Chemotherapy Induced Peripheral Neuropathy (CIPN)

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Disclosure

- Nothing to disclose

- Medication options reviewed in this presentation may not have FDA labeled indication for the post-treatment side effects discussed, however only guideline supported treatment options are presented

Learning Objectives

- Discuss etiology of chemotherapy induced peripheral neuropathy
- Compare and contrast pharmacologic treatment options for chemotherapy induced peripheral neuropathy
- Summarize efficacy and safety of pharmacologic treatments used to manage chemotherapy induced peripheral neuropathy
- Design a treatment plan based on patient reported chemotherapy induced peripheral neuropathy

Chemotherapy Induced Peripheral Neuropathy (CIPN)

- Most common neuropathies caused by chemotherapy
- Can occur with a high single dose or after cumulative exposure
- Symptoms vary in intensity and duration
  - Acute
  - Transient thermal sensations
  - Permanent changes (chronic pain, irreversible nerve damage)
- Symptoms get progressively worse
  - May persist for months of years post chemo

Zajączkowska R, Kocot-Kępska M, Leppert W, Wrzosek A, Mika J, Wordliczek J. Mechanisms of Chemotherapy-Induced Peripheral Neuropathy. *International Journal of Molecular Sciences*. 2019; 20(6):1451. https://doi.org/10.3390/ijms20061451

CIPN

- Sensory, rather than motor symptoms
  - Numbness
  - Tingling
  - Altered touch sensation
  - Painful sensations
    - Burning, shooting, or electric shock like pain
- Symmetric
- Distal
- Length-dependent “glove and stocking” distribution

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CIPN

- Chemotherapy combinations with high incidences of peripheral neuropathy:
  - Platinum drugs
    - Oxaliplatin, cisplatin
  - Taxanes
    - Paclitaxel, docetaxel
  - Ixabepilone
  - Thalidomide (and its analogues)
  - Vinca alkaloids
    - Vincristine, vinblastine
  - Bortezomib
  - Cause damage to peripheral sensory, motor and autonomic neurons

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CIPN – Prevention

- No current recommendations for prevention
- Preliminary evidence suggests potential benefit from some preventative measure
- Larger sample-sized definitive studies are needed to confirm efficacy and safety
- Assess the risks and benefits
  - Underlying neuropathy
  - Conditions that predispose to neuropathy such as diabetes
  - Family or personal history of hereditary neuropathy

Charles L. Loprinzi, Christina Lacchetti, Jonathan Bleeker, Dawn L. Hershman et. al. Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: ASCO Guideline Update Journal of Clinical Oncology 2020; 38:28, 33253348 https://DOI: 10.1200/JCO.20.01399

CIPN – Prevention

Interventions	Strength of Recommendation	Strength of the Evidence	Benefits	Harms[a]
Prevention				
Acetylcysteine	Moderate against	Intermediate	Low	Low
Acetyl-L-carnitine	Strong against	High	No evidence of efficacy	High
Acupuncture	No recommendation	Low	Low	Moderate
Amifostine	Moderate against	Intermediate	Low	Moderate
Amitriptyline	Moderate against	Intermediate	No evidence of efficacy	Moderate
Calcium and magnesium	Moderate against	Intermediate	Low	Low
Cannabinoids	Moderate against	Intermediate		
Calmangafodipir	Moderate against	Intermediate	Low	Low
Carbamazepine/oxcarbazepine	Moderate against	Intermediate	Low	Low
L-carnosine	Moderate against	Intermediate	Low	Low
Compression therapy	No recommendation	Low	Low	Low
Cryotherapy	No recommendation	Low	Low	Moderate
DDTC	Moderate against	Intermediate	No evidence of efficacy	High

Interventions	Strength of Recommendation	Strength of the Evidence	Benefits	Harms[a]
Exercise	No recommendation	Low	Low	Low
Gabapentin/pregabalin	Moderate against	Intermediate	Low	Low
GM-1	No recommendation	Low	Low	Low
Glutamate/glutamine	Moderate against	Intermediate	Low	Low
GSH	Moderate against	Intermediate	Low	Low
GJG–Kampo medicine	Moderate against	Intermediate	Low	Low
Metformin	Moderate against	Intermediate	Low	Low
Minocycline	Moderate against	Intermediate	Low	Low
Nimodipine	Moderate against	Intermediate	No evidence of efficacy	Moderate
Omega 3	Moderate against	Intermediate	Low	Low
Org 2766	Moderate against	Intermediate	Low	Low
Retinoic acid	Moderate against	Intermediate	Low	Moderate
rhuLIF	Moderate against	Intermediate	No evidence of efficacy	Low
Venlafaxine	Moderate against	Intermediate	Moderate	Moderate
Vitamin B	Moderate against	Intermediate	Low	Low
Vitamin E	Moderate against	Intermediate	Low	Low

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CIPN – Prevention

- Consider dose delaying, dose reduction, substitution or stopping chemotherapy if patients develop CIPN
- Acetyl-L-carnitine should NOT be used or recommended
- No recommendations can be made on the use of the following (outside a clinical trial)
  - Acupuncture
  - Cryotherapy
  - Compression therapy
  - Exercise therapy
  - Ganglioside-monosialic acid (GM-1)

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CINP – Treatment

Interventions	Strength of Recommendation	Strength of the Evidence	Benefits	Harms[a]
Treatment				
Acupuncture	No recommendation	Low	Low	Low
Duloxetine	Moderate for	Intermediate	Moderate	Low
Exercise	No recommendation	Low	Low	Low
Gabapentin/pregabalin	No recommendation	Low	Low	Low
BAK	No recommendation	Low	Low	Low
Oral cannabinoids	No recommendation	Low	Low	Low
Tricyclic antidepressants	No recommendation	Low	Low	Low
Scrambler therapy	No recommendation	Low	Low	Low

Abbreviation: BAK= topical amitriptyline, ketamine ± baclofen

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CINP – Treatment

- Recent preliminary evidence suggests a potential for benefit
- Larger sample–sized definitive studies are needed to confirm efficacy and clarify risks:
  - Exercise
  - Acupuncture
  - Scrambler therapy
    - Electrocutaneous treatment approach

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CINP – Treatment
Duloxetine

- Duloxetine: 30 mg by mouth once a day x 1 week
- Then 60 mg by mouth once a day
  - Off label use of Serotonin/Norepinephrine Reuptake Inhibitor (SNRI) Antidepressant
  - Data: randomized, placebo-controlled, cross-over trial of 231 patients with CIPN
  - Reported significant decrease in average pain compared to placebo (P.003)
  - Reported decrease in numbness and tingling symptoms

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CINP – Treatment
Duloxetine

- Common side effects (>10%):
  - Headache, drowsiness (dose related), fatigue (dose related)
  - Nausea, xerostomia (dose related)
  - Weakness (dose related)
- [US Boxed Warning]: Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18 to 24 years of age) with major depressive disorder (MDD) and other psychiatric disorders

DULOXETINE. LEXI-DRUGS. LEXICOMP. WOLTERS KLUWER HEALTH, INC. RIVERWOODS, IL. AVAILABLE AT: HTTP://ONLINE.LEXI.COM. ACCESSED 9/3/2024

CINP – Treatment
Gabapentin

- Gabapentin:
  - Established efficacy for other forms of neuropathic pain options
  - Limited CIPN treatment options
  - Patients should be informed about the limited scientific evidence, potential harms, benefits, and costs
- General dosing recommendations (off-label use):
  - Initial: 100 to 300 mg 1 to 3 times daily increase dose based on response and tolerability to a target dose range of 300 mg to 1.2 g 3 times daily by mouth (immediate release)
- Common side effects (>10%):
  - Dizziness, drowsiness, ataxia, fatigue

HERSHMAN DL, LACCETTI C, DWOEKIN RH, ET AL. J CLIN ONCOL 2014;32:18:1941-1967. DOI: 10.1200/JCO.2013.54.0914
GABAPENTIN. LEXI-DRUGS. LEXICOMP. WOLTERS KLUWER HEALTH, INC. RIVERWOODS, IL. AVAILABLE AT: HTTP://ONLINE.LEXI.COM. ACCESSED 9/3/2024

CINP – Treatment

- Pregabalin:
  - Established efficacy for other forms of neuropathic pain options
  - Limited CIPN treatment options
  - Patients should be informed about the limited scientific evidence, potential harms, benefits, and costs
- General dosing recommendations:
  - Initial: 25 to 150 mg/day once daily or in 2 divided doses; may increase in increments of 25 to 150 mg/day at intervals ≥1 week based on response and tolerability up to a usual dose of 300 to 600 mg/day in 2 divided doses (immediate release)
- Common side effects (>10%):
  - Peripheral edema, Dizziness, drowsiness, headache, fatigue, weight gain, xerostomia, visual field loss, blurred vision

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CINP – Treatment

- Tricyclic-antidepressants
  - Have efficacy for other neuropathic pain conditions
  - Nortriptyline (target maximum dose of 100 mg/day)
  - Amitriptyline (target maximum dose of 50 mg/day)
  - Desipramine(target maximum dose of 250 mg/day)

- Discuss with the patients the limited scientific evidence for CIPN, potential harms, benefits, cost, and patient preferences

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CINP – Treatment

- Topical gel treatment:
  - Baclofen (10 mg), amitriptyline HCL (40 mg), and ketamine (20 mg)
  - Single trial
  - Available only through compounding pharmacies

- Oral cannabinoids:
  - Nabiximols an oral mucosal cannabinoid spray
  - Single trial
  - Side effects of fatigue, dry mouth, dizziness and nausea led to decrease interest in this option

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CINP

- Summary:
  - Patient who received platinum and/or taxane containing chemotherapy regimens at high risk for CINP
  - No strong evidence for prevention
  - Duloxetine is only agent with sufficient data to use as treatment
  - None-pharmacological treatments have shown benefit however larger studies need to be done

- Questions?

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Thank you!

References

- Zajączkowska R, Kocot-Kępska M, Leppert W, Wrzosek A, Mika J, Wordliczek J. Mechanisms of Chemotherapy-Induced Peripheral Neuropathy. *International Journal of Molecular Sciences*. 2019; 20(6):1451. https://doi.org/10.3390/ijms20061451
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- Hershman DL, Laccetti C, Dwoekin RH, et. al. Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: ASCO Clinical Practice Guideline. Journal of Clinical Oncology 2014;32:18:1941-1967. DOI: 10.1200/JCO.2013.54.0914
- LEXI-DRUGS. LEXICOMP. Wolters Kluwer Health, INC. Riverwoods, IL. Available at: http://online.lexi.com. Accessed September 3rd 2024