Symptom Management Guidelines: Chemotherapy – Induced Peripheral Neuropathy (CIPN)

NCI CTCAE GRADE AND MANAGEMENT | RESOURCES | CONTRIBUTING FACTORS | APPENDIX

Definition(s)

- **Chemotherapy – Induced Peripheral Neuropathy (CIPN):** injury, or degeneration of the peripheral nerve fibers (motor, sensory, autonomic) caused by certain neurotoxic systemic therapy agents. Symptoms usually start in the fingers and toes and spread proximally in a glove and stocking distribution.
- **Neuropathic pain:** nerve pain initiated by damaged nerves, often described as sharp, tingling, burning, cold, and/or a pins and needles
- **Allodynia:** pain caused by a stimulus that does not normally cause pain (e.g. light touch, contact with clothing)
- **Areflexia:** absence of reflexes
- **Dysesthesia:** abnormal spontaneous sensations (burning, stinging, stabbing) from activities that do not normally cause pain
- **Paresthesia:** an abnormal skin sensation in the absence of a stimulus (described as burning, prickling, itching, tingling)
- **Glove and stocking syndrome:** symmetrical manifestation of neuropathy in toes and fingers
- **Hyperesthesia:** increased sensitivity to sensory stimuli
- **Hypoesthesia:** decreased sensitivity to sensory stimuli
- **Coasting Effect:** when symptoms progress for months after treatment cessation
- **Carpal Tunnel Syndrome:** median nerve is compressed at the wrist, causing numbness, tingling, burning and pain in the affected hand and fingers

FOCUSED HEALTH ASSESSMENT

PHYSICAL ASSESSMENT

Vital Signs

- Frequency as clinically indicated
- Assess patient for orthostatic hypotension and heart rate

Observe Patient General Appearance:

- Observe gait as patient walks - note any hesitation, stumbling, unsteadiness, holding onto walls
- Observe for any involuntary movements, tremors, spasms, wrist or foot drop
- Observe any difficulty with closing buttons, shaky handwriting, holding objects, keyboard use

SYMPTOM ASSESSMENT

***Consider contributing factors**

Normal

- Do you have any pre-existing peripheral neuropathy?

Onset

- When did the symptoms begin?

Provoking / Palliating

- What brings it on?
- What makes it worse? Better?
- Does it get better in between treatment?

Quality (in last 24 hours)

- Can you describe symptoms?
  - **Sensory**: numbness, tingling, pain, or burning
  - **Motor**: falls, tripping, muscle weakness, abnormal gait, or paralysis, fine motor changes
  - **Autonomic**: constipation, urinary dysfunction, sexual dysfunction, orthostatic hypotension
- Are symptom(s) intermittent or constant?

Region / Radiation

- Where are you experiencing your symptoms? (e.g. toes, fingers, symmetrical)

Severity / Other Symptoms

- How bothersome is this symptom to you? (on a scale of 0 – 10, with 0 not at all and 10 being the worst imaginable)
- Are there any accompanying symptoms? (e.g. pain)

Treatment

- What medications or other strategies are you using right now? How effective? Side effects?

	• What medications or strategies have been effective in the past? **Understanding / Impact on You** • Do your symptoms affect your role function, mood or ability to do activities of daily living? (e.g. buttoning shirt, writing, pick up small items)? • Do your symptoms affect your ability to sleep (insomnia)? **Value** • What do you believe is causing this problem? • What is your comfort goal or acceptable level for this symptom (0 – 10 scale)?

PERIPHERAL NEUROPATHY GRADING SCALE(S) NCI Common Terminology Criteria for Adverse Events (CTCAE) (Version 5.0)				
NORMAL	**GRADE 1 (Mild)**	**GRADE 2 (Moderate)**	**GRADE 3 (Severe)**	**GRADE 4 (Life - threatening)**
Motor Grade				
Normal	Asymptomatic; clinical or diagnostic observations only;	Moderate symptoms; limiting instrumental activities of daily living (IADLs) (e.g. preparing meals, shopping, managing money)	Severe symptoms; limiting self-care ADLs (e.g. bathing, dressing, feeding self, using the toilet, taking medications) ; assistive device indicated	Life–threatening, consequences; urgent intervention indicated
Sensory Grade				
Normal	Asymptomatic	Moderate symptoms; limiting IADLs (e.g. preparing meals, shopping, managing money)	Severe symptoms; limiting self-care ADLs (e.g. bathing, dressing, feeding self, using the toilet, taking medications)	Life–threatening, consequences; urgent intervention indicated

***Step-Up Approach to Symptom Management:**
Interventions Should be Based on Current Grade Level and Include Lower Level Grade Interventions as Appropriate

PREVENTION – GRADE 1

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NON – URGENT: **Prevention, support, teaching, mild symptoms & follow-up care as required**	
Patient Care and Assessment	• Collaborate with physician: – If patient on Immunotherapy – To rule out other causes or concomitant causes of peripheral neuropathy or need for further assessment in outpatient setting (r/o spinal cord compression). Facilitate arrangements as necessary.
	– Lab tests may be ordered: e.g. vitamin B12 level, thyroid testing, fasting blood sugar or HGa1c, folate level • If on active chemotherapy treatment, may require treatment delays or reductions until symptoms resolve. Refer to specific chemotherapy protocols for direction: http://www.bccancer.bc.ca/health-professionals/professional-resources/chemotherapy-protocols

Prevention of Thermal Injury	• Avoid exposure of fingers and toes to very hot or very cold temperatures • Avoid ice packs or heating pads. Ensure water temperature in shower or tub is less than 43 °C • Use gloves when washing dishes or gardening, potholders when cooking • Reinforce principles of hand and foot care, including daily visual inspection for sores or blisters For patients receiving Oxaliplatin: • Sensory symptoms exacerbated by cold • Wear gloves, socks and scarf to protect against cold temperatures • Avoid eating cold food or drinks for few days after treatment
Fall Prevention	• Clear walkways of clutter, turn on lights when entering a room • Use skid free shower/ bathroom mats • Remove throw rugs or other objects that could cause falls • If gait unsteady, use assistive device (e.g. cane, walker) • Avoid going barefoot or using loose, or tight-fitting shoes
Exercise/Activity	• Passive range of motion exercises - may enhance reinnervation of denervated muscles • Resistance exercises – can help strengthen muscles weakened by neuropathy • Refrain from activities that require precise handwork (e.g. operating power tools or needlework) until symptoms lessen
Autonomic Symptoms	Orthostatic hypotension • Dangle legs prior to getting up, hold onto secure surfaces when getting up and change positions slowly Constipation (See Resources & Referrals) • Adequate daily fluid intake & high fibre diet Urinary retention • Adequate daily fluid intake, bladder re-training exercises, empty bladder at same time every day Sexual dysfunction • Consider pharmacological intervention e.g. Viagra
Non-Pharmacological Management	• Complementary Alternative Medicine (CAM) therapy may be helpful for some individuals • Relaxation techniques, deep-breathing, meditation, yoga, visual or guided imagery • Neurofeedback – cognitive therapy • Massage, Acupuncture, Transcutaneous electrical nerve stimulation(TENS) • Cryotherapy for weekly paclitaxel eg, by using frozen socks and gloves before, during, and after drug infusion) may be useful to diminish objective and subjective symptoms of CIPN
Pharmacological Management	• In collaboration with physician and pharmacist the following may be prescribed: Mild to moderate neuropathic pain and accompanying symptoms – Acetaminophen, or NSAIDs – Serotonin -norepinephrine reuptake inhibitor (SNRI) (eg. Duloxetine) – Anticonvulsants (e.g. gabapentin or pregabalin), or tricyclic antidepressants (e.g. amitriptyline, nortriptyline, imipramine) – Topical analgesic agents (e.g. capsaicin, lidocaine cream) – Compounded topical gels (baclofen/amitryptiline/ketamine) – A stepped protocol for constipation
Patient Education and Follow-Up	• All patients should receive information about: – Specific neurotoxic effects that can be expected from their chemotherapy regimen – Platinum-induced neuropathy can progress for several months after completion of chemotherapy – Report signs and symptoms of PN (sensory, motor, autonomic) to health care provider as soon as they are first noticed – Strategies around self-care and personal safety **Follow-up:** – Instruct patient/family to call back if symptoms worsen or do not improve – Arrange for nurse initiated telephone follow-up – Physician follow – up in ambulatory care setting may be indicated

GRADE 2 - GRADE 3

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URGENT:

Requires medical attention within 24 hours

Patient Care and Assessment	• Collaborate with physician: – If patient on Immunotherapy – To rule out other causes or concomitant causes of peripheral neuropathy or need for further assessment in outpatient setting (r/o spinal cord compression). Facilitate arrangements as necessary. – Lab tests may be ordered: e.g. vitamin B12 level, thyroid testing, fasting blood sugar or HGa1c, folate level If on active chemotherapy treatment, may require treatment delays or reductions until symptoms resolve. Refer to specific chemotherapy protocols for direction: http://www.bccancer.bc.ca/health-professionals/professional-resources/chemotherapy-protocols
Pharmacological Management	• In collaboration with physician and pharmacist the following may be prescribed: – Increased titration of dosages of anticonvulsant such as gabapentin, or tricyclic antidepressant such as nortriptyline (equal first-line). SNRIs such as duloxetine are third-line options – Opioid (short or long acting) – Corticosteroid (Refer to protocol specific algorithm if patient is on Immunotherapy) – Methadone – Mexiletine, Lidocaine infusion, Ketamine – Compounded Topical Gel (baclofen/amitriptyline/ketamine) – Medical Cannabinoids

GRADE 4

OR

Signs of Spinal Cord Compression (e.g. back pain, motor weakness/loss, autonomic dysfunction)

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EMERGENT:

Requires IMMEDIATE medical attention

Patient Assessment and Care	• If patient at home, instruct patient or family to call 911 or go to closest EMERGENCY ROOM • Notify physician of nursing assessment and facilitate arrangements as necessary • If patient on Immunotherapy, remind patient to present Immunotherapy alert card Immunotherapy alert card • Notify physician if on active chemotherapy treatment, will require treatment delays until
	symptoms resolve or discontinuation. Refer to specific chemotherapy protocols for direction: http://www.bccancer.bc.ca/health-professionals/professional-resources/chemotherapy-protocols • Monitor vital signs and assess for other complications (available to internal BC Cancer staff) – Spinal cord compression alert guidelines

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RESOURCES & REFFERALS	
Possible Referrals	• Telephone Care for follow-up • Physiotherapist • Occupational Therapist • Massage therapist • Acupuncturist • Patient and Family Counseling • Pain and Symptom Management/Palliative Care (PSMPC) (if interfering with ADLs and if pt willing to try pharmacological management)- • Home Health Nursing • Neurologist – referral for nerve conduction studies, electromyography • Sexual Health Clinic – referral for autonomic symptoms affecting sexual health
Immunotherapy	• Immunotherapy Alert Card • Please refer to protocol specific algorithms to guide management of immune mediated side effects.
Related Online Resources	• E.g. Fair Pharmacare; BC Palliative Benefits. Can be found in "Other Sources of Drug Funding Section" • Patient handout – Nerve Damage http://www.bccancer.bc.ca/managing-symptoms-site/Documents/Peripheral-Neuropathy.pdf • Sleep-Wake Disturbances SMG http://www.bccancer.bc.ca/nursing-site/Documents/17.%20Sleep-Wake%20Disturbance.pdf • Constipation SMG http://www.bccancer.bc.ca/nursing-site/Documents/3.%20Constipation.pdf http://www.bccancer.bc.ca/health-professionals/professional-resources/pharmacy/drug-funding
Bibliography List	• http://www.bccancer.bc.ca/health-professionals/clinical-resources/nursing/symptom-management

Contributing Factors	
Chemotherapy Agents	• High dose, high cumulative doses, or concurrent neurotoxic chemotherapy increases risk • Platinum drugs, Vinca Alkaloids, Taxanes, Cytarabine, Interferon, Thalidomide, Bortezomib ***Appendix A: Chemotherapy Induced Neurotoxicity below***
Other Systemic Therapy Agents	• Immunotherapy – checkpoint inhibitors (bortezomib) , antiangiogenic agents (Thalidomide, Pomalidomite, Lenalidomide • Biologic Agents – brentuximab • Hormonal Therapy – anastrozole
Other	• Peripheral neuropathy from pre-existing condition may develop into a more severe or persistent CIPN (e.g. alcoholism, Vitamin B deficiency, diabetes, HIV, congenital neuropathy, hypothyroidism, connective tissue diseases, toxic neuropathy, post-herpetic neuralgia) • Tumor infiltration & compression of spinal nerves • Paraneoplastic syndromes (cytokines excreted from tumor cells) • Radiation therapy involving the spine • Surgical trauma • Genetic Predisposition – variations in genetic makeup may contribute to risk of developing CIPN

Consequences

- **Sensory symptoms**: Dys/paresthesia, numbness and hypersensitivity, hypo/areflexia, pain, diminished vibratory or cutaneous sensations
- **Motor symptoms**: Weakness, gait and/or balance disturbance, difficulty with fine motor skills, wrist or foot drop
- **Autonomic symptoms**: Constipation, urinary dysfunction, sexual dysfunction, orthostatic hypotension
- Quality of life - exacerbation of other symptoms (e.g. pain, fatigue, depression, insomnia)
- Interference with ADLs and IADLs, compromised role function at home & work (may need gradual return to work-)
- Chemotherapy dose delays, reductions, discontinuation of treatment
- Patient safety – risk for falls, tripping, burns, frostbite
- Coasting effect – symptoms may progress and become chronic even after treatment cessation

Appendix A: Chemotherapy Induced Neurotoxicity

(Table adapted from Up-to-date 2018 table: Neurotoxicity Associated with Cytotoxic Chemotherapy Agents)

Drug	Sensory	Motor	Autonomic	Recovery
Platinum Compounds				
Cisplatin and Oxaliplatin (Chronic toxicity)	Distal, symmetric sensory loss Painful paresthesias or numbness	Normal	Rare	May progress for few months once drug discontinued
Carboplatin	Similar to Cisplatin but less severe	Normal	Rare	Similar to Cisplatin
Oxaliplatin (Acute neurotoxicity)	Paresthesias and dysthesias in hands, feet and perioral area; often induced or worsened by cold	Cramps, jaw tightness, and spasms in throat muscles	None	Often resolves within 1 week
Vinca Alkaloids				
Vincristine Vinblastine Vinorelbine	Distal sensory loss in lower extremities	Less common; distal, symmetric weakness in lower limbs, may progress to foot drop	Constipation common with Vincristine Orthostatic hypotension less	Often resolves within 3 months; can persist with Vincristine

			common	
Taxanes				
Paclitaxel **Docetaxel**	Mild, distal sensory loss (greater in feet than hands) Painful paresthesias	Occasional mild weakness in feet	Rare	Often resolves within 3 months; can persist
Other				
Bortezomib	Mild-mod distal symmetric sensory loss in lower extremities Painful paresthesia	Occasional mild distal weakness in lower limbs	Occasional, including orthostatic hypotension, diarrhea and constipation	Often resolves within 3 months; can persist
Thalidomide **Pomalidomide** **Lenalidomide**	Mild-mod distal symmetric sensory loss	Weakness, tremor, muscle cramps, fasciculation's are common	Constipation	Can persist for more than 1 yr
Brentuximab	Predominantly sensory	Rare	Rare	Often resolves in 3 months after treatment cessation, but may persist
Anastrozole	Carpal Tunnel Syndrome	Occasional weakness in affected limb	Normal	May persist after treatment cessation

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Contributing Authors:
Revised by: Jeevan Dosanjh, RN BScN, Michelle LaFreniere, RN (2025)
Revised by: Jen Pesut, RN BScN
Created by: Vanessa Buduhan, RN MN; Rosemary Cashman, RN MSc(A), MA (ACNP); Elizabeth Cooper, RN BScN, CON(c); Karen Levy, RN MSN; Colleen Sherriff, RN; Ann Syme RN Phd(C)

Reviewed by: Dr. Pippa Hawley, Palliative Medicine Specialist, Pain & Symptom Management, Colleen Riley (NP)