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Cryotherapy to Prevent Taxane-induced Sensory Neuropathy of the Hands and Feet

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Protocol Submission Template

Please check the Focus Research Team funding source:

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Statistician: David Hodge

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***FORMAT*: Please limit Sections I-VI to 10 single-spaced pages using one-inch (1") margins, Times New Roman, 12 pt. font size. Protocols not adhering to these guidelines are subject to being returned without review.**

Abstract

DESCRIPTION:

Taxane based chemotherapy forms an integral component of breast cancer treatment in the adjuvant and neoadjuvant settings. Unfortunately, taxane based agents are associated with peripheral neuropathy of the hands and feet, which can result in significant decline in quality of life and also has the potential to affect survival by limiting the dose of paclitaxel received. Several attempts have been made to prevent or limit taxane induced peripheral neuropathy but unfortunately have been unsuccessful. Recently, studies have examined the use of cryotherapy to prevent the development of taxane induced side effects such as skin and fingernail toxicity. Furthermore, there is preliminary evidence to suggest benefit of cryotherapy in minimizing the incidence and severity of peripheral neuropathy. Given the high incidence and severity of taxane-based chemotherapy, this study was designed to assess the efficacy and tolerability of cryotherapy in the form of frozen mittens and foot wraps. Both subjective and objective outcome measures will be assessed. If cryotherapy in our study is found to be effective in reducing the incidence of peripheral neuropathy, it has the potential to transform supportive care in oncology allowing patients to complete the desired dose intensity of chemotherapy improving the survival outcomes as well as minimizing the risk of debilitating side effects that can compromise quality of life.

Research Plan

I. Specific Aims

We plan to investigate the efficacy and tolerability of cryotherapy (Elasto Gel® frozen mittens and foot wraps) and to evaluate whether they can prevent or ameliorate taxane-induced sensory peripheral neuropathy. The hypothesis of our pilot study is that patients receiving cryotherapy during infusion of taxane therapy will have lower incidence of peripheral neuropathy, better physical function, and higher quality of life as compared to patients previously reported in literature.

II. Background and Significance

Chemotherapy induced peripheral neuropathy (CIPN) occurs in approximately 25-35% of patients treated with chemotherapy, most notably with taxanes.(1) Taxanes are a standard chemotherapy option for treatment of breast cancer (NCCN, 2018). Peripheral neuropathy (PN) is a dose limiting toxicity of taxane-based chemotherapy. While mild neuropathy tends to improve after completion of chemotherapy, many patients, especially those with moderate to severe CIPN, can have prolonged symptoms causing pain and limiting function including vocation. This can last months to years or even become a permanent long-term consequence of the chemotherapy significantly affecting their QOL. Additionally, the presence of CIPN can lead to chemotherapy interruptions, delays or dose reductions that may negatively affect the outcome of their cancer.

At this time there are no effective preventative strategies for taxane induced PN(2,3). Several measures including amifostine, minocycline, and recombinant human leukemia inhibitory factor and acetyl-l-carnitine(4-6) have been evaluated to prevent or limit taxane induced PN without much success.

It is well known that the therapeutic regional hypothermia (cryotherapy) is helpful to prevent or decrease chemotherapy induced (Doxorubicin and taxane based) alopecia(7,8), chemotherapy induced (5-FU based) mucositis(9), and chemotherapy induced onycholysis(10,11). Hypothermia to the peripheral nerves is thought to inhibit uptake of the chemotherapy into the neurons, thereby preventing neuropathy(12). A recent study from Japan reported in the Journal of the National Cancer Institute(12) prospectively evaluated the use of cryotherapy to prevent CIPN from weekly paclitaxel regimen. Among the 36 evaluable patients who wore frozen gloves and socks on the dominant side (non-dominant side serving as control), the incidence of objective and subjective CIPN was clinically and statistically significantly lower on the intervention side than on the control side.

Elasto Gel® frozen mittens and footwraps are a commercially available form of cryotherapy that can be purchased at online retailers at low cost. In the last year we have started to routinely recommend the use of prophylactic cryotherapy to our patients during taxane administration and we have observed that our patients who use the gloves and slippers seem to experience significantly less neuropathy than previous patients. If the frozen gloves and slippers are indeed effective at preventing taxane induced PN, it would completely transform oncology practice

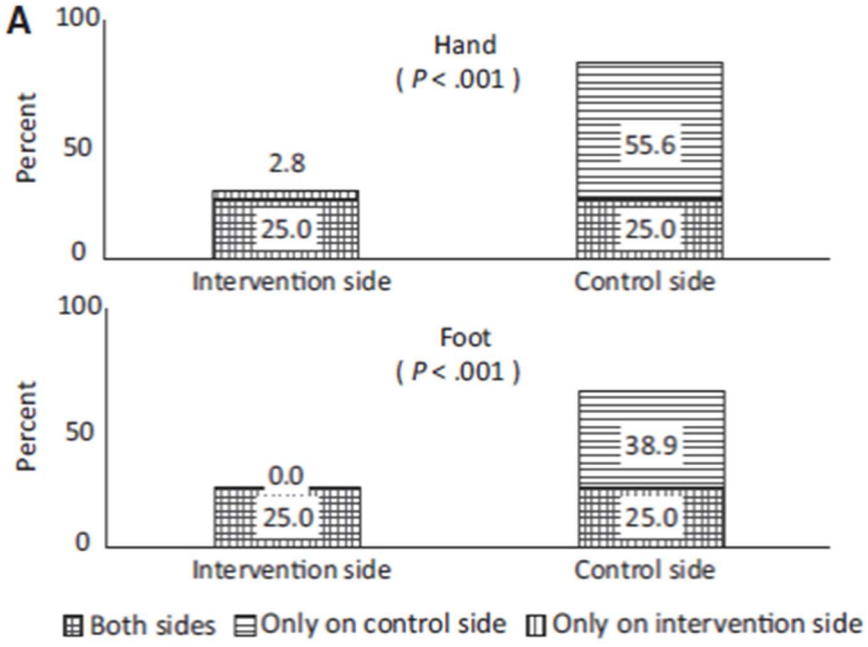
from the current model of treating pain and efforts to minimize functional decline, to one of prevention, allowing patients to resume their usual activities and level of function much quicker than is possible with the limited treatment options for taxane induced PN that are currently available.

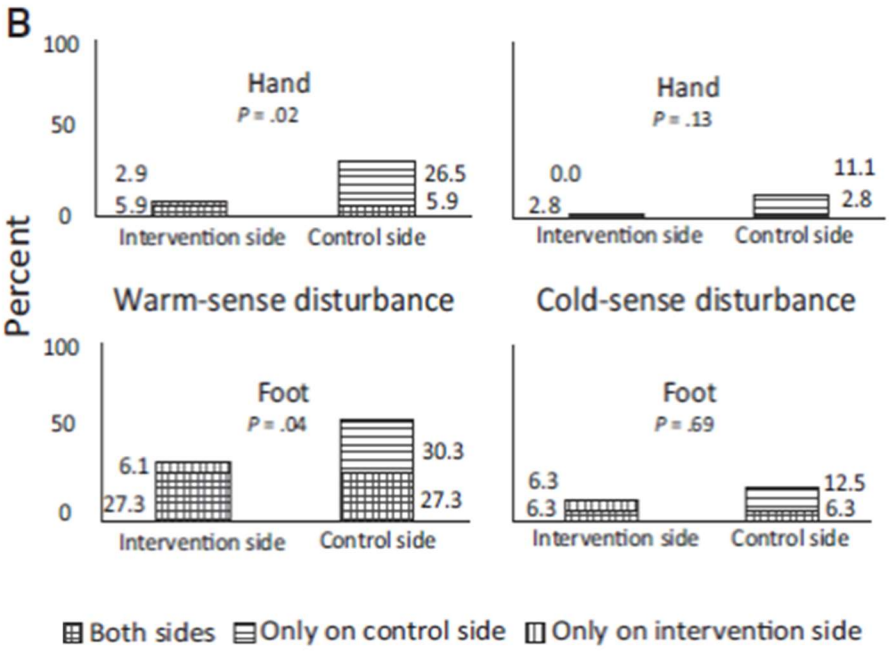
III. Progress Report and Preliminary Studies

The potential utility for frozen gloves/socks worn during paclitaxel infusion to prevent neurotoxicity was recently reported. This study suggested that continuous limb hypothermia at a coolant temperature of 22 degrees Celsius may reduce paclitaxel induced peripheral neuropathy and was noted to be safe and well tolerated in 20 evaluable patients(13).

In a recently reported self-controlled clinical trial, 36 evaluable patients wore frozen flexible gloves and socks on the dominant hand and foot from 15 minutes before paclitaxel administration to 15 minutes after the infusion was completed (12). The non-dominant side acted as the untreated control. The primary end point was the incidence of CIPN (any grade), defined as a decline in tactile sensation from the pretreatment baseline as assessed by the Semmes-Weinstein monofilament test. Secondary outcome measures included physician-rated thermosensory deficits using a thermal stimulator at 3 and 48°C, vibration perception using a 128 Hz tuning fork, performance speed as assessed by a grooved pegboard test, abnormal electrophysiologic signs as assessed by electrophysiologic testing of the median nerve, and current perception thresholds using a neurometer. Subjective symptoms were also assessed using a patient neuropathy questionnaire in which individual items were scored as A (no neuropathy), B (mild neuropathy), C (moderate neuropathy not interfering with activities of daily living [ADL]), D (moderate neuropathy that interferes with ADL), or E (severe neuropathy). Grades D and E were scored as severe neuropathy.

The investigators noted a clinically and statistically significant reduction in patient-reported subjective symptoms, diminished objective signs (tactile and thermosensory-see figure A and B below) and prevention of manipulative dexterity. Significant differences were reported for both objective and subjective signs of CIPN. On the control (nondominant) side, 81 and 64 percent of patients had a decrease in tactile sensation in their hands and feet, respectively, while on the intervention (dominant) side, only 28 and 25 percent were reported to have had a decrease in tactile sensation in their hands and feet, respectively. Subjects reported less severe neuropathy on the intervention side (for the hand, 3 versus 42 percent; for the foot, 3 versus 36 percent), and there were differences in perception of warmth and reaction speed but no differences in vibration threshold or electrophysiological testing between the intervention and control sides.





In further support of the concept that cryotherapy may be helpful, Tsuyuki et al evaluated the effect of wearing 1 size too small surgical gloves (two gloves per hand) on only one hand for 90 mins in 42 patients receiving nanoparticle albumin bound paclitaxel (nabpaclitaxel).(14) The goal was to reduce the flow of blood to the hand during chemotherapy. The investigators reported that surgical glove compression therapy significantly decreased the temperature of each fingertip (measured by thermography) by 1.6 – 2.2°C as compared with the temperature before chemotherapy ($p < 0.0001$). The occurrence of grade 2 or higher sensory and motor peripheral neuropathy was significantly lower for surgical glove protected hands then for control hands (sensory neuropathy 21.4 vs. 76.1 %; motor neuropathy 26.2 vs. 57.1 %) (14)

IV. Research Design and Methods

a. Study Design or Overview – This is a longitudinal quasi-experimental pilot study. Patients will be identified for this study during a standard of care visit with a physician in the Breast Center (medical oncologist) to discuss the patient's treatment plan. This visit could take place pre- surgery to discuss neoadjuvant treatment or post-surgery to discuss adjuvant treatment. If the patient decides to proceed with taxane-based treatment, the physician or study coordinator will discuss this study with the patient and review the consent form. If the patient would like to participate, inclusion criteria will be confirmed and the study consent will be obtained either by the physician or study coordinator.

Prior to the patient's first chemotherapy infusion (this can include the planned chemotherapy education visit which occurs prior to chemotherapy initiation), the study coordinator will complete questionnaires with the patient including the FACT-G Version 4, FACT/GOG-NTX Version 4 and the Chemotherapy Induced Peripheral Neuropathy Rasch-Built Overall Disability Scale (CIPN-R-ODS). Dr. Cindy Tofthagen, a nurse-scientist at Mayo Clinic, Florida, with expertise in understanding both the immediate and long-term effects of CIPN on function and quality of life will conduct sensory testing using Quantitative Sensory Testing (QST) Computer Aided Sensory Evaluation (CASE IV), Von Frey Monofilament Kit, and Testworks Neurological Testing Management Software Version 3.2 (WR Medical Electronics). The study coordinator will conduct the Timed Up and Go test to measure physical function, balance, and fall risk. All data collected will be recorded into the REDCap database by the study coordinator, along with demographics and pre-specified medical history information retrieved from the patient's medical record.

One set each of Elasto Gel® Therapy Mittens and Foot Wraps will be provided to each patient and are expected to be worn on both hands and feet at each chemotherapy infusion during their three months of treatment. Patients will start wearing the mittens and foot wraps 15 minutes prior to each infusion, during the entire infusion, and for 15 minutes after the completion of each infusion. We will have extra frozen mittens and foot-wraps on site to replace the mittens/foot-wraps after the first 30-45 minutes as needed. These extra pairs will be appropriately sterilized after patient use and stored. A research coordinator will record the time that the mittens and foot wraps were

Upon completion of the three months of treatment, patients will return to the Breast Center for an end of intervention visit with their providers. During this standard of care visit, the study coordinator will meet with the patient to complete the study-related questionnaires including the FACT-G Version 4, FACT/GOG-NTX Version 4, and the Chemotherapy Induced Peripheral Neuropathy Rasch-Built Overall Disability Scale (CIPN-R-ODS). Repeat objective testing using Quantitative Sensory Testing (QST) Computer Aided Sensory Evaluation (CASE IV), Von Frey Monofilament Kit, and Testworks Neurological Testing Management Software Version 3.2 (WR Medical Electronics) will be conducted at this point. The study coordinator will conduct the Timed Up and Go test to measure physical function, balance, and fall risk. All data collected will be recorded into the REDCap database by the study coordinator.

The end of study visit will occur approximately three months (+/- one month) after the last chemotherapy infusion during a standard of care appointment in the Breast Center. During this standard of care visit, the study coordinator will meet with the patient to complete the study- related questionnaires including the FACT-G Version 4, FACT/GOG-NTX Version 4, and the Chemotherapy Induced Peripheral Neuropathy Rasch-Built Overall Disability Scale (CIPN-R-ODS). Repeat objective testing using Quantitative Sensory Testing (QST) Computer Aided Sensory Evaluation (CASE IV), Von Frey Monofilament Kit, and Testworks Neurological Testing Management Software Version 3.2 (WR Medical Electronics) will be conducted at this point. The study coordinator will conduct the Timed Up and Go test to measure physical function, balance, and fall risk. All data collected will be recorded into the REDCap database by the study coordinator, along with pre-specified medical history information retrieved from the patient's medical record.

The clinical data and outcome measures data entered in the database will then be analyzed by the biostatistician.

	Pre-chemo MD visit	Chemotherapy Education Appointment	End of Chemo MD visit	3 months post-chemo MD visit
Consent	x	x*		
FACT-G questionnaire		x	x	x
FACT/GOG-NTX questionnaire		x	x	x
CIPN-R-ODS		x	x	x
Timed Up and Go Test		x	x	x
Data entry		x	x	x

*If not collected during pre-chemo visit with MD

b. Study Subjects – Adults ages 18 and older with diagnosis of breast cancer undergoing 3 months of taxane based chemotherapy (4 cycles of weekly paclitaxel (1 cycle = 3 week) or docetaxel every 3 weeks x 4-6 cycles)

Inclusion Criteria:

- Patients ≥18 years of age with a diagnosis of breast cancer
- Patients receiving 12-18 weeks of chemotherapy with a taxane-based regimen (4 cycles of weekly x3 paclitaxel or 4-6 cycles of docetaxel every 3 weeks)
- Absence of sensory peripheral neuropathy, skin or nail disorders at the start of treatment
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.
- Ability to complete questionnaires by themselves or with assistance.
- Ability to give signed informed consent

Exclusion Criteria:

- History of prior sensory/motor peripheral neuropathy from any cause

- History of prior Raynaud's phenomenon
- History of cryoglobulinemia
- Active peripheral vascular disease
- Cold intolerance
- Prior exposure to neurotoxic chemotherapy in the last 10 years
- Hand-foot syndrome
- Tumor metastasis in bone, soft tissue, or skin of the hands or feet
- Absence of one or more fingers or toes
- Prior exposure to taxane chemotherapy

c. Sample Size – We will seek to recruit 100 breast cancer patients (with at least 30% being African American/Black, Native American, Asian, and/or Hispanic/Latino patients) to receive cryotherapy with the Elasto-Gel® Therapy Mittens and Foot Wraps as they receive taxane based chemotherapy. One of our exploratory analysis goals is to compare safety and efficacy of cryotherapy between white and non-white patients.

d. Data Collection – We will assess for PN, physical functioning, and quality of life prior to initiation of taxane based therapy (T1), immediately after completion of taxane based chemotherapy (T2), and again at 3 months following completion of therapy (T3).

PN has both subjective and objective components that are equally important outcomes. Monofilament testing will be performed at three time points by a specially trained research coordinator using Quantitative Sensory Testing (QST) Computer Aided Sensory Evaluation (CASE IV), Von Frey Monofilament Kit, and Testworks Neurological Testing Management Software Version 3.2 (WR Medical Electronics). Monofilament testing for touch pressure sensation will be performed using previously established procedures established by Dr. Peter Dyck and colleagues.(15) Monofilament testing will be performed on the dorsal terminal phalanges of the 5 toes and fingers on one side of the body using 9 monofilaments ranging from 0.05 gm (A) to 148.4gm (I). Participants will close their eyes during testing. Two or three practice sessions will be done on the hand or forearm with monofilament E to familiarize the patient with the procedure and appropriate responses. Testing will begin with monofilament E and use a forced choice 2:1 algorithm to assess touch pressure threshold. Ten pairs of computer selected stimulus events (a stimulus and a null stimulus) are given at each level of stimulus required, based upon patient response. During both the stimulus and non-stimulus, the technician will identify periods 1 and 2 verbally without giving any verbal or non-verbal indication of which period contained the stimulus. During the stimulus, the technician will slowly make contact with the skin on the selected site, increasing pressure so that the monofilament bends about 5/6 of its length before withdrawing the monofilament. Null stimulus is done without skin contact. After each pair of stimuli, the participant will be asked to identify whether they felt the touch during 1 or 2 (WR Medical Electronics Testworks 3 user guide). Reliability and validity of this approach, using the CASE IV equipment was demonstrated in a multi-site study that demonstrated significantly different results in healthy age matched controls (n=6) to those of individuals with diabetic polyneuropathy (n=6). High correlations between quantitative sensory testing results and clinician assessment of neuropathy signs and symptoms, as well as nerve conduction provide evidence of validity. Intra and inter-rater reliability were also demonstrated. Testing will be performed on the left hand/foot only unless there are physical problems that necessitate use of the right side instead. Testing will not be performed on broken or exfoliating skin. Testing will not be performed on any patient who is not attentive, sedated, or too ill to cooperate. Vibratory and thermal sensation will not be

evaluated in this study as we are primarily interested in touch pressure sensation as an outcome variable.

We will assess patient reported symptoms of peripheral neuropathy using the FACT-GOG neurotoxicity –scale (FACT-GOG-NTX), plus an 11-item measure neurotoxicity subscale. Scores on the neurotoxicity subscale range from 0-44 with higher scores indicating more severe neuropathy. Evidence of validity was provided by Calhoun and colleagues, who found significant correlations between the FACT/GOG-Ntx and neurological examination evaluating sensory symptoms, pin sensibility, strength, deep tendon reflexes, vibration sensibility, and nerve conduction.(16) Significant differences in scores from chemotherapy naïve individuals and those with known

CIPN demonstrated construct validity. Cronbach's ranged from .78 to .88. Reliability and validity were also demonstrated in 240 patients receiving paclitaxel and carboplatin. Consistent with previous studies, we will define a 3.3–4.4 point change in score as a clinically important change in the 11-item NTX subscale.

Chemotherapy-Induced Peripheral Neuropathy Rasch-built Overall Disability Scale (CIPN-R-ODS) will be used to measure physical functioning related to chemotherapy-induced peripheral neuropathy.(17) It is a 28-item scale that assesses participant's ability to perform specific physical tasks. Possible responses for each task are 0=unable to perform; 1=perform with some difficulty and 2=no difficulty performing. Higher scores indicate better physical functioning. Correlations with the National Cancer Center- Common Toxicity Criteria for sensory neuropathy demonstrate construct validity. Internal consistency reliability was high (0.92) and the test-retest reliability also demonstrated reliability in individuals receiving neurotoxic chemotherapy, including patients with colorectal cancer.

The Timed Up and Go is a well validated measure of physical function, balance, and fall risk that will be used as an objective measure of physical functioning.(18,19) To perform the procedure, a piece of tape is placed on the floor 3 meters away from the chair so that it is easily seen. Participants are prompted to stand up, walk to the line on the floor, turn around and walk back to the chair and sit back down, walking at their regular pace. Participants wear their regular footwear, may use any gait aid that they normally use during ambulation, but may not be assisted by another person. There is no time limit. They may stop and rest (but not sit down) if they need to. Scores under 10 seconds indicate good balance and physical function and low fall risk. A score of greater than 14 seconds indicated a high risk of falls.

The 27 item FACT-G(20) will be used to assess quality of life. It is measure to be used in people with any type of cancer, contains 4 quality of life subscales; physical, emotional, social/family, and functional. Each item is scored from 0 (not at all) to 4 (very much). Higher scores on the FACT-G correspond with better quality of life. The FACT-G was developed for and has been used extensively in cancer research and demonstrates excellent reliability and validity.

Clinical data will be collected from the patient's medical record and this will include age, race, sex, age at diagnosis, breast cancer stage, neoadjuvant/adjuvant setting of chemotherapy administration, baseline medical conditions, karnofsky performance status, patient hand dominance, history of

smoking, history of alcohol use, type of chemotherapy received, dose intensity of chemotherapy, chemotherapy dose reductions/modifications (if any), use of prescription medications at baseline, use of supplements including multivitamins at baseline.

e. Data Handling – All clinical data and outcome data which includes subjective and objective outcome of peripheral neuropathy (as outlined in section IV, part d) will be collected by the data coordinator and inputted into a password secured REDCap database in a de-identified manner. Only research staff designated by the PI will have access to the data. Hardcopy data will be kept in locked filing cabinets within secured department areas. All study data will be entered by a staff member designated by the PI. In order to maintain patient confidentiality and to de-identify study data, patients will be given a study code which will be used on all data collected and entered in the database.

After this data is entered into the REDCap database, the biostatistician will then perform the statistics.

f. Data Analysis – The overall estimate of PN in the group will be estimated with a simple percentage, and 95% confidence intervals will be calculated for that estimate. In additional other measures of symptoms or other parameters will be summarized in the group. Categorical parameters will be estimated using percentages, and continuous measures will be summarized using means, or medians. The decision about which measure to use for the continuous measures will depend on the distribution of the data of interest. Overall the primary aim of the study is to provide preliminary data for a potential larger trial. These measures will be used to estimate the sample size and power for that future trial.

g. Feasibility and Time Frame – We anticipate to recruit 100 patients amongst the four medical oncologists-Dr. Advani, Dr. Chumsri, Dr. Moreno and Dr. Sideras. We see a large volume of patients each year in the breast clinic. In the year 2018, we treated 1,359 breast cancer patients with chemotherapy (in 2019 YTD-617 patients), and majority of these patients receive a taxane based chemotherapy regimen.

h. Strengths – This project helps address a very important side effect of chemotherapy in patients with breast cancer. As survival outcomes of patients improve with advances in (neo)adjuvant therapies, oncologists need to strive towards mitigating chemotherapy related side effects, some of which can be debilitating and impact quality of life.

In this regard, we have partnered with Dr. Cindy Tofthagen who is a nurse-scientist at Mayo Clinic, Florida. Her work has focused on understanding both the immediate and long-term effects of CIPN on function and quality of life, as well as on development and evaluation of non-pharmacologic interventions to alleviate symptoms of CIPN. She also has expertise in development and psychometric evaluation of patient-reported outcomes in CIPN. She secured funding to purchase smart sensation quantitative testing (SQST) equipment to enhance objective measurement of sensory deficits in research conducted at MCF. The monofilament testing we propose will be conducted using some of this equipment. Dr. Tofthagen is also a clinical expert in CIPN. As a faculty member at the University of South Florida, she founded a free multidisciplinary clinic for individuals with CIPN and other forms of neuropathy. She served as

director of that clinic, prior to coming to Mayo Clinic. She has served as an advisor for several neuropathy related organizations including the Neuropathy Association, Foundation for Peripheral Neuropathy, and Neuropathy Support Network. She also serves as the Oncology Nursing Society's lead faculty on their committee to develop evidence-based guidelines for CIPN and has served on that committee since 2009.

The intervention proposed in this study (frozen gloves and mittens) is relatively inexpensive and is easily available for purchase on the internet. If the results of this study are promising, this intervention has the potential for a large impact across several patient population groups including that from lower socio-economic strata.

At the Robert and Monica Jacoby Center for Breast Health in Mayo Clinic Florida, we see a large volume of breast cancer patients each year and the smaller number of patients proposed in this study due to its pilot nature allows for this recruitment in a relatively short period of time.

Taxane-based chemotherapy is also used in several other cancers such as ovarian, lung, bladder, melanoma, prostate, pancreatic and esophageal cancer thereby expanding the use of cryotherapy to prevent neuropathy in these patient population groups as well.

i. Limitations – The relatively small number of patients may limit the statistical significance of the study results. Additionally, this is a non-randomized study and this can affect the interpretation of results in terms of cause and effect relationship establishment and impact internal validity.

Due to the preliminary data reporting the benefit of cryotherapy and more recently frozen mittens and foot wraps, my colleagues and I as medical oncologists have been sharing this empiric information with patients and many of them have opted to proceed with wearing frozen mittens and foot wraps at the time of chemotherapy infusion and reported benefit in protection from neuropathy. Hence, we wanted to perform a non-randomized pilot study first to assess the benefit of this intervention prior to conducting a larger randomized clinical trial which is the overarching goal of our team. Additionally, there is pre-existing data in the literature on incidence of CIPN from taxanes and although not ideal, for this initial pilot study, we can use this data to compare the incidence of CIPN from that reported in literature to patients enrolled in our study.

V. Human Subjects

a. Population – Adults ages 18 and older with diagnosis of breast cancer undergoing 3 months of taxane based chemotherapy (4 cycles of weekly paclitaxel (1 cycle = 3 week); or docetaxel every 3 weeks x 4-6 cycles) will be included in the study.

Special classes of subject, such as fetuses, pregnant women, children, prisoners, institutionalized individuals, or others who are likely to be vulnerable will not be included in the study.

b. Research Materials – Clinical data and subjective and objective outcome measures data (as outlined in section IV, part d) will be collected from each patient. This data will be used specifically for research purposes and stored in a custom-made REDcap database.

c. Recruitment of Subjects – Participants meeting Inclusion/Exclusion criteria will meet with a clinical coordinator to review the study consent form. They will be given ample opportunity to ask any questions they may have and to discuss their potential participation with friends or family members if they so desire.

d. Potential Risks – We do not anticipate any significant physical risk to the patient with cryotherapy intervention as patients will be carefully selected after a thorough review of the inclusion and exclusion criteria. Those with pre-existing conditions that may predispose harm to digits of the hands and feet such as frostbite will be excluded from the study. Additionally, patients will be closely monitored for any side effects from cryotherapy such as painful digits, cold intolerance, frostbite and ulceration of the digits. Those patients that report any of these side effects will be evaluated by the PI with consideration to discontinue the study and initiation of immediate therapy for stated side effect.

e. Benefits – CIPN can be disabling and negatively affect quality of life and survivorship of patients. This study has the potential to directly impact patient care by improving patient outcomes and quality of life during chemotherapy as well in the survivorship phase. Reducing the incidence and severity of CIPN allows avoiding dose reduction, delay or interruption in the chemotherapy schedule that may also negatively affect the oncologic outcome. This pilot study is relatively low risk to the patient and utilizes an inexpensive intervention to help ameliorate the risk of chemotherapy induced neuropathy. We eventually plan on conducting a larger prospective randomized study based on the data generated from this preliminary study. Based on the results of these studies, if cryotherapy is found effective, it will have a huge impact on prevention and improvement in quality of life in patients receiving taxane chemotherapy.

VI. Gender/Minority Mix

All eligible patients will be encouraged to enroll regardless of ethnicity, gender, or race.

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