

UNC Lineberger Cancer Network
PATIENT CENTERED CARE Live Webinar
 April 13, 2022

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1

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UNC University of North Carolina
Lineberger Cancer Network

What symptoms are involved with Chemotherapy-induced Peripheral Neuropathy?

- Pain, tingling, burning, or numbness **A**
- Sensitivity to hot or cold **B**
- Difficulty with fine motor skills **C**
- All of the above **D**

7

DISCLOSURES

This activity has been planned and implemented under the sole supervision of the course directors, in association with the UNC Office of Continuing Professional Development (UNC CPD). William A Wood, MD, MPH, and CPD staff have no relevant financial relationships with commercial interests as defined by the ACCME.

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Dr. Charles Loprinski has relevant financial relationships with Pfizer/Pharma, Disarm Therapeutics, Asahi Kasei, Merus Pharmaceuticals, NEMAX, Novartis, Osmol Therapeutics, Nuro Bio, Heng Rui Medicines, On Quality and Mitsubishi Tanabe. These relationships have been mitigated and have not influenced the planning or implementation of this activity.


8

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9

**Cryotherapy for Preventing
Chemotherapy-induced Neuropathy:
Proven, Promising-appearing, or
Hogwash?**

Charles L. Loprinzi, MD
Regis Professor of Breast Cancer Research
Mayo Clinic, Rochester MN




10

Financial Relationships


Commercial Interest	Nature of Relationship
Pfizer	Chemotherapy Neuropathy consultation
Disarm Therapeutics	Chemotherapy Neuropathy consultation
Asahi Kasei	Chemotherapy Neuropathy consultation
Metys Pharmaceuticals	Chemotherapy Neuropathy consultation
NKMax	Chemotherapy Neuropathy consultation
Novartis	Chemotherapy Neuropathy consultation
Osmol Therapeutics	Chemotherapy Neuropathy consultation
Nura Bio	Chemotherapy Neuropathy consultation
HengRui Medicines	Chemotherapy Neuropathy consultation
OnQuality	Skin Toxicity consultation
Mitsubishi Tanabe	Fatigue consultation

Virtually all I discuss will be off label

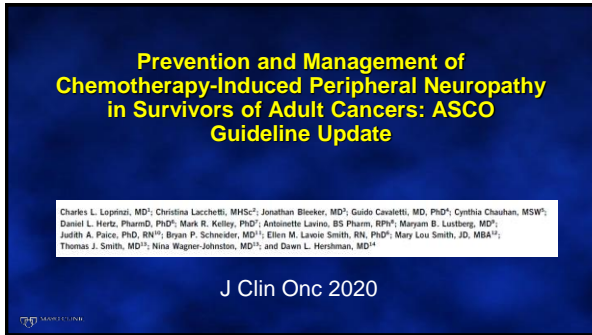


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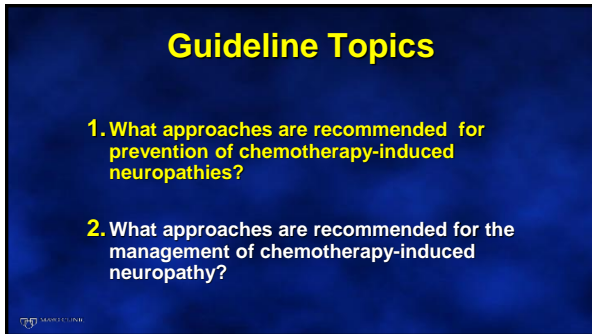
CIPN is a Major Clinical Problem



12



13



14




15

Chemotherapy-induced Peripheral Neuropathy Prevention

Recommendation 1.1

Clinicians should assess the risks and benefits of agents known to cause CIPN

- In patients with underlying neuropathy, and
- In patients with conditions that predispose to neuropathy such as
 - Diabetes
 - A family history of hereditary neuropathy




16

Chemotherapy-induced Peripheral Neuropathy Prevention

Recommendation 1.2

Acetyl-L-carnitine for the prevention of CIPN in cancer patients should:

- Not be offered
- Actually be discouraged




17

Chemotherapy-induced Peripheral Neuropathy Prevention

Recommendation 1.4

There is a long list of agents that should not be recommended for the preventing neuropathy in patients getting chemotherapy




18

Chemotherapy-induced Peripheral Neuropathy Prevention

Recommendation 1.3

The following cannot be recommended to try to prevention of CIPN, outside of a clinical trial:

- Acupuncture
- Exercise
- Ganglioside-monosialic acid (GM-1)
- **Cryotherapy**
- Compression




22



23

Let's Focus on Cryotherapy in General, First

- **I. Alopecia prevention**
- **II. 5 FU-induced mucositis prevention**
- **III. Onychomycosis**
- **IV. CIPN**



24

History of Cryotherapy for Alopecia

- When was the first published report that suggested that scalp cryotherapy was helpful for decreasing chemotherapy-induced alopecia?
- When were the convincing trials published that made scalp cryotherapy relatively common?
- How many years did such take?

25

Vol. 13 No. 1 2013 *Journal of Pain and Symptom Management*

Review Article

Supportive Cryotherapy: A Review From Head to Toe

Kunal C. Kaulakia, MD, Shaina A. Rosell, MD, Anish A. Botala, BS, and Charles L. Loprinzi, MD
 Division of Internal Medicine (K.C.K., S.A.R.), Mayo Clinic, Rochester, Minnesota; Feinberg School of Medicine (A.A.B.), Northwestern University, Chicago, Illinois; and Division of Medical Oncology (C.L.L.), Mayo Clinic, Rochester, Minnesota, USA

Scalp Cryotherapy
 First report 1973
 As of 2013
 Over 59 non-randomized reports
 7 randomized trial reports

26

JAMA | Original Investigation

Effect of a Scalp Cooling Device on Alopecia in Women Undergoing Chemotherapy for Breast Cancer: The SCALP Randomized Clinical Trial

Jiule Nangia, MD, Tao Wang, PhD, Cynthia Osborne, MD, Polly Miraveth, MD, Kristan Otta, BA, Steven Rapch, MD, Frankie Holmes, MD, Jame Abraham, MD, Mario Lacouture, MD, Jay Courtright, MD, Richard Fisman, BSc, Matt Rude, ANP, Susan Hilsenbeck, PhD, C. Kent Osborne, MD, Mollieffer Rittman, MD

JAMA. 2017;317(6):596-605. doi:10.1001/jama.2016.20939

JAMA | Original Investigation

Association Between Use of a Scalp Cooling Device and Alopecia After Chemotherapy for Breast Cancer


Hope S. Rago, MD, Pratik Shah, MD, Susan Arora, MD, Sara A. Hantel, MD, Michelle E. Mabbitt, MD, Anna Kovacs, MD, Cliff Trah, PharmD, Jules Mitchell, PhD, Erikka Elgerman, PhD, Ralph B. D'Agostino Jr, PhD, Elizabeth S. Van Heres, MA, Laura Cooper, MD, MHA, Tessa Collier, MD

JAMA. 2017;317(6):606-614. doi:10.1001/jama.2016.21038

27

History of Cryotherapy for Alopecia


- When was the first published report that suggested that scalp cryotherapy was helpful for decreasing chemotherapy-induced alopecia? **1973**
- When were the convincing trials published that made scalp cryotherapy relatively common? **2017**
- How many years did such take? **44 years**



28

Cryotherapy Topics

- I. Alopecia prevention
- II. **5 FU-induced mucositis prevention**
- III. Onychomycosis
- IV. CIPN



29

Oral cryotherapy works

Inhibition of fluorouracil-induced stomatitis by oral cryotherapy

Mahood DJ, Dose AM, Loprinzi CL, Veeder MH, Athmann LM, Therneau TM, Sorensen JM, Gainey DK, Mailliard JA, Gusa NL, et al

J Clin Oncol 1991




30

30 = 60 minutes

A randomized clinical trial of two different durations of oral cryotherapy for prevention of 5-fluorouracil-related stomatitis

Rocke LK, Loprinzi CL, Lee JK, Kunselman SJ, Iverson RK, Finck G, Lifsey D, Glaw KC, Stevens BA, Hatfield AK, et al


Cancer 1993



31

Cryotherapy Topics


- I. Alopecia prevention
- II. 5 FU-induced mucositis prevention
- **III. Onychomycosis**
- IV. CIPN



32

Cryotherapy for Onychomycosis


- First report 2005
- Multiple subsequent reports-many positive



33

Cryotherapy Topics


- I. Alopecia prevention
- II. 5 FU-induced mucositis prevention
- III. Onychomycosis
- **IV. CIPN**



34

Topical cryotherapy for preventing paclitaxel neuropathy

- The story starts about 2010, in terms of rumors.




35

Breast Cancer Res Treat (2015) 142:109–118
DOI 10.1007/s12088-015-2708-2

CLINICAL TRIAL

Risk of docetaxel-induced peripheral neuropathy among 1,725 Danish patients with early stage breast cancer


L. Fekihoff · A. S. Knoop · M.-B. Jensen · B. Ejlersten · M. Ewertz



36

Eckhoff et al., 2013

- Retrospective report, regarding docetaxel-induced peripheral neuropathy among 1725 Danish breast cancer patients
- Pts who used frozen gloves and socks (40% of the patients) during treatment had a 44% reduction in subsequent neuropathy problems (P < 0.0001)




37

The role of limb hypothermia in preventing paclitaxel-induced peripheral neuropathy

Raghav Sundar, Aishwarya Bandla, Stacey Tan, Nesaretnam Barr Kumarakulasinghe, Anand Devaprasath Jeyasekharan, Samuel Guan Wei Ow, Jingshan Ho, David Shao Peng Tan, Joline Si Jing Lim, Joy Vijayan, Zarinah Hairom, Sally Ang, Lun-De Liao, Soo-Chin Lee, Nitish Thakor, Einar Wilder-Smith
Singapore


ASCO 2016; Abstract No: e21696
Front Oncol. 2017 ; PMID: 28119855



38

Methods

- Breast cancer patients treated with weekly with paclitaxel (80 mg/m²) for at least 12 cycles
- Limb perfusion cryoRx given on the dominant hand and foot for 90 min
- Non-dominant side was untreated control
- Primary endpoint: Semmes–Weinstein monofilament test (MF; tactile changes from baseline) at 12 weeks



39

Results

- 44 patients registered, 36 evaluable




40

Results

Test	Cryotherapy	Control	P
Monofilament test*			
Hands	28%	81%	<0.01
Feet	25%	64%	
Neurotoxicity Questionnaire*	19%	67%	<0.01
Rx tolerability	No dropout from cold		

*Deterioration at end of 12 cycles, from baseline



41

Mayo Clinic Pilot CIPN Cryotherapy Trial



42



49


Efficacy of compression therapy using surgical gloves for nanoparticle albumin-bound-paclitaxel-induced peripheral neuropathy:

A phase II multicenter study by the Kamigata breast cancer study group

Tsuyuki S et al; Japan

SABCS 2016; PD4-08


Breast 2019; 47: 22-27



50

Methods


- 2 Surgical Gloves that were smaller than what would usually fit on one hand for 90 minutes.
- The other hand, served as a control.



51

Results

- 43 pts enrolled; 42 evaluable
- CTCAE G2 sensory neuropathy
 - 76% in control hands
 - 57% in gloved hands
- PNQ results: G4 CIPN was significantly higher in the control hands than in the gloved hands




52

Cryocompression for enhanced limb hypothermia in preventing paclitaxel-induced peripheral neuropathy

Raghav Sundar, et al
National University Health System
Singapore, Singapore


ASCO abstract 10095; 2018




53

Results

- 13 pts underwent 142 cycles of cryo-compression concomitant with chemotherapy
- Mean skin temperature reduction of $3.8 \pm 1.7^\circ\text{C}$ achieved and well tolerated
- Only 1 pt required an intra-cycle temperature increase, with no early termination of cryo-compression in any subject
- Suggestion of benefit




54


Randomized Controlled Selection Trial of Cryotherapy vs. Compression Therapy for the Prevention of Taxane-induced Peripheral Neuropathy in Breast Cancer Patients

CUMC IRB #AAAR9515
Protocol (v. 7/20/18)


Dawn Hershman, MD, MS
Principal Investigator



55

Factors that support the use of Cryo-compression therapy


- The magnitude of the clinical problem of CIPN
- The promising-appearing early results discussed above
- The absence of other established means of preventing CIPN
- Data supporting that cryotherapy will decrease nail toxicity



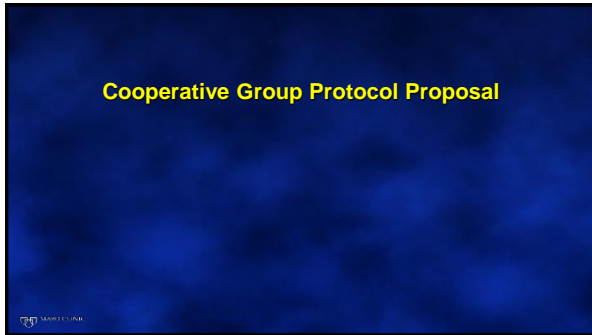
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Factors that discourage the use of Cryo-compression therapy

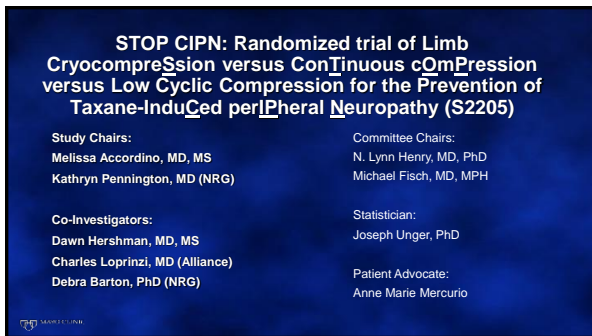
- The rare reports of frostbite with this approach
- Patient discomfort with cryotherapy
- Logistical difficulties with providing this therapy (for patients, families, and nursing staff)
- The lack of definitive proof that this approach decreases CIPN



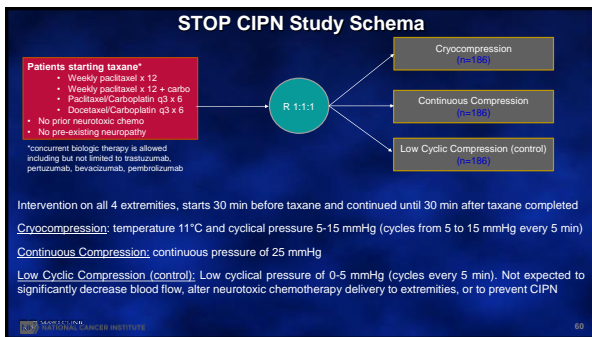
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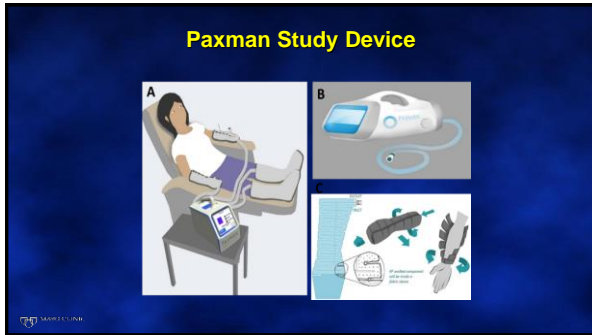
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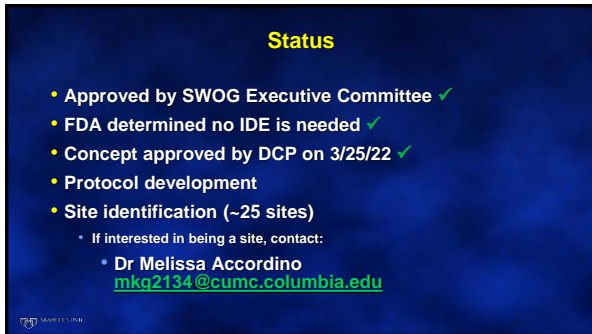
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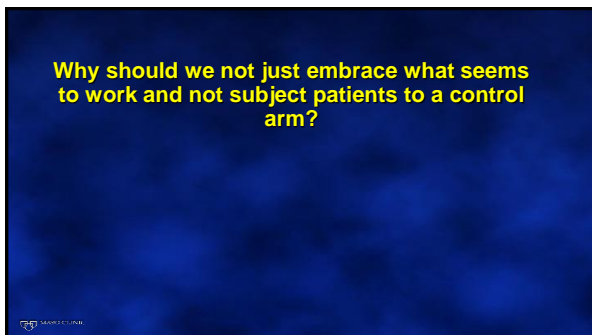
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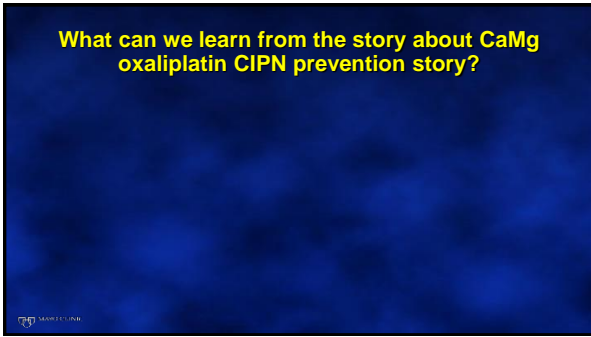
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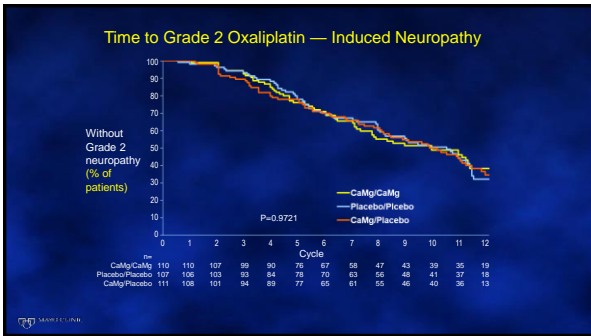
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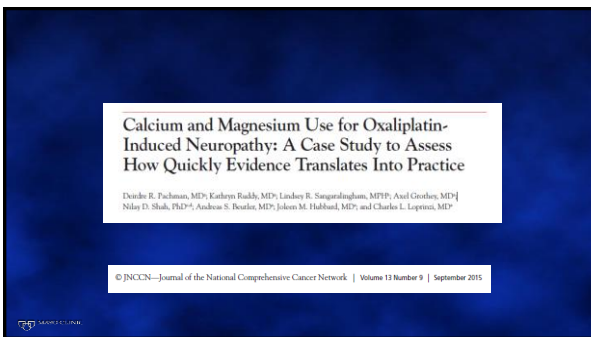
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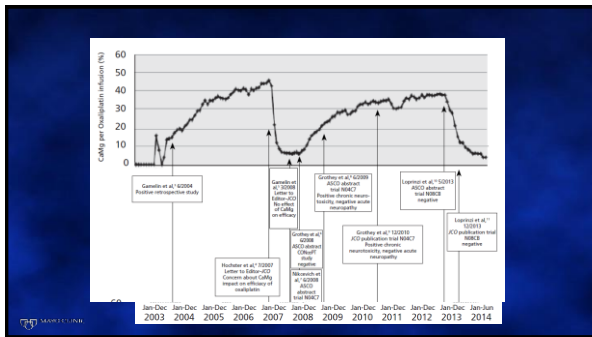
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65



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67

This supports proving that a therapeutic intervention really works, prior to widely endorsing it

68

- Conclusions**
- CIPN is a big problem
 - Nothing has been proven to prevent, other than holding neurotoxic chemotherapy
 - Cryotherapy has been shown to work for
 - Alopecia prevention
 - Bolus dose 5FU mucositis prevention
 - Onychomycosis prevention
 - Cryotherapy looks promising for preventing CIPN

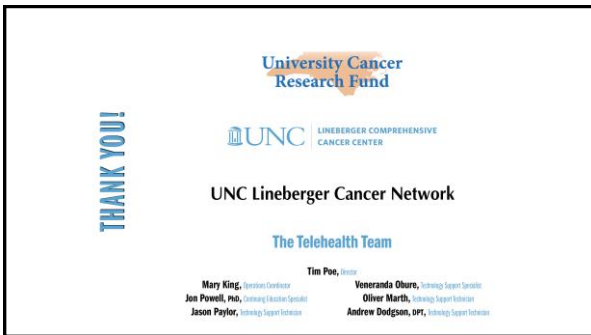
69



70



71



72

UPCOMING LIVE WEBINARS

<p>ADVANCED PRACTICE PROVIDER</p> <p>April 20 4:00 PM</p> <p>Cancer Survivorship Care in Primary Care Helen Tackitt, MD</p>	<p>RESEARCH TO PRACTICE</p> <p>April 27 12:00 PM</p> <p>Advances in Peri-Operative Therapy in Bladder and Kidney Cancer Tracy L. Rose, MD, MPH</p>
<p>SIXTH EDITION AMERICAN INDIAN CANCER CENTER QUALITY PROFESSIONAL</p> <p>May 4 12:00 PM</p> <p>Indigenous Intergenerational Intervention to Address Cancer Among Washington State Tribes Myra Parker, PhD, JD, MPH Craig Dee, MPH(Ed)</p>	<p>PATIENT CENTERED CARE</p> <p>May 11 12:00 PM</p> <p>The Vital Role of Primary Care Providers in Breast Cancer Survivorship Care Allison Beam, MPA, Ph.D.</p>

Complete details on upcoming LIVE webinars:
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73

SELF-PACED, ONLINE COURSES

<p>ADVANCED PRACTICE PROVIDER</p> <p>Psycho-Oncology: Supporting the Mental Health of Oncology Patients Melissa Holt, DNP, PMHNP-BC, MSW</p>	<p>SIXTH EDITION AMERICAN INDIAN CANCER CENTER QUALITY PROFESSIONAL</p> <p>Bridging the Bench and Bedside: The Amalgam of Academic Medicine and Its Effect on a Cancer Patient Experience Hannah E. Woriox, MD</p>
<p>ADVANCED PRACTICE PROVIDER</p> <p>Cardiotoxicity of Cancer Therapies: A Review for the Oncology Provider Brian Colwell Jensen, MD</p>	

Today's webinar will be available in June 2022 as a FREE, Self-Paced, Online Course. Complete details on Self-Paced Online Courses:
learn.unclcn.org/spec

74

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75
