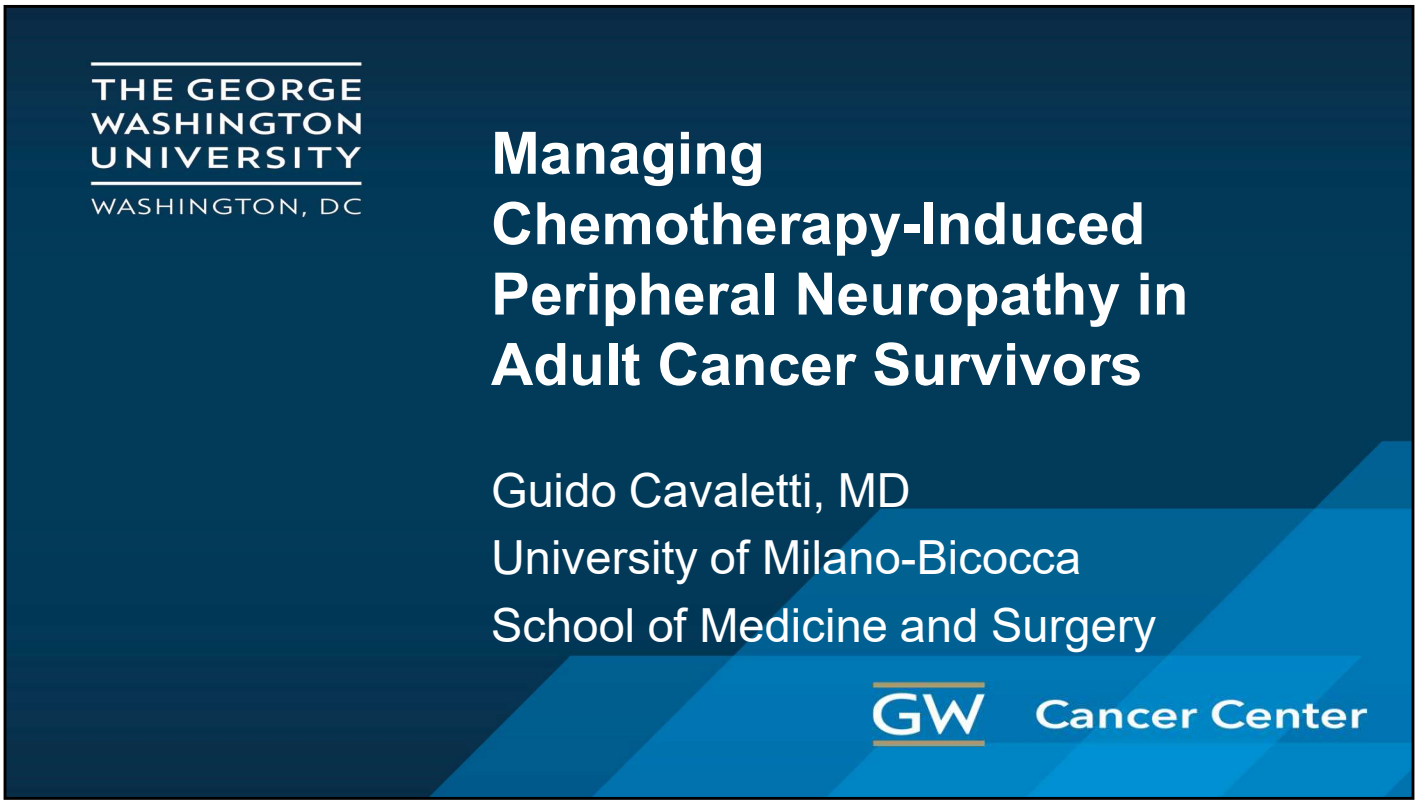
This content was adapted from the GW Cancer Center the Oncology Patient Navigation Training: The Fundamentals (PI: Pratt-Chapman) developed and maintained by CDC cooperative agreements #NU38DP004972, #5NU58DP006461 and #NU58DP007539. The content added, changed, or adapted by our organization do not necessarily represent the views of the GW Cancer Center or the CDC.



Welcome to this presentation on managing chemotherapy-induced neuropathies in adult cancer survivors. My name is Guido Cavaletti, MD and I am a Professor at the University of Milano-Bicocca.

Disclosure

This American Society of Clinical Oncology (ASCO) Guideline summary was prepared by GW Cancer Center. Any summaries or commentary appearing herein were not prepared or reviewed by American Society of Clinical Oncology, Inc. (ASCO) or the editors of Journal of Clinical Oncology® (JCO). The ideas and opinions expressed herein do not necessarily reflect those of ASCO, the editors of JCO, or GW Cancer Center. The mention of any company, product, service, or therapy does not constitute an endorsement by ASCO. It is the responsibility of the treating physician or other health care provider, relying on independent experience and knowledge of the patient, to determine drug dosages and the best treatment for the patient. ASCO, the editors of JCO, and GW Cancer Center assume no responsibility for any injury or damage to persons or property arising out of or related to any use of these materials or any errors or omissions. This material has been reviewed by the speaker and deemed to be appropriate for continuing education.

THE GEORGE WASHINGTON UNIVERSITY
WASHINGTON, DC

GW Cancer Center

Please note our disclosures. This content was created by a review of ASCO guidelines and was not prepared by ASCO or JCO. Learners should always seek out the latest information and guidelines before making clinical care decisions.

Learning Objectives

- Identify chemotherapy agents associated with neuropathy in adult patients with cancer and associated symptoms
- Describe strategies to prevent chemotherapy-induced peripheral neuropathy
- Describe strategies to treat chemotherapy-induced peripheral neuropathy that develops during or after neurotoxic chemotherapy

THE GEORGE WASHINGTON UNIVERSITY
WASHINGTON, DC

GW Cancer Center

By the end of this presentation, you will be able to:

- Identify chemotherapy agents associated with neuropathy in adult patients with cancer, and describe the associated symptoms
- Describe strategies to prevent chemotherapy-induced peripheral neuropathy, and
- Describe strategies to treat chemotherapy-induced peripheral neuropathy that develops during or after the administration of neurotoxic chemotherapy

Chemotherapy-Induced Neuropathy

- Chemotherapy-induced neuropathy is a serious clinical problem caused by cytotoxic drugs
- Oxaliplatin and paclitaxel cause acute neuropathy

Photo from iStock library authorized by subscription

Loprinzi et al, 2020

THE GEORGE WASHINGTON UNIVERSITY
WASHINGTON, DC

GW Cancer Center

We'll start with a brief overview of chemotherapy-induced neuropathy, which is a serious clinical problem caused by cytotoxic drugs used as chemotherapy agents. Different chemotherapy agents cause neuropathy through damage to the neurons, although the similarities and differences between the effects of many of these drugs are not well-defined. The two most prominent chemotherapy drugs, oxaliplatin and paclitaxel, are both neurotoxic, cause acute neuropathy, and have been increasingly studied in recent years.

Acute Oxaliplatin-Induced Neuropathy

- Characterized by
  - Cold sensitivity
  - Sore throat & discomfort swallowing cold liquids
  - Muscle cramps
- Severity peaks 2-3 days after each dose
- Subsequent treatment cycles double the magnitude of severity

Photo from Canva library authorized by subscription

Loprinzi et al, 2020

THE GEORGE WASHINGTON UNIVERSITY
WASHINGTON, DC

GW Cancer Center

With oxaliplatin use, neuropathy is primarily characterized by cold sensitivity, throat discomfort, discomfort swallowing cold liquids, and muscle cramps. Symptom severity usually peaks 2-3 days after each dose is administered. With each subsequent treatment cycle, the magnitude of severity typically doubles. However, there is no information on how long the acute symptoms last after the final dose.

Acute Paclitaxel-Induced Neuropathy

- Causes manifestation of acute neuropathy
  - Peaks 2-3 days after each dose
- Symptoms are primarily pain in the truncal/ hip distribution
- Symptoms tend to resolve between doses

Photo from Canva library authorized by subscription

Loprinzi et al, 2020

THE GEORGE WASHINGTON UNIVERSITY
WASHINGTON, DC

GW Cancer Center

Paclitaxel is another cytotoxic chemotherapy agent associated with acute neuropathy. Like oxaliplatin, the symptoms peak 2-3 days after each dose. However, the symptoms primarily manifest as pain in the truncal or hip region. Further, paclitaxel-induced neuropathy symptoms tend to resolve more between each dose, and usually don't worsen between cycles, in contrast to oxaliplatin where the symptom magnitude doubles with each cycle.

Other Chemotherapy-Induced Peripheral Neuropathies

- Vinca alkaloids: Most severe symptoms appear a few days after administration of the drug, autonomic nervous system impairment may be severe
- Cisplatin: May affect upper and lower limbs, and the symptoms may last for months
- Bortezomib: Neuropathy is very painful and may be experienced after the very first cycles of treatment

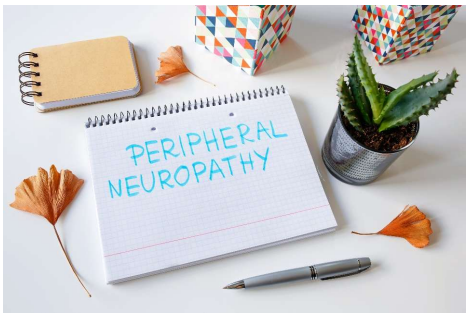


Photo from iStock library authorized by subscription

Aronson, 2016; Bilińska et al., 2013; Moudi et al., 2013; Strabova & Vetter, 2017; Yamamoto & Egashira, 2021

THE GEORGE WASHINGTON UNIVERSITY
WASHINGTON, DC

GW Cancer Center

Vinca alkaloids are commonly used in combination chemotherapy regimens. While there are a few different types of vinca alkaloids, only three are approved for use in the United States: Vincristine (VCR), vinblastine (VBL), and vinorelbine (VRL). Some of the symptoms of these agents include loss of reflexes in the ankle tendons and numbness, pain, burning, and tingling sensations. Such symptoms are followed by loss of touch, a sensation of vibration, dizziness, nausea, headache, pain in the jaw, and vocal cord paralysis. Usually, such symptoms appear a few days after the administration of the agent.

Cisplatin is used for solid tumor treatment, mainly in the lung, testicle, ovary, brain, and bladder areas. Cisplatin-induced neuropathy symptoms are cumulative and usually characterized as tingling sensation, numbness, and mechanical and thermal hyperalgesia (increased sensitivity to pain). Cisplatin-induced CIPN affects sensory and motor systems, inducing a sense of loss of vibrations, taste, and tremors. Mostly upper and lower limbs are affected, and symptoms may last for a few months and may get worse.

Bortezomib – used for multiple myeloma and mantle cell lymphoma. The neuropathy symptoms include numbness and paresthesia (sensation of “pins and needles”). On average, such symptoms may be experienced within five first cycles of treatment.

Chronic Chemotherapy-Induced Neuropathy

- Similar distal distribution for oxaliplatin and paclitaxel
- Primarily sensory neuropathy, but with different sensory modalities involvement
- After chemotherapy
  - Paclitaxel: Improves over time
  - Oxaliplatin: Worsens for 2-3 months and then frequently starts to improve

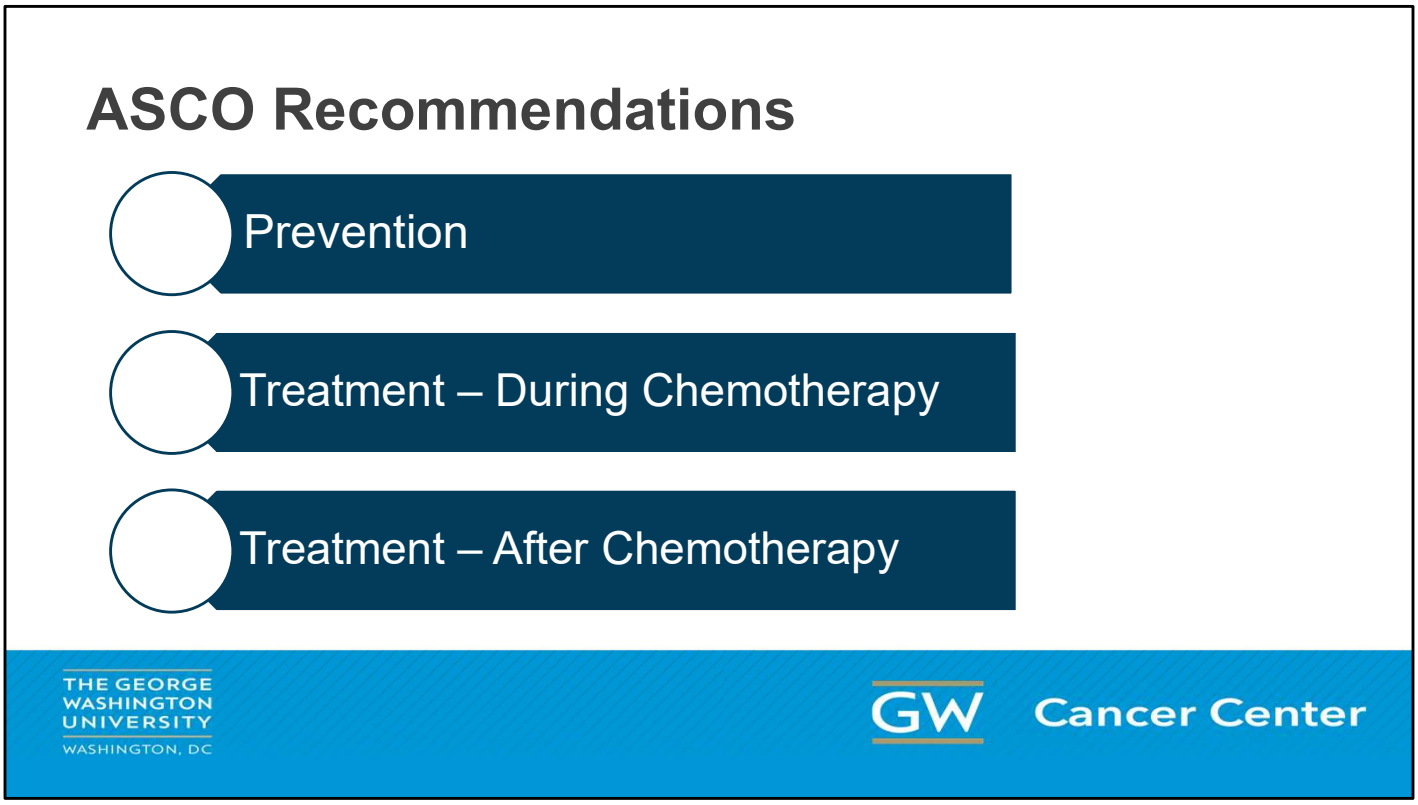
Photo from Canva library authorized by subscription

Loprinzi et al, 2020

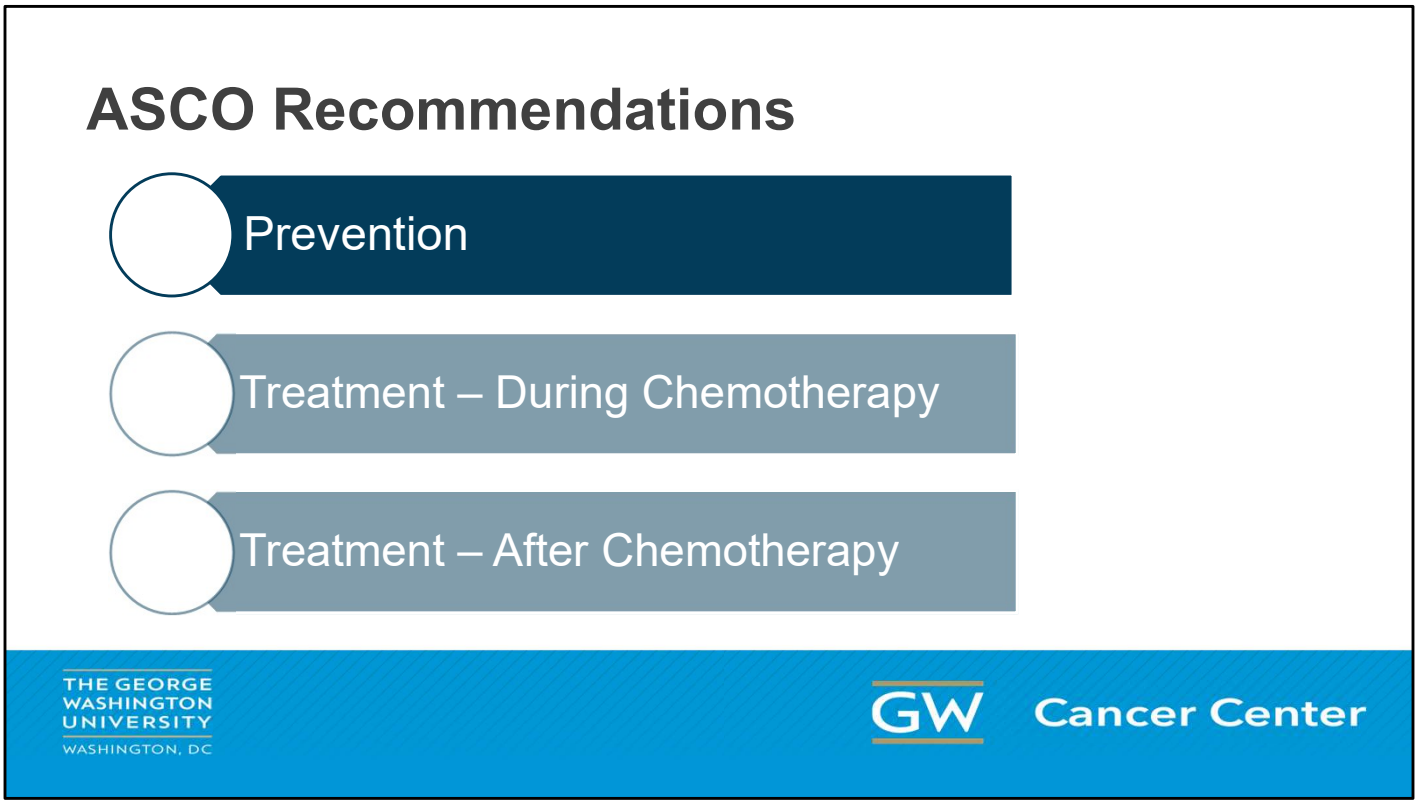
THE GEORGE WASHINGTON UNIVERSITY
WASHINGTON, DC

GW Cancer Center

In terms of chronic neuropathies, the effects of oxaliplatin and paclitaxel are similar. The chronic neuropathy tends to be sensory, as opposed to motor or autonomic. Symptoms typically include numbness, tingling, and pain. Numbness and tingling both tend to present earlier, and are more significant symptoms, than pain. Where the two drugs differ in their chronic effects is the location of the symptoms. With paclitaxel, symptoms tend to be more prominent in the lower extremities while with oxaliplatin, the symptoms are more prominent and severe in the upper extremities. After completion of chemotherapy, paclitaxel-induced chemotherapy tends to improve while oxaliplatin-induced neuropathy tends to worsen for about 2-3 months before starting to improve. Although symptoms can improve over time, the pain can be long-lasting, debilitating, affect quality of life, and may negatively affect cancer outcomes by limiting the amount of chemotherapy a provider can give their patient.



We will now discuss recommendations for prevention and treatment of neuropathy before, during, and after chemotherapy.



We will start with prevention.

Prevention of Chemotherapy-Induced Peripheral Neuropathy (CIPN)

- Clinicians should assess the risk and benefits of agents known to cause CIPN in patients with predisposition to or existing neuropathy
- Clinicians should NOT offer and should discourage use of acetyl-L-carnitine

Photo from Canva library authorized by subscription

Loprinzi et al, 2020

THE GEORGE WASHINGTON UNIVERSITY
WASHINGTON, DC

GW Cancer Center

To prevent chemotherapy-induced peripheral neuropathy, or CIPN, clinicians should first assess the risks and benefits of chemotherapy agents known to cause CIPN, especially for patients with existing neuropathy or predisposition to neuropathy. Some conditions that may increase predisposition to neuropathy include diabetes, family history, or personal history of hereditary neuropathy. Additionally, clinicians should not offer and should discourage the use of acetyl-L-carnitine, which has been shown in trials to worsen the symptoms of neuropathy.

Clinicians Should **Not** Offer These Therapies to Prevent CIPN:

All-trans retinoic acid	Amifostine	Amitriptyline	Calcium magnesium	Calmangafodipir	Cannabinoids
Carbamazepine	L-carnosine	DDTC	Gabapentin/ pregabalin	Glutamate	Glutathione
GJG	Metformin	Minocycline	N-acetylcysteine	Nimodipine	Omega-3 fatty acids
Org 2766	Oxcarbazepine	Recombinant human leukemia inhibitory factor	Venlafaxine	Vitamin B	Vitamin E

Loprinzi et al, 2020

THE GEORGE WASHINGTON UNIVERSITY
WASHINGTON, DC

GW Cancer Center

We have provided a list of additional therapies that should not be offered to prevent CIPN in patients undergoing chemotherapy with cytotoxic agents due to low benefit observed in clinical studies, such as all-trans retinoic acid, amifostine, amitriptyline, and others. Please take a moment to review this list.

Additional information about the evidence behind each therapy and recommendation can be found in the 2020 ASCO Guidelines for Prevention and Management of CIPN in Cancer Survivors, referenced at the end of this presentation.

Prevention of CIPN

- Outside of clinical trials, no recommendation can be made for
  - Acupuncture
  - Cryotherapy
  - Compression therapy
  - Exercise therapy
  - Ganglioside-monosialic acid

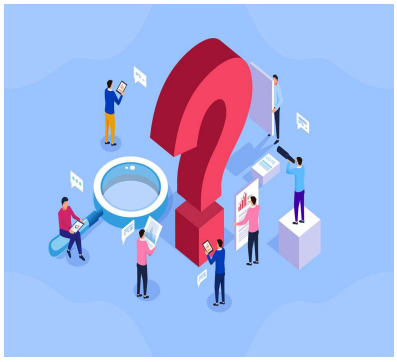


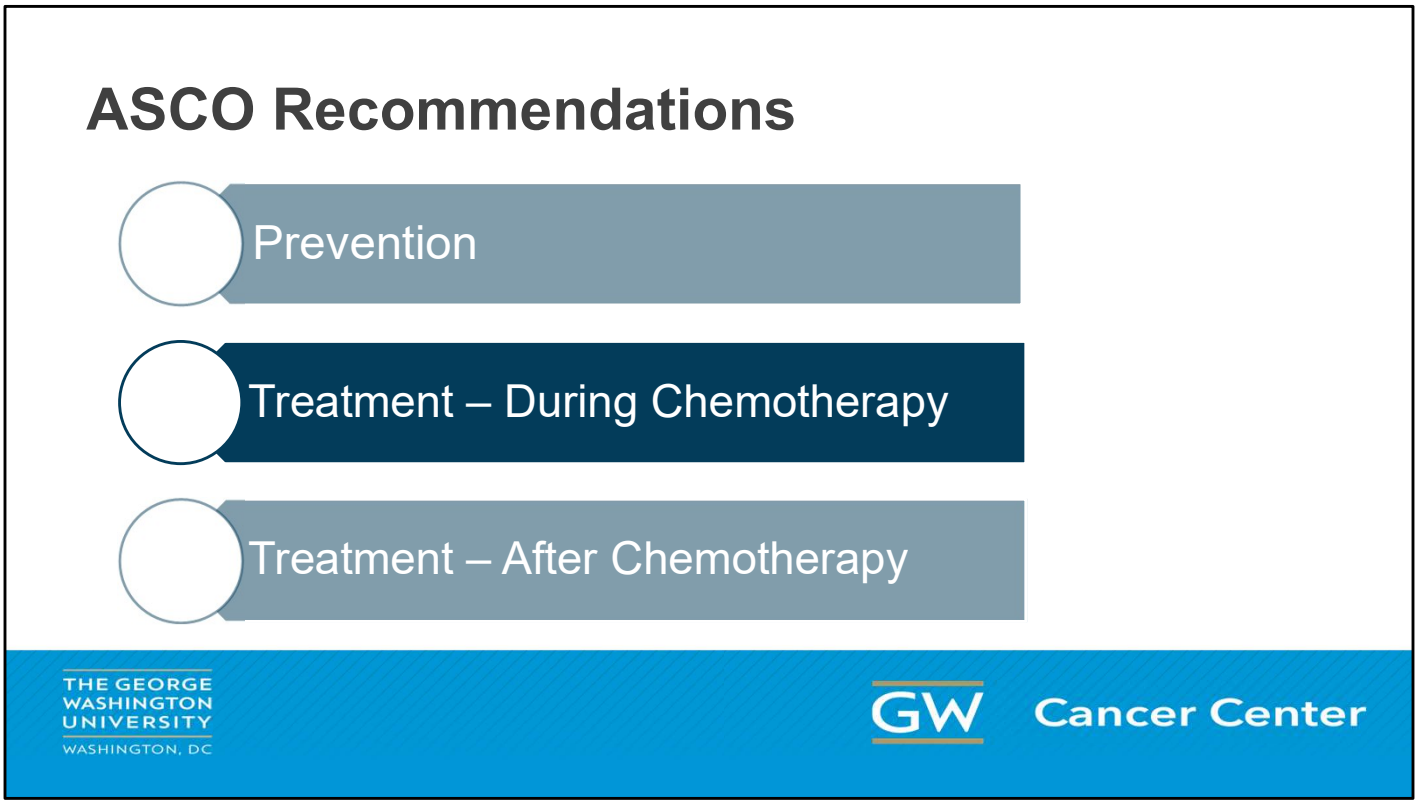
Photo from iStock library authorized by subscription

Loprinzi et al, 2020

THE GEORGE WASHINGTON UNIVERSITY
WASHINGTON, DC

GW Cancer Center

Due to a lack of sufficient evidence, no recommendation can be made for the use of acupuncture, cryotherapy, compression therapy, exercise therapy, or ganglioside-monosialic acid for prevention of CIPN outside of a clinical trial. Preliminary evidence indicates these may be effective therapies, but studies with larger sample sizes are needed to confirm efficacy and potential risks.



Next, we will discuss recommendations for treating CIPN that develops during chemotherapy.

Treatment of CIPN

- For CIPN that develops during neurotoxic chemotherapy, clinicians should assess and discuss with the patient
  - Substituting for agents that do not cause CIPN
  - Appropriateness of dose delaying
  - Dose reduction
  - Stopping chemotherapy

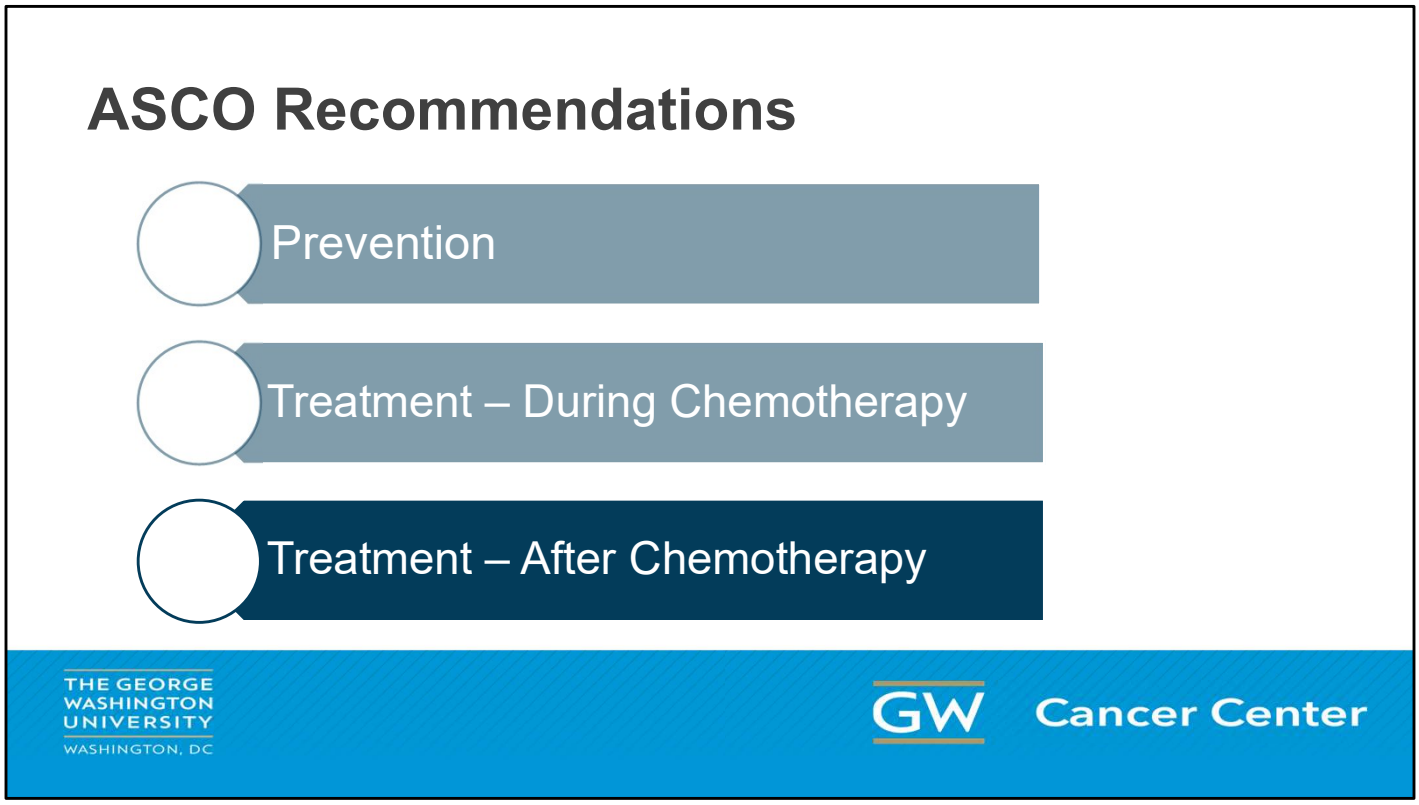
Photo from iStock library authorized by subscription

Loprinzi et al, 2020

THE GEORGE WASHINGTON UNIVERSITY
WASHINGTON, DC

GW Cancer Center

If, during neurotoxic chemotherapy, the patient develops intolerable CIPN or functional nerve impairment, the clinician should assess and discuss with their patient possible changes to the treatment plan, including the appropriateness of dose delaying, reducing the dose, stopping chemotherapy, or switching to another agent that does not cause CIPN. The clinician should assess the expected survival benefit and other patient characteristics. Understanding the patient's perspective is an important part of the decision-making process.



Finally, we will review treatment options for CIPN that develops or continues after chemotherapy.

Treatment of CIPN

- For patients who have completed neurotoxic chemotherapy and are experiencing painful CIPN, clinicians may offer duloxetine

Illustration from iStock library authorized by subscription

Loprinzi et al, 2020

THE GEORGE WASHINGTON UNIVERSITY
WASHINGTON, DC

GW Cancer Center

For patients who have completed neurotoxic chemotherapy, but are experiencing CIPN, clinicians may offer duloxetine.

Treatment of CIPN

- Outside of clinical trials, no recommendation can be made for
  - Exercise therapy
  - Acupuncture
  - Scrambler therapy
  - Gabapentin/ pregabalin
  - Topical gel treatment containing baclofen, amitriptyline HCL, plus/ minus ketamine
  - Tricyclic antidepressants
  - Oral cannabinoids

Illustration from iStock library authorized by subscription

Loprinzi et al, 2020

THE GEORGE WASHINGTON UNIVERSITY
WASHINGTON, DC

GW Cancer Center

As of the publication of these guidelines in 2020, no recommendation can be made for exercise therapy, acupuncture, scrambler therapy, gabapentin/pregabalin, topical gel treatment containing baclofen, amitriptyline HCL, with or without ketamine, tricyclic antidepressants, or oral cannabinoids. While recent preliminary evidence suggests a potential for benefit from exercise, acupuncture, and scrambler therapy, larger sample–sized definitive studies are needed to confirm efficacy and clarify risks.

Exercise and CIPN

- Exercise may significantly
  - Improve quality of life
  - Relieve neuropathic pain
  - Improve upper and lower limb strength and balance

Photo from Canva library authorized by subscription

Guo et al., 2022

THE GEORGE WASHINGTON UNIVERSITY
WASHINGTON, DC

GW Cancer Center

At the time the 2020 ASCO neuropathy guidelines were published, there was only preliminary evidence to support a potential benefit from exercise, and the guidelines called for additional research to confirm efficacy and clarify risks. A 2022 systematic review and meta-analysis included 16 studies and found evidence that exercise significantly improved quality of life and relieved neuropathic pain. Further, muscular strength and balance were better in the exercise group, compared to usual care. This is important to note: While there was no evidence to support exercise, as a method to improve CIPN symptoms, exercise did relieve the patient of other symptoms. Therefore, it is important to monitor the actual outcomes of clinical trials to identify which interventions are most appropriate for which patients.

Conclusion

- Neuropathy is a potential effect of neurotoxic chemotherapy agents, and may affect the patient's quality of life or cancer outcomes
- Providers should consult with the patient when considering any changes
- Additional research is needed to clarify the effects and risks of possible CIPN treatments

Photo from Canva library authorized by subscription

Loprinzi et al, 2020

THE GEORGE WASHINGTON UNIVERSITY
WASHINGTON, DC

GW Cancer Center

To recap, neuropathy is a possible effect of neurotoxic chemotherapy agents, and the pain may affect the patient's quality of life or cancer outcomes if chemotherapy is reduced, altered, or stopped. Whenever changes to the cancer treatment plan are considered, the provider should listen to the patient's perspective and input. Further, additional research is needed to clarify the effects and risks of many proposed treatments, including exercise and acupuncture. Finally, there is little research into health disparities related to CIPN and providers should work to ensure diverse and inclusive care.

References

Aronson, J.K. (2016). Meyler's Side Effects of Drugs (Sixteeth Edition), 1047-1047. Elsevier

Bilińska, M., Usnarska-Zubkiewicz, L., & Pokryszko-Dragan, A. (2013). Bortezomib-induced painful neuropathy in patients with multiple myeloma. *Contemporary oncology (Poznan, Poland)*, *17*(5), 421–426. https://doi.org/10.5114/wo.2013.37214

Guo, S., Han, W., Wang, P., Wang, X., & Fang, X. (2022). Effects of exercise on chemotherapy-induced peripheral neuropathy in cancer patients: a systematic review and meta-analysis. *Journal of Cancer Survivorship*. https://doi.org/10.1007/s11764-022-01182-3

Loprinzi, C. L., Lacchetti, C., Bleeker, J., Cavaletti, G., Chauhan, C., Hertz, D. L., Kelley, M. R., Lavino, A., Lustberg, M. B., Paice, J. A., Schneider, B. P., Lavoie Smith, E. M., Smith, M. L., Smith, T. J., Wagner-Johnston, N., & Hershman, D. L. (2020). Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: ASCO guideline update. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, *38*(28), 3325–3348. https://doi.org/10.1200/JCO.20.01399

Moudi, M., Go, R., Yien, C. Y., & Nazre, M. (2013). Vinca alkaloids. *International Journal of Preventive Medicine*, *4*(11), 1231–1235.

Starobova, H., & Vetter, I. (2017). Pathophysiology of chemotherapy-induced peripheral neuropathy. *Frontiers in Molecular Neuroscience*, *10*, 174. https://doi.org/10.3389/fnmol.2017.00174

Yamamoto, S., & Egashira, N. (2021). Pathological mechanisms of bortezomib-induced peripheral neuropathy. *International Journal of Molecular Sciences*, *22*(2), 888. https://doi.org/10.3390/ijms22020888

THE GEORGE WASHINGTON UNIVERSITY
WASHINGTON, DC

GW Cancer Center

The references used to develop this presentation are listed here, including the ASCO guidelines referenced throughout this presentation, which includes additional information for the evidence and strength for each recommendation discussed here.

Acknowledgments

This training was supported by Cooperative Agreement #NU58DP006461-04 from the Centers for Disease Control and Prevention (CDC).

The views expressed in written workshop materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services, nor does the mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government.

THE GEORGE WASHINGTON UNIVERSITY
WASHINGTON, DC

GW Cancer Center

This work was supported by cooperative agreements from the CDC. It's contents are solely the responsibility of the authors and do not necessarily represent the official views of the CDC. No industry funding was used to support this work.

Thank you!

Guido Cavaletti, MD
guido.cavaletti@unimib.it

Follow us on Twitter: @GWCancer

www.gwcancercenter.org

Sign-up for the GW Cancer Center's Patient Navigation and Survivorship E-Newsletter: **bit.ly/PNSurvEnews**

Sign-up for the GW Cancer Center's Cancer Control Technical Assistance E-Newsletter: **bit.ly/TAPenews**

THE GEORGE WASHINGTON UNIVERSITY
WASHINGTON, DC

GW Cancer Center

If you have any questions for me or the GW Cancer Center, you can connect with us using the emails and links available on this slide, and thank you for participating in this module.