered mitochondrial function
  - Release of ROS
  - Activation of apoptotic pathways

Altered excitability of peripheral neurons
VINCRISTINE-INDUCED NEUROPATHY

- Immune system: Activation of immune cells, Release of pro-inflammatory cytokines
  - Endothelial tissue: Migration and activation of CX3CR1 macrophages, release of TNFα and IL-6
  - Dorsal root ganglia: Expression of CXCL12, Attraction and activation of CXCR4+ lymphocytes and monocytes
  - Activation of innate and adaptive immune system

- Peripheral tissue: Integrin expression

- Peripheral neurons:
  - Microtubules: Altered retrograde and anterograde transport
  - Myelin: Changes to cell shape and cell stability
  - Loss of peripheral sensory fibers
  - Altered calcium homeostasis
  - Altered mitochondrial function

- Neuronal cell membrane remodeling: Wallerian degeneration, Membrane remodeling
  - Release of ROS
  - Neuronal cell membrane remodeling
  - Altered excitability of peripheral neurons
  - Altered function of Ion channels: Na⁺, K⁺, TRP, Ca²⁺
  - Neuronal cell function
  - Activation of apoptotic pathways
TAXANE-INDUCED NEUROPATHY

Immune system
- Increased migration of macrophages
  - Activation TLR4 pathway
- Release of pro-inflammatory cytokines
  - Release of interleukins, activation of innate immune system and inflammation
- Attraction and activation of immune cells

Paclitaxel

Microglia
- Release of TNFα

Peripheral neurons
- Axon morphology
  - Loss of neuronal fibers
  - Demyelination
  - Axon degeneration
  - Retrograde and anterograde transport
  - Changes to cell shape and cell stability
- Microtubules
- Mitochondria
  - Altered mitochondrial function
- Alteration of ion channels: Na⁺, K⁺, TRP, Ca₂⁺
  - Neuronal cell membrane remodeling
  - Release of ROS
  - Altered calcium homeostasis
  - Altered function of respiratory chain
  - Activation of apoptotic pathways

Altered excitability of peripheral neurons
CHEMOPROTECTANTS: No good evidence of efficacy

- **Amifostine.** This agent is an organic thiophosphate that has been studied in several randomized trials as an agent that might prevent neurotoxicity resulting from both taxanes and platinum agents. Results of these trials have been mixed, 2014 ASCO systematic review concluded that the inconsistency of the data, as well as the increased risk of side effects, made amifostine an inappropriate choice for CIPN prevention.

- **Nimodipine.** While this calcium channel blocker showed promise in animal models as a protective agent for platinum-related neuropathy, it failed to show benefit in a randomized double-blind placebo-controlled trial involving 51 patients treated with cisplatin for ovarian cancer. Patients who received nimodipine had significantly inferior outcomes with respect to neurotoxicity, leading to premature discontinuation of the trial.

- **Neurotropin.** This extract of small peptides from the skin of rabbits injected with the vaccinia virus was tested in a phase II pilot trial involving 80 colon cancer patients treated with oxaliplatin-based chemotherapy; the results have suggested protection against grade 2 or greater neurotoxicity. However, there have been no large phase III trials to provide confirmation of these results.

- **Diethyldithiocarbamate (DDTC).** This agent showed promise in animal models but failed to perform as well in a randomized placebo-controlled trial of 221 patients treated with cisplatin for ovarian cancer. Patients who received DDTC were more likely to be withdrawn from treatment early due to toxicity, raising safety concerns for this agent.

- **ACTH analog ORG 2766.** There have been six trials evaluating the use of ACTH analog ORG 2766 for CIPN prevention in patients receiving either cisplatin or vincristine. A Cochrane meta-analysis considering four of these trials concluded that this agent was not beneficial for the prevention of CIPN. Similarly, the systematic review from ASCO, which considered all six trials, found mixed results that did not support the use of this agent for CIPN prevention.
• Vitamins, minerals, and other ‘natural’ approaches with no evidence of efficacy

**Goshajinkigan.** This is a traditional Japanese medicine that is produced from a specific formulation of 10 distinct herbs used to treat diabetic neuropathy. Phase III randomized double-blind placebo-controlled trial evaluating this agent in patients receiving FOLFOX was stopped after accrual of 142 of the planned 310 patients when grade 2 or greater neurotoxicity was found to be significantly higher in the treatment arm.

**Calcium and magnesium.** A definitive phase III randomized placebo-controlled double-blind study of intravenous calcium and magnesium as a preventive strategy in colon cancer patients receiving adjuvant oxaliplatin-based therapy showed no reduction in neuropathy with calcium and magnesium supplementation.

**Acetyl-L-carnitine.** A randomized placebo-controlled trial of prevention of taxane-induced neuropathy in women undergoing adjuvant chemotherapy for breast cancer found it to be associated with an increased rate of CIPN.

**Alpha-lipoic acid.** This antioxidant was evaluated in a randomized double-blind placebo-controlled trial as a preventive agent in patients receiving platinum-based chemotherapy; there were no significant differences in pain scores between the two groups.

**Vitamin E.** The largest randomized placebo-controlled double-blind trial evaluating use of vitamin E, which involved 207 patients treated with taxanes or platinum agents, failed to show significant differences in incidence of neuropathy, time to neuropathy onset, or need for chemotherapy dose reduction.

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New Practical Approaches to Chemotherapy-Induced Neuropathic Pain: Prevention, Assessment, and Treatment Neil Majithia, MDCharles L. Loprinzi, MDThomas J. Smith, MD Nov 15, 2016 Volume: 30Issue: 11 Oncology Journal, Cancer Complications
Vitamins, minerals, and other ‘natural’ approaches that appear promising but for which more evidence is required

**Omega-3 fatty acids.** One small trial in Iran randomized 60 patients starting paclitaxel to placebo or omega-3 fatty acid pearls, 640 mg TID (10% eicosapentaenoic acid and 54% docosahexaenoic acid), during and for 1 month after chemotherapy. The incidence of CIPN was 30% with omega-3 fatty acids vs 59% with placebo, as measured by the reduced Total Neuropathy Score, and with confirmatory preserved sural nerve conduction, ascertained by peak-to-peak amplitude measurement of sensory action potentials.

**Topical Menthol Application:** One small study of 24 patients showed a 50% reduction in the expected neuropathy with twice daily application of 1% topical menthol to hands and feet twice daily.

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New Practical Approaches to Chemotherapy-Induced Neuropathic Pain: Prevention, Assessment, and Treatment; Neil Majithia, MD; Charles L. Loprinzi, MD; Thomas J. Smith, MD Nov 15, 2016 Volume: 30 Issue: 11 Oncology Journal, Cancer Complications

Phase II Study of preventive effect for topical menthol for chemotherapy induced peripheral neuropathy. Nakamura et al. J Clin Oncol 33, 2015 (suppl; abstr 9610)
EXERCISE

• Emerging data support the notion that exercise protects against CIPN and may help repair damaged nerves after CIPN develops.
• These data include information regarding patients who were exercising more prior to receiving neurotoxic chemotherapy, patients randomized to more exercise while receiving neurotoxic chemotherapy, and patients who exercised more following neurotoxic chemotherapy.
• The largest randomized trial of exercise for CIPN prevention enrolled 314 patients who were scheduled to receive chemotherapy and randomized them to usual care or usual care plus Exercise for Cancer Patients, a standardized, individualized, moderate-intensity, home-based, 6-week progressive walking and resistance exercise program.
• The exercise group reported a 0.26-point reduction (on a 0-to-10 scale) in CIPN, which was significant \( (P = .0432) \) compared with the effect of duloxetine \( (0.53 \text{ effect size, with an observed mean difference—compared with placebo—of 0.72 on a 0-to-10 scale}) \).
• Exercise had other major benefits and no harms.
FROZEN SOCKS AND GLOVES
CRYOTHERAPY TO PREVENT PERIPHERAL NEUROPATHY IN PATIENTS RECEIVING PACLITAXEL

ITEMS TO BRING TO TREATMENT:

- 2 pairs of socks
- One pair of cotton gloves (optional)
- Ziplock bags (sandwich or snack size)
- Towel or napkins
- Basins to put feet and hands in.

INSTRUCTIONS FOR PATIENTS:

15 minutes prior to starting the Taxol infusion please place ice filled ziplock bags below your sock covered foot and then place another sock to cover the bags and to keep it in place. If gallon bags are used then ice bag could be on the bottom of the foot or hand and folded over the top of the foot or hand. You can remove the bags if it causes discomfort at any time and then place it back again.

You can fold the ziplock bags with ice over the fingers of both hands during the duration of the infusion and remove it intermittently depending on your comfort level. It is best to bring a caregiver to help you.

DURATION:

15 minutes before the Taxol infusion, during the infusion and 15 minutes after the infusion.
CRYOTHERAPY

- Breast cancer patients treated weekly with paclitaxel (80 mg/m² for one hour) wore frozen gloves and socks on the dominant side for 90 minutes, including the entire duration of drug infusion.
- Symptoms on the treated sides were compared with those on the untreated (nondominant) sides.
- The primary end point was CIPN incidence assessed by changes in tactile sensitivity from pretreatment baseline in a monofilament test at a cumulative dose of 960 mg/m².
- We also assessed thermosensory deficits, subjective symptoms (Patient Neuropathy Questionnaire [PNQ]), manipulative dexterity, and the time to events and hazard ratio by PNQ.
- Results: Among the 40 patients, four did not reach the cumulative dose (due to the occurrence of pneumonia, severe fatigue, severe liver dysfunction, and macular edema), leaving 36 patients for analysis.
- None dropped out due to cold intolerance.
- The incidence of objective and subjective CIPN signs was clinically and statistically significantly lower on the intervention side than on the control (hand: tactile sensitivity ¼ 27.8% vs 80.6%, odds ratio [OR] ¼ 20.00, 95% confidence interval [CI] ¼ 3.20 to 828.96, P < .001; foot: tacile sensitivity ¼ 25.0% vs 63.9%, OR ¼ infinite, 95% CI ¼ 3.32 to infinite, P < .001; hand: warm sense ¼ 8.8% vs 32.4%, OR ¼ 9.00, 95% CI ¼ 1.25 to 394.48, P ¼ .02; foot: warm sense: 33.4% vs 57.6%, OR ¼ 5.00, 95% CI ¼ 1.07 to 46.93, P ¼ .04.
- Conclusions: Cryotherapy is useful for preventing both the objective and subjective symptoms of CIPN and resultant dysfunction.
CRYOTHERAPY

• Forty-six patients were accrued, three of whom withdrew and one of whom was ineligible. Of the remaining 42 (21 cryotherapy, 21 control), 39 (19 cryotherapy, 20 control) were analyzable for AUC based on availability of both baseline and follow-up measures.

• The cryotherapy was reasonably well tolerated, with 16 cryotherapy and 17 control arm patients completing study therapy.

• EORTC QLQ-CIPN20 data did not reveal significant differences between the 2 study arms in any neuropathy outcome.

• However, patients in the control arm of the current trial experienced substantially less neuropathy than did those in the placebo arms of two similar trials that assessed minocycline and pregabalin in this setting.

• When the cryotherapy arm of the current trial was compared to the combined control arms from all three trials, it appeared that there was less neuropathy in this cryotherapy arm than the combined control arms (Wilcoxon Rank Sum p = 0.004).
Dose reduction, delay, and intermittent treatment — In general, patients with mild neuropathy can continue to receive full doses; however, if symptoms increase in severity or the neuropathy interferes with function, the risk of potentially disabling neurotoxicity must be weighed against the benefit of continued treatment. Sometimes, a patient can be switched to an alternative less neurotoxic agent, if one is available.

For patients who develop more severe chemotherapy-induced peripheral neuropathy (CIPN) during active treatment, subsequent treatment delay or dose reduction can improve symptoms in some cases, notably with taxanes and bortezomib.

For patients with advanced colorectal cancer who develop oxaliplatin-related neuropathy, it is reasonable to discontinue oxaliplatin temporarily while maintaining a fluoropyrimidine with or without bevacizumab. Another option is to switch to an alternative non-oxaliplatin-containing regimen.
Duloxetine and other antidepressants — Benefit for duloxetine in patients with painful CIPN was demonstrated in a multi-institutional, double-blind cross-over trial in which 231 patients with taxane or platinum-related painful CIPN (59 percent attributed to oxaliplatin) and at least grade 1 sensory neuropathy and an average pain score >4/10 that persisted for three or more months, with stable use of analgesics, were randomly assigned to duloxetine (30 mg daily for one week, then 60 mg daily for four additional weeks) or placebo. After the initial five weeks, there was a taper and washout period for two weeks, and all patients crossed over to the alternative treatment. Individuals receiving duloxetine during their initial five-week period had a significantly larger average decrease in mean pain score than did those who initially received placebo (mean decrease 1.06 versus 0.34, p = 0.003). Furthermore, patients randomized to duloxetine also had a greater degree of improvement in functional and QOL scores, and more patients reported improved numbness and tingling in the feet (41 versus 23 percent) but not the hands (36 versus 34 percent). Using this schedule, the drug was well tolerated with no significant differences in toxicities noted between active and placebo arms. Exploratory subgroup analysis suggested that duloxetine might be more efficacious for oxaliplatin-induced rather than taxane-induced painful neuropathy.

The benefit of duloxetine for treating chemotherapy neuropathy was further supported by a small, randomized Japanese trial, employing 34 patients, comparing duloxetine to vitamin B12 [106].

Despite the recommendation for use of duloxetine, the magnitude of benefit is modest and much less than is desirable.
There are three options that may be offered for patients despite not yet having been proven to be helpful for CIPN. These options are

1. Tricyclic antidepressant (such as nortriptyline).
2. Gabapentin or another medication with the same mechanism of action, pregabalin;
3. A compounded topical gel containing baclofen (10 mg), amitriptyline HCL (40 mg), and ketamine (20 mg).

Limitations:

1. Tricyclic agents can cause toxicity, especially in elderly patients.
2. There is a single negative randomized trial evaluating gabapentin for the treatment of CIPN (which may have been underpowered and did not have painful CIPN as the primary end point).
3. Although a trial of topical baclofen (10 mg), amitriptyline HCL (40 mg), and ketamine (20 mg) decreased CIPN symptoms, this compounded agent is not commercially available and can only be manufactured by a compounding pharmacy. In addition, the long-term safety of this preparation has not been established.
Complementary, rehabilitative, and interventional treatments — If pharmacologic modalities fail, amelioration of neuropathic pain from CIPN may be achieved through use of complementary, rehabilitative, and integrative methods (eg, acupuncture) as well as physical modalities such as cutaneous electrical stimulation. A device that delivers patient-specific electrocutaneous stimulation to the skin (called "Scrambler therapy") has shown promise for treatment of neuropathic pain, including that associated with CIPN. Non-randomized pilot trials suggest that Scrambler therapy can reduce chemotherapy-induced neuropathy symptoms, even if symptoms have been present for >1 year.

Neurofeedback — An intriguing pilot study suggests potential benefit for electroencephalogram (EEG)-based neurofeedback. Over time, the group completing the neurofeedback experienced significant improvements in pain scores when compared with the waitlist control group, and there were also improvements in numbness, symptom interference, physical functioning, and fatigue; these benefits persisted four months after treatment was completed. The treatment appeared to be very well tolerated, and there were no reports of adverse events. The generalizability of these results is limited by the small patient sample, the lack of an active or sham control group, and the nonblinded assessment of outcomes. However, additional study of neurofeedback and other approaches to physiologic self-regulation (eg, relaxation training, yoga) are warranted.
Acute neurotoxicity is predominantly seen in patients receiving oxaliplatin and the taxanes, paclitaxel and docetaxel. These are usually short-lived effects, and specific treatment may or may not be needed.

Taxane-induced acute pain syndrome may be quite debilitating, and consistently successful preventive agents/strategies have not been identified.

Optimal treatment is also not established. Nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently used first-line. Similarly, reports on the benefits of glucocorticoid therapy are limited to anecdotal experience and uncontrolled series. Anecdotally, opioids do relieve the pain.
PREVENTION

• There are no established agents that can be recommended for the prevention of chemotherapy-induced peripheral neuropathy (CIPN) in patients with cancer undergoing treatment with neurotoxic agents.

• **Vitamin E (Grade 2C).** Not recommended However, given the absence of other effective preventive therapy, the relative safety of low-dose vitamin E, and the significant unmet need in treating established neuropathy, some patients receiving potentially neurotoxic chemotherapy, especially **cisplatin**, who are particularly concerned about neuropathy and less concerned about the uncertainty of benefit may choose to take vitamin E.

• Accumulating reports suggest potential benefit for exercise in reducing the frequency of CIPN. Although we consider the data to be preliminary and not definitive, it is reasonable to suggest exercise to patients receiving potentially neurotoxic chemotherapy given all of the myriad benefits associated with exercise, including its potential to mitigate CIPN.

• For patients receiving **oxaliplatin** consider interspersing a non-oxaliplatin-containing "maintenance" chemotherapy regimen with the **oxaliplatin** regimen in patients undergoing palliative chemotherapy for metastatic colorectal ca

• For patients receiving **bortezomib**, weekly rather than twice-weekly treatment schedules and subcutaneous as compared with intravenous administration are associated with less frequent and less severe neurotoxicity. We recommend subcutaneous rather than intravenous administration of bortezomib (Grade 1A). In addition, weekly rather than twice-weekly administration is preferred for most patients unless an urgent treatment response is needed initially.

• For patients receiving weekly therapy with **paclitaxel**, cryotherapy (eg, using frozen socks and gloves before, during, and after drug infusion) may be useful to diminish objective and subjective symptoms of CIPN. However, the data are less than robust, and we await confirmation in additional larger studies before specifically recommending this approach. Limb hypothermia is contraindicated in patients with cold agglutinin disease, cryoglobulinemia, and posttraumatic cold dystrophy; those with extreme sensitivity to cold may not tolerate the cooling process.

• Because of the high incidence of constipation, patients receiving **vincristine** should take prophylactic stool softeners and/or laxatives.
Treatment

• For patients with cancer who are experiencing CIPN, we suggest duloxetine (Grade 2B).
• There is insufficient evidence to support a recommendation for any other treatment.
• 2014 recommendations from ASCO, suggested that a therapeutic trial of gabapentin/pregabalin or a tricyclic antidepressant (eg, nortriptyline or desipramine) is reasonable given the limited therapeutic options and the demonstrated efficacy of these drugs for other neuropathic pain conditions. Given the single borderline positive trial in patients with CIPN, it is also reasonable to try a compounded topical gel containing baclofen, amitriptyline HCl, and ketamine, understanding that this can only be manufactured by a compounding pharmacy and that ideally confirmatory results from other randomized trials regarding this treatment are needed.
THANK YOU!

QUESTIONS?