Executive Summary
National Cancer Institute Symptom Management and Health-related Quality of Life Steering Committee Clinical Trial Planning Meeting

Chemotherapy Induced Peripheral Neuropathy: Developing Novel Trials Informed by Translational Science
March 1, 2017

Meeting Co-chairs: Susan Dorsey, PhD, RN, FAAN and Michelle Janelsins, PhD, MPH

Meeting Description

The National Cancer Institute (NCI) Symptom Management and Health-related Quality of Life Steering Committee (SxQoL SC) convened a Clinical Trial Planning Meeting on Chemotherapy Induced Peripheral Neuropathy: Developing Novel Trials Informed by Translational Science on March 1, 2017 in Rockville, MD. The primary goal of the meeting was to develop recommendations for one or more clinical trial(s) in chemotherapy induced peripheral neuropathy (CIPN) with an emphasis on utilizing informative biomarkers that will advance our knowledge of its underlying mechanisms. The meeting also focused on the "Lessons Learned" in conducting CIPN research by clinical and translational researchers and NCI Community Oncology Research Program (NCORP) Investigators. The meeting convened clinical and translational science researchers to identify research that is ready to translate from the bench to bedside. In addition, the meeting attendees included SxQoL SC members, behavioral scientists, biostatisticians, patient advocates, and subject matter experts in the clinical management of CIPN , clinical trial design and NCI staff.

Background: What is CIPN, who is affected by it and how is it currently treated?

An estimated 30 to 40 percent of cancer patients treated with chemotherapy experience symptoms of CIPN.

Several important features include:

- The symptoms may vary depending on the inciting agent and may include sensory as well as motor dysfunction.
- The symptoms usually start in the hands and/or feet and spread proximally to affect both lower and upper extremities in a characteristic "glove and stocking" distribution. Patients will report a variety of sensations, including tingling, numbness, shooting pain, burning sensations, sharp, stabbing pain, sensitivity to temperature, or some combination of these sensations.
- CIPN can cause loss of functional abilities, making it difficult to perform normal day-to-day tasks like buttoning a shirt, sorting coins in a purse, or walking.
- CIPN is one of the most common reasons that cancer patients stop their treatment early.

For some people, the symptoms can be mitigated by lowering the dose of chemotherapy or temporarily stopping it, which diminishes the pain within a few weeks. But, for other patients, the symptoms last beyond their chemotherapy for months, years, or even indefinitely. Due to dose reduction or temporary dose cessation, many patients do not report or underreport CIPN symptoms so that they can continue life-saving or life-preserving therapy.

Unfortunately, currently we cannot predict who will suffer from CIPN or to what degree they will be affected. Lacking specific therapies and predictive toxicity biomarker(s) for CIPN, current practice has been to use approaches for similar types of nerve pain as listed below. It is important to note that these therapies have not demonstrated true efficacy for CIPN, and virtually all of the drugs to treat peripheral neuropathy carry side effects of their own.

- physical therapy
- complementary therapies such as massage and acupuncture
- medications that can include steroids, antidepressants, anti-epileptic drugs, and opioids for severe pain

Meeting Highlights

There were a series of scientific CIPN presentations that progressed from preclinical studies and animal models to presentations on recent findings in studies with patients.

- Paclitaxel reduces axonal Bclw to initiate IP3R1-dependent axon degeneration (Rosalind Segal)
- Targeting sphingosine 1-phosphate receptor 1 to block and reverse CIPN - insight from preclinical animal models (Daniela Salvemini)
- Targeting cannabinoid receptors and endogenous analgesic systems to suppress chemotherapy-induced neuropathic pain in preclinical models (Andrea Hohmann)
- Mechanisms of axon degeneration in CIPN and therapeutic approaches in animal models (Ahmet Hoke)
- Genetics of CIPN susceptibility and next steps regarding replication and validation studies of prior GWAS findings (Howard McLeod)
- Effects of exercise on CIPN and the role of the brain in CIPN: Evidence from human studies (Ian Kleckner)

The scientific presentations were followed by a panel comprised of clinical experts that discussed the potential clinical trial opportunities based on the presentations and considered the appropriateness/readiness of the pre-clinical findings for clinical research.

The scientific presentations and clinical panel discussions were followed by two, 2 hour breakout groups focused on either CIPN intervention trials or a CIPN longitudinal study. The breakout groups reported back to the meeting participants and the group discussed possible next steps for conducting critical translational trials in CIPN. The consensus from the group was that research in the form of a large longitudinal study to identify trajectories and mechanisms of CIPN as well as intervention research to identify therapies to prevent CIPN or treat CIPN are needed.

Next Steps

Working groups will be convened following the CTPM to develop clinical trial concepts (interventional approaches) or study designs (longitudinal study).

Three WGs will develop concepts focused on the following interventions:

- Duloxetine to prevent CIPN
- S1PR1-targeted agents as CIPN therapeutics
- Exercise interventions for CIPN

Clinical Trials Planning Meeting on Chemotherapy Induced Peripheral Neuropathy: Developing Novel Trials Informed by Translational Science

March 1, 2017
Shady Grove/NCI in Room TE406

7:30	**Registration**	
8:00-8:15	**Introductions and Opening Remarks: Overall Goal of the Meeting and Developing Study Design Proposals**	Susan Dorsey and Michelle Janelsins CTPM Co-Chairs Debra Barton and Karen Mustian SxQoL SC Co-Chairs
8:15-8:45	**NCI: Programmatic Overview of CIPN Portfolio**	Ann O'Mara DCP/NCI Diane St. Germain DCP/NCI
8:45-10:00	**CIPN Research Ideas Potentially Ready for Clinical Research Studies: Biomarkers/Mechanisms and Interventions**	
10 min/ speaker	Paclitaxel reduces axonal Bclw to initiate IP3R1-dependent axon degeneration	Rosalind Segal
	Targeting sphingosine 1-phosphate receptor 1 to block and reverse CIPN - insight from preclinical animal models	Daniela Salvemini
	Targeting cannabinoid receptors and endogenous analgesic systems to suppress chemotherapy-induced neuropathic pain in preclinical models	Andrea Hohmann
	Mechanisms of axon degeneration in CIPN and therapeutic approaches in animal models	Ahmet Hoke
	Genetics of CIPN susceptibility and next steps regarding replication and validation studies of prior GWAS findings	Howard McLeod
	Effects of exercise on CIPN and the role of the brain in CIPN: Evidence from human studies	Ian Kleckner
10:00-10:30	**Break** *(on your own, cafeteria on Terrace Level)*	
10:30-11:45	**Clinical Research Panel Discussion of Ideas and Appropriateness for Conduct of NCORP Clinical Research Studies in CIPN**	Charles Loprinzi, Ellen Lavoie Smith, Supriya Mohile, Dawn Hershman, Judy Paice and Guido Cavaletti
11:45-1:00	**Lunch** *(non-working, on your own, cafeteria on Terrace Level)*	
1:00-2:30	**Concept Development Break-Out Groups** **Longitudinal Studies** **Treatment/Intervention Trials**	 Facilitators: Dorsey, Barton, and NCI Facilitators: Janelsins, Mustian and NCI
2:30-3:00	**Break**	
3:00-4:00	**Concept Development Break-Out Groups (cont.)**	
4:00-4:30	**Report-outs from the Break-Out Groups**	Susan Dorsey, Michelle Janelsins, Ann O'Mara, Diane St. Germain, Karen Mustian, Debra Barton and Participants
4:30-5:00	**Summary of Proposed Trials/Studies and Next Steps**	Susan Dorsey and Michelle Janelsins
5:00	**Adjourn**	

SXQOL STEERING COMMITTEE CLINICAL TRIALS PLANNING MEETING
CHEMOTHERAPY INDUCED PERIPHERAL NEUROPATHY
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SxQoL Steering Committee Clinical Trials Planning Meeting in Chemotherapy Induced Peripheral Neuropathy: Developing Novel Trials Informed by Translational Science.

NCI Shady Grove
Rockville, Maryland

March 1, 2017

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