

Academic and Community Cancer Research United (ACCRU)

Pilot Clinical Trial Evaluating the Utility of Topical Cryotherapy to Decrease Chemotherapy-Induced Peripheral Neuropathy (CIPN) and Paclitaxel-Induced Acute Pain Syndrome (P-APS): A Randomized Controlled Trial

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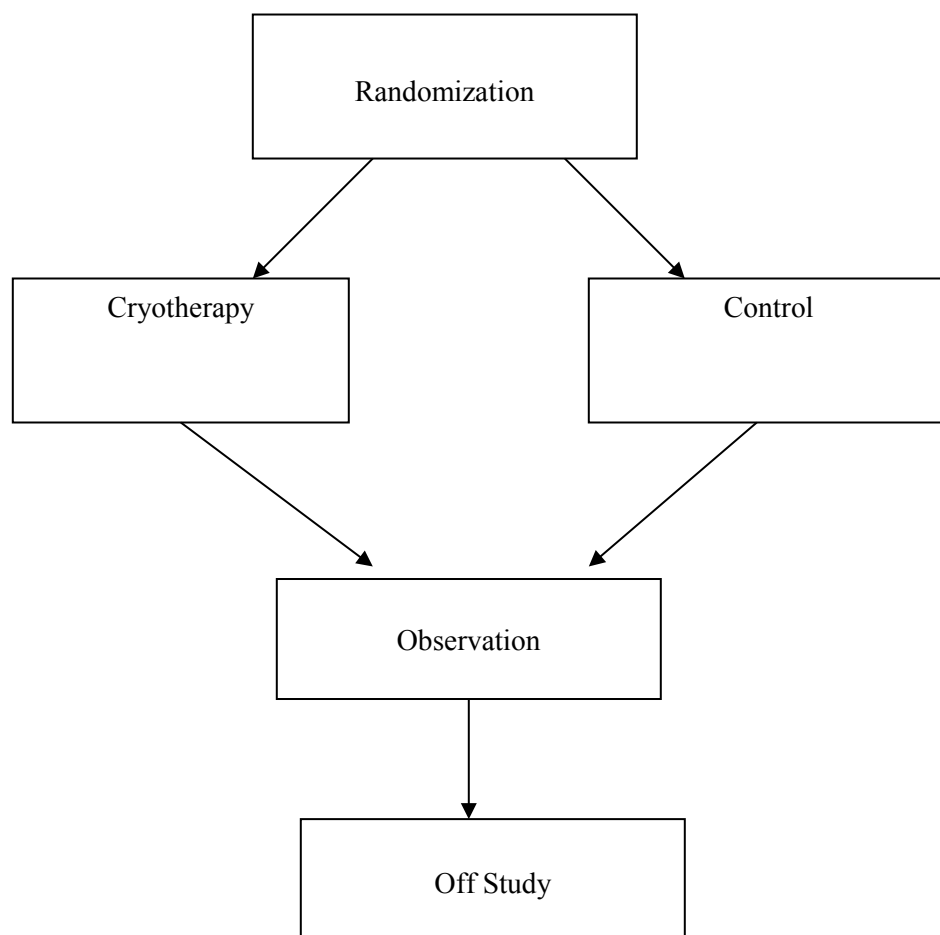
*No waivers of eligibility per ACCRU

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Schema

Treatment cycle length: 7 days during paclitaxel. Propose using this therapy for the 12 weeks of adjuvant paclitaxel.

Observation cycle length: 30 days for 6 months after completion of paclitaxel.

1.0 Background

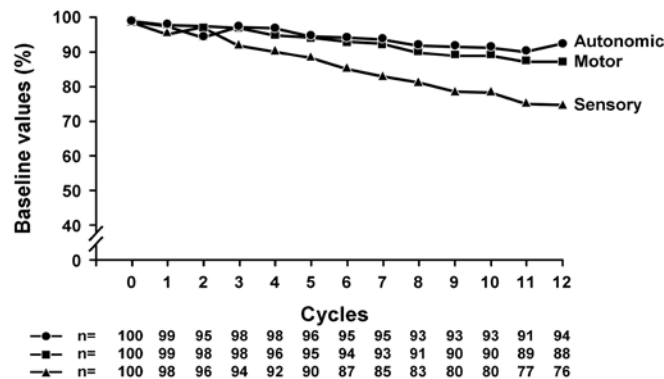
1.1 Paclitaxel causes peripheral numbness, tingling, and pain

It is well appreciated that paclitaxel, one of the more widely used chemotherapeutic agents in oncologic practice, can cause peripheral numbness, tingling and pain, usually starting in the hands and feet. These symptoms often begin in the first several weeks of therapy, become more prominent over time with continued drug use, and tend to improve over time, after paclitaxel is discontinued. It is well accepted that these symptoms are related to nerve pathology and this has been termed chemotherapy-induced peripheral neuropathy (CIPN), which is also caused by other neurotoxic chemotherapy agents.

The EORTC CIPN-20 instrument was utilized in a recent NCCTG natural history trial (N08C1) to obtain paclitaxel-induced peripheral neuropathy data. Two cohorts of patients from this study have been analyzed: a group who received weekly paclitaxel (70-90 mg/m²) without another neurotoxic agent and another group who received higher doses of paclitaxel (i.e. 175 mg/m²) every 3 weeks, concomitantly with carboplatin. The data from the first cohort of patients are provided below; data from the second cohort show similar findings.¹

The EORTC CIPN-20 instrument provides sensory, motor, and autonomic subscales. Figure 1, derived from the weekly paclitaxel cohort, illustrates changes in these scores, over time. Mean decreases from baseline, until the 12th dose of paclitaxel, were 23.4 points for the sensory score, 11.5 points for the motor score and 5.8 points for the autonomic score. To test which type of neuropathy was most problematic, the changes from baseline were tested between each pair of variables. With this, the change in sensory scores was greater than the change in the autonomic scores and the change in the motor scores.²

Figure 1:

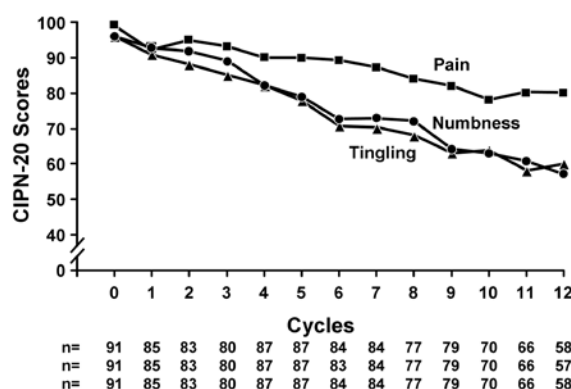


These sensory neuropathy changes were evaluated in more detail in this same cohort by examining data from the following three individual questions, which the EORTC CIPN-20 instrument contains (which are used, with other questions, to determine the sensory neuropathy subscale of this tool):

- Do you have tingling fingers or hands?
- Do you have numbness in your fingers or hands?
- Do you have shooting or burning pain in your fingers or hands?

Figure 2 illustrates that, during the time of paclitaxel therapy, numbness and tingling are very closely related to each other, while pain is less prominent. Three questions, similar to the ones above, are also asked by the EORTC QLQ-CIPN20 instrument, relating to the toes and feet, as opposed to the fingers and hands. Data from the lower extremities closely replicate what is observed in the upper extremities. Data from the cohort of patients receiving higher dose paclitaxel and carboplatin every 3 weeks revealed similar data for both hands and feet.¹

Figure 2:



Data from Hershman et al. reveal that, while neuropathy tends to improve after completion of chemotherapy, about 50% of patients can still have some problematic paclitaxel-induced neurotoxicity a year following drug discontinuation.³

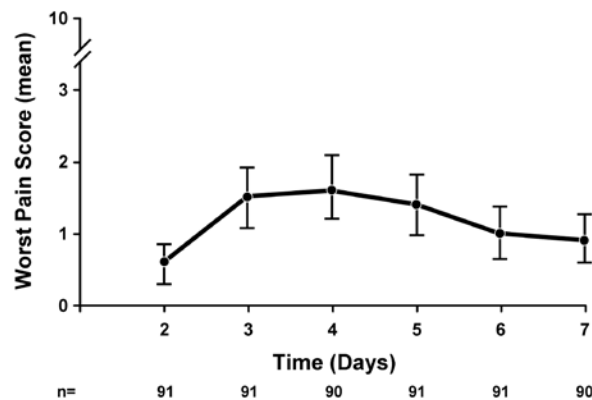
1.2 Paclitaxel acute pain syndrome (P-APS)

Paclitaxel also produces a disabling syndrome of sub-acute aches and pains that had been commonly referred to as arthralgias and myalgias, in a majority of patients.⁴ Until recently, the exact characterization of P-APS had not been well defined. There had been little known about how patients characterize these symptoms or how these symptoms compare to, or contrast with, symptoms of neuropathy. Based on animal data that illustrated that rat dorsal root ganglions had evidence of nerve toxicity 24 hours after they received a clinically appropriate dose of paclitaxel (illustrated by increased expression of ATF-3, a marker of nerve injury), it was hypothesized that this pain syndrome may be from nerve pathology.⁵ Subsequent discussions with patients suffering from this syndrome supported that the pains did not appear to be of joint or muscle origin. To obtain further information, 18 patients at the Mayo Clinic, who noted the presence of sub-acute aches and pains following paclitaxel, participated in structured interviews to characterize their symptoms.⁶ Eighty-three percent of the patients (15/18) specifically denied joint or muscle pain. The pain commonly started 1-2 days after the paclitaxel infusion, with the median duration of pain being 4-5 days. Patients commonly described the discomfort as “aching” or “deep pain” that was “radiating,” “stabbing,” or “shooting.” The pain was usually generalized and located in the back, hips, shoulders, thighs, legs and feet and, at times, radiated down the legs, arms, or back. It was concluded that the sub-acute paclitaxel-induced pain appeared to be likely related to a pathologic process in nerve tissue (e.g. sensitization of nociceptors or nociceptive fibers) as opposed to being from a musculoskeletal injury.

The natural history of the P-APS was further investigated in the above noted prospective natural history study that was also designed to detail the natural history of paclitaxel-induced peripheral neuropathy, including an attempt to define the relationship, if any, that might exist between these two entities. It was hypothesized that a correlation between the degree of P-APS and subsequent neuropathy would support that the P-APS was a form of neurotoxicity. It was felt that a greater understanding of the nature and etiology of the P-APS might provide further insight into ways to potentially alleviate this bothersome toxicity.

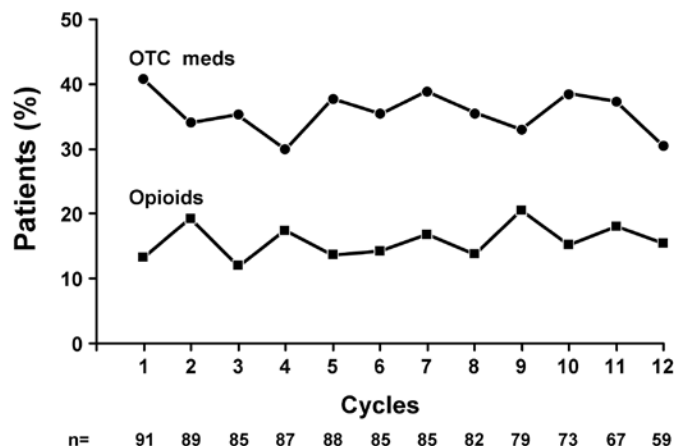
In this study, patients were asked, daily for the first six days after the first dose of paclitaxel, "Please rate any aches/pains that are NEW since your last dose of paclitaxel, and that you think might be related to your chemotherapy treatment by circling ONE number that best describes your aches/pains at its WORST in the last 24 hours." Seventy-one percent of the patients noted pain, ranging from 1-10 on a 0-10 scale. With each subsequent dose of paclitaxel, affirmative answers were seen in 56-69% of respondents. The pain associated with paclitaxel administration peaked on day 4 status post-paclitaxel commencement. Figure 3 illustrates the data from a cohort of patients receiving weekly paclitaxel, at a dose of 70-90mg/m².

Figure 3:



With regards to analgesic use for this problem, non-prescription medications were used, over the 12 weekly cycles of therapy by 30-41% of patients per week, while opioids were used by 12-20% of patients during their weekly cycles of therapy (Figure 4).

Figure 4:



Data from the second cohort of patients, receiving higher paclitaxel doses every 3 weeks, demonstrated similar findings except that the pain was more severe (mean scores P-APS scores of about 4, on a 10-point scale, versus about 1.5, on a 10 point scale, with the lower dose weekly treatments) and patients took more analgesics.¹ At this time, these data, in total, strongly support that it is much more likely that this acute pain syndrome is related to nerve injury as opposed to being related to muscle or joint pathology.

1.3 Prevention/treatment approaches for P-APS and paclitaxel induced peripheral neuropathy

Given that both of these paclitaxel toxicity syndromes appear to be related to nerve pathology, studying agents that treat neuropathic pain makes sense, as a means of trying to prevent and treat both of these problems. The first published randomized, placebo-controlled, double-blinded, cross-over trial published to date, examining a treatment to prevent the P-APS, was done by our group, evaluating glutamine.⁷ More recently, we published the results of a placebo-controlled, pilot trial, evaluating the utility of pregabalin for P-APS and paclitaxel-induced peripheral neuropathy. Unfortunately, the results did not support further evaluation of this approach.

1.4 Topical Cryotherapy for preventing CIPN

A relatively recent review article, titled: Supportive Cryotherapy: A Review from Head to Toe, details the history of cryotherapy as a part of the management of patients with cancer (Kadakia et al., 2014). Cryotherapy was initially reported to be helpful for decreasing Adriamycin-induced alopecia, with initial studies dating back to the 1970s. There has been a recent resurgence of this approach with newer methods of providing scalp cryotherapy. Oral cryotherapy was first reported to be helpful for preventing 5-fluorouracil induced mucositis in 1991, in a manuscript published by the NCCTG and now is recommended for clinical use, by MASCC mucositis guidelines, following multiple confirmatory trials. Cryotherapy has also been reported to be beneficial for decreasing 5-fluorouracil-induced

ocular toxicity. Additionally, it has been shown to decrease chemotherapy-induced onycholysis (Matsumoto 2009).

There are several sources of information that support that cryotherapy can decrease paclitaxel-induced neuropathy. I (CLL) initially heard about cryotherapy potentially being helpful for preventing paclitaxel-associated neuropathy in about 2011, when [REDACTED] mentioned it to me. I was aware of it being helpful for preventing docetaxel-associated nail toxicity, but not neuropathy.

In September 2012, I saw a communication from [REDACTED] who wrote the following:

"I saw a 36 yr old female with T3N0 triple-negative left breast cancer last week. Her lumpectomy specimen after 6 cycles of TAC chemotherapy showed complete sterilization of disease. She will now be starting radiation by me. Her major problem is severe numbness and tingling of fingers and toes. I have searched Pubmed and found no reliable treatment options for CIPN.

My daughter was diagnosed with triple-negative breast cancer in October 2010 at age 31 and also had a complete pathologic response after TAC. During the hour long infusion of Taxol every 21 days, she kept her fingers and toes in ice water slush to ensure vascular constriction around peripheral nerve endings during first pass of Taxol. She never experienced any hint of neuropathy and at present has no numbness or tingling, patiently awaiting the birth of her first child later this month. Since Finger/Toe cryotherapy during taxane infusion has become standard at my cancer center, we have seen no more Grade 2 or 3 taxane-induced neuropathy. Prevention is the way to go."

Follow-up discussions in 2015 revealed that [REDACTED] continues to use topical cryotherapy in his practice and remains impressed with its benefit.

In 2012, a protocol was underway at Northwestern University try to study this issue, using a frozen glove product, but there was notation that the study was a challenge. Part of the challenge was related to the gloves being labor intensive and having to change gloves midway through the chemotherapy treatment. Results of this trial have not become available.

To the best of my recollection, a Canadian group was also trying to study this issue a few years ago. Again, no report has become available regarding this effort.

In 2013/2014, I had a patient who had previously received paclitaxel and had developed marked fingernail toxicity along with some peripheral neuropathy. A few years later, when I saw her again, she had developed another primary breast cancer. Her neuropathy had resolved along with her fingernail problems. This time, to prevent nail toxicity, we had her keep her fingers and toes in an ice slush bath during her paclitaxel therapy. With this, she did not develop anything nail toxicity and she also did not develop any recurrent neuropathy.

In April 2015, [REDACTED] a dermatologist now at [REDACTED] contacted me with the following e-mail message:

“The reason that I am emailing you is because I have been having patients placing ice packs on hands and feet during taxane therapy...which has resulted of course in few if any cases of grade 2 changes BUT they are also reporting NO neuropathy, as you showed with ice chips for 5FU mucositis.”

After I asked him to provide more detail regarding how they provided the cryotherapy, because I thought this was worth studying further, I received the following message:

“I was at the breast center today, and what they use (we tried the gel gloves but logistically not feasible, too much time, space were needed) is just small biohazard bags and ice from the ice machines patients use. We could standardize the size of the bags, and patients to hold them 15 before, during, and 15 min after.

Pretty much every patient here is being given the ice bags, and anecdotally, no nail changes (as reported by Scotte JCO 2005) and minimal to no neuropathy. Patients that are receiving taxanes for a second time as for recurrent disease are emphatic about the absence of neuropathy.”

Additionally, a retrospective report, regarding docetaxel-induced peripheral neuropathy among 1725 Danish breast cancer patients, noted that patients who used frozen gloves and socks (40% of the patients) during treatment had a 44% reduction in subsequent neuropathy problems ($P < 0.0001$) (Eckhoff et al., 2013).

When I presented this concept proposal at the 2015 Spring Alliance meeting, three physicians claimed to be using topical cryotherapy practice (out of about 20 physicians present). Afterwards, I spoke with [REDACTED] who noted that they have an ongoing phase II clinical trial (no control arm). There was a patient advocacy group who was a strong proponent of this approach, not allowing her to have a control group. As of May 2015, they had enrolled 33 of 39 planned patients. 16 patients had completed the trial. To this date, 3 patients had experienced grade 1 neuropathy and 1 patient grade 2. The patients with grade 1 neuropathy only reported paresthesias in their feet. The patient who experienced grade 2 neuropathy did have a history of pre-existing neurologic disease which may have contributed to her symptoms.

As far as proposing a mechanism that can explain why cryotherapy might be beneficial, there are data to demonstrate that patients receiving paclitaxel lose epithelial nerve fibers (Ko et al., 2014, Boyette-Davis et al., 2013, and Bennett et al., 2011). Potentially, this is from a local reaction from chemotherapy getting to the distal epithelial nerve fibers. Cryotherapy should cause vasoconstriction and decrease the amount of paclitaxel getting to the distal epithelial nerve fibers, thus resulting in decreased neuropathy.

A potential concern regarding this approach is that paclitaxel has a reported half-life of about five hours (Gianni et al., 1995). Given this, it would seem that decreasing blood flow during the time of chemotherapy administration would not have much effect. However, docetaxel has a terminal half-life of 13.5 hours (Extra et al., 1993), yet cryotherapy has repeatedly been shown to decrease nail toxicity (Kadakia et al., 2014). Additionally, Adriamycin has reported half-life of 30 hours (Benjamin et al., 1977), yet scalp cryotherapy can decrease alopecia, when only given for a couple of hours (Kadakia et al., 2014). In all

three of these situations, it may be that the cryotherapy decreases blood flow to target tissues when there are peak drug concentrations in the plasma, and this decreases the toxicity.

The above data support further evaluation of cryotherapy as a means to prevent paclitaxel-associated neuropathy. Pilot study data are needed prior to connecting a larger phase III, more definitive, trial. The data from this trial will provide an estimate of the amount of potential benefit from this approach.

1.5 Proposed Clinical Trial Design

This trial will be a controlled pilot study of topical cryotherapy versus a control arm. There will not be a double-blinded placebo arm, as it is virtually impossible to try to replicate cryotherapy treatment, in a double blinded manner.

1.6 Treatment duration

We propose using this therapy for the 12 planned weeks of adjuvant paclitaxel.

2.0 Goals

- 2.1 To estimate whether topical cryotherapy can alleviate paclitaxel-induced peripheral neuropathy.
- 2.2 To estimate whether topical cryotherapy can alleviate P-APS.
- 2.3 To examine the possible relative toxicities related to topical cryotherapy in this study situation.

3.0 Patient Eligibility

3.1 Inclusion Criteria

- 3.11 Age \geq 18 years
- 3.12 Ability to complete questionnaires by themselves or with assistance.
- 3.13 Planned paclitaxel at a dose of 80 mg/m² I.V. given, in the adjuvant breast cancer (postoperative or neo-adjuvant) setting, every week for a planned course of 12 weeks without any other concurrent cytotoxic chemotherapy (NOTE: trastuzumab and/or other antibody and/or small molecule treatment is allowed, except for PARP inhibitors), at the entering ACCRU institution.
- 3.14 Life expectancy >6 months
- 3.15 ECOG performance status 0 or 1. (Form is available on the ACCRU web site <https://www.accru.org/acru/forms/NonProtocolSpecificForms/index.html>)
- 3.16 Patient has score of 0 or 1 on the neurotoxicity evaluation, as determined by the healthcare provider (Appendix X).

3.2 Exclusion Criteria

- 3.21 Previous diagnosis of diabetic neuropathy or peripheral neuropathy from any cause.
- 3.22 Diagnosis of fibromyalgia
- 3.23 Any prior exposure to neurotoxic chemotherapy.
- 3.24 History of Raynaud's disease, cryoglobulinemia.

4.0 Test Schedule

Test Schedule					
Tests and procedures		Active Monitoring Phase			
	<u>Baseline ≤ 28 days prior to registration</u>	Day 1	Days 2-7 of paclitaxel cycle	Day 8 Prior to each paclitaxel cycle ²	Observation once every 30 days +/- 5 days following completion of paclitaxel treatment for 6 months
History and exam, performance status	X				
Baseline Pre-Paclitaxel Questionnaire (App. III)	X ⁴				
Daily Post-Paclitaxel Questionnaire (App. IV)			X		
Acute Pain Syndrome Symptom Summary Questionnaire (App.V)				X ²	
EORTC QLQ-CIPN20 Questionnaire (App.VIII)	X ⁴			X ²	X
Monthly Questionnaire (App.VI)					X
Nurse Follow-up Phone Call (App.VII)			X ¹		X
CTCAE neuropathy grading (App. X)	X			X	
Cryotherapy toleration form (App. IX)		X ³			

1. Call patients on day 2 of cycle 1 (or one business day after initiation of cycle 1 paclitaxel) to encourage compliance with questionnaires and answer patient questions. The only documentation necessary is the date of the phone call.
2. To be completed day 1 of each subsequent paclitaxel treatment PRIOR to receiving paclitaxel. For the last cycle of paclitaxel, day 8 will obviously not be the day of the next cycle of paclitaxel.
3. To be completed after treatment by the nurse on day 1 of each paclitaxel cycle if patient is enrolled to cryotherapy arm.
4. This should be done *after* registration, but prior to chemotherapy.

5.0 Stratification Factors:

- 5.1 Age (years): ≤ 50 vs. > 50
- 5.2 History of diabetes: yes vs. no

6.0 Registration/Randomization Procedures

6.1 Registration Procedures

- 6.11 To register a patient, access the ACCRU web page at [REDACTED] click on “Training Page” and enter the registration/randomization application. The registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the Academic and Community Cancer Research United (ACCRU) Registration Office at [REDACTED] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available using the Help button. Prior to initiation of protocol treatment, this process must be completed in its entirety and a ACCRU subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the ACCRU Registration Office [REDACTED]. If the patient was fully registered, the ACCRU Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to “Instructions for Remote Registration” in section “Finding/Displaying Information about A Registered Subject.”

- 6.12 Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office [REDACTED]. If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary.

- 6.13 Prior to accepting the registration/randomization, the registration/randomization application will verify the following:
 - IRB approval at the registering institution
 - Patient eligibility

- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.14 Treatment cannot begin prior to registration and must begin ≤ 28 days after registration.

6.15 Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.16 Treatment on this protocol must commence at an ACCRU institution under the supervision of a health care professional, with plans for all the paclitaxel to be given at this institution

6.17 Patient questionnaire booklet is available on site; copies are not acceptable for this submission.

6.2 Randomization Procedures

6.21 The factors defined in Section 5.0, together with the registering membership, will be used as stratification factors.

6.22 After the patient has been registered into the study, the values of the stratification factors will be recorded, and the patient will be assigned to one of the following treatment groups using the Pocock and Simon dynamic allocation procedure which balances the marginal distributions of the stratification factors between the treatment groups (Pocock & Simon 1975):

- topical cryotherapy
- control

7.0 Protocol Treatment

7.1 Treatment Schedule

Agent	Cycle 1 - 12
Topical cryotherapy	Cryotherapy will be used for 15 minutes prior to each paclitaxel dose, during paclitaxel infusion and for 15 minutes following paclitaxel completion.

7.2 Methods of delivering cryotherapy

Hands

- Fill provided quart bag (with outside pocket/sleeve) 2/3 full of crushed ice.
- Fill another quart bag (no sleeve on this one) 2/3 full of crushed ice.

- Put light cotton mitten on one hand and put the hand in the pocket/sleeve of the one ice bag (use of the mittens is recommended, but optional).
- Place this bag (with the hand in the pocket/sleeve) in another one gallon bag.
- Put the other bag over the hand, inside the gallon bag.
- Put a towel underneath to catch any leakage and then consider putting all on a tray.
- Repeat for the other hand.
- Note that, if an IV is in a hand, then that site should not be covered by a glove or by ice (so that nurses and patients can see the site in the rare case that there is a drug extravasation). The hand can still have the palmar surface on the ice.

Feet

- Fill provided quart bag (with outside pocket/sleeve) 2/3 full of crushed ice.
- Fill a 1-gallon ice bag ½ full of crushed ice.
- Put light cotton ped on one foot (use of the peds is recommended, but optional).
- Put one foot into the sleeve and then on the bottom of an 11 x 13 x 6 inch plastic container.
- Put the second ice bag over the foot.
- Repeat for the other foot.
- Can use both feet in one container or use individual containers for each foot.
- An alternative is to use a 1-gallon ice bag ½ full of crushed ice (instead of the pocket bag), put this bag in the container, place a foot on it and put another ice bag over the top of the foot.

General

- Make sure that ice is replenished if it melts.
- If the treatment gets too cold, the patient can temporarily remove extremity from part or all of the ice contact, understanding that the goal is to keep the extremities as cold as is possible to decrease blood supply when there are high concentrations of the paclitaxel in the blood.

- 7.3 At clinician's discretion participants will also be recommended a usual regimen of non-opioid analgesic (acetaminophen 500mg every 6 hours as needed) for "breakthrough" pain on the days following chemotherapy (i.e. the paclitaxel acute pain syndrome) with the option of low dose opioid pain medications agents (e.g., oxycodone 5mg every 1-2 hours as needed).

8.0 Treatment Modification Based on Adverse Events

8.1 Cryotherapy

If the patient develops any clinically significant adverse event attributed to topical cryotherapy it should be temporarily or permanently stopped, per nurse/physician discretion. Temporary cessation can consist of having a patient withdraw fingers/feet from the ice and put them back in the cryotherapy as tolerated. The patient should continue to be followed according to protocol criteria; this includes completing questionnaires.

9.0 Ancillary Treatment/Supportive Care

- 9.1 Other treatment as necessary for the control of chemotherapy related symptoms is allowed, with the exception of therapy for prevention of paclitaxel-associated acute pain syndrome and/or prevention of paclitaxel-induced peripheral neuropathy (noting that treatment of pain can be used, as outlined in section 7.2).

10.0 Adverse Event (AE) Reporting and Monitoring

The site principal investigator is responsible for reporting any/all serious adverse events to the sponsor as described within the protocol, regardless of attribution to study agent or treatment procedure.

The sponsor/sponsor-investigator is responsible for notifying FDA and all participating investigators in a written safety report of any of the following:

- Any suspected adverse reaction that is both serious and unexpected.
- Any findings from laboratory animal or *in vitro* testing that suggest a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug.
- Any clinically important increase in the rate of a serious suspected adverse reaction over the rate stated in the protocol or Investigator's Brochure (IB).

Definitions

Adverse Event

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction

Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Expedited Reporting

Events reported to sponsor within 24 hours, 5 days or 10 days of study team becoming aware of the event.

Routine Reporting

Events reported to sponsor via case report forms

Events of Interest

Events that would not typically be considered to meet the criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the review of safety data (may be requested by the FDA or the sponsor).

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site:

(http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

- a. Adverse event monitoring and reporting is a routine part of every clinical trial.

- b. Identify the grade and severity of the event using the CTCAE version 4.0.
- c. Determine whether the event is expected or unexpected (see Section 10.2).
- d. Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).
- e. Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4).
- f. Determine if other reporting is required (see Section 10.5).
- g. Note: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.6 and 18.0).

10.11 Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT).

NOTE: A severe AE, as defined by the above grading scale, is NOT the same as serious AE which is defined in the table in Section 10.4.

10.2 Expected vs. Unexpected Events

Expected events - are those described within the Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), and/or the investigator brochure, (if an investigator brochure is not required, otherwise described in the general investigational plan).

Unexpected adverse events or suspected adverse reactions are those not listed in Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), or in the investigator brochure (or are not listed at the specificity or severity that has been observed); if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan.

Unexpected also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.

Unanticipated Adverse Device Event (UADE)

Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects

10.3 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event *is clearly related* to the agent(s).

Probable - The adverse event *is likely related* to the agent(s).

Possible - The adverse event *may be related* to the agent(s).

Unlikely - The adverse event *is doubtfully related* to the agent(s).

Unrelated - The adverse event *is clearly NOT related* to the agent(s).

Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug and the adverse event.

10.4 Expedited Reporting Requirements for Studies using Commercial Agent(s) ONLY:

Expedited Reporting Requirements for Adverse Events that Occur in a Non-IND/IDE trial within 30 Days of the Last Administration of a Commercial Agent^{1,2}

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

- 1) Death
- 2) A life-threatening adverse event
- 3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
- 4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- 5) A congenital anomaly/birth defect.
- 6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the sponsor within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	7 Calendar Days			24-Hour 3 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		7 Calendar Days	

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

¹Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

² For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

Follow site-specific reporting guidelines.

Commercial agent expedited reports must be submitted to the FDA via MedWatch.3500A
<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf>

or

<http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/ListFormsAlphabetically/default.htm>

Instructions for completing the MedWatch 3500A:

<http://www.fda.gov/downloads/Safety/MedWatch/HowToReport/DownloadForms/UCM387002.pdf>

Submit copies to the ACCRU SAE Coordinator via fax [REDACTED] The ACCRU SAE Coordinator will forward to (insert sponsor name).

The ACCRU SAE Coordinator will forward to [REDACTED] *as appropriate*.
 The ACCRU IND Coordinator will assist the sponsor-investigator in notifying the FDA *if required*.

NOTE: The Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form is not being used for this study.

10.5 Other Required Reporting

- 10.51 Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per the CTCAE v4.0 grading unless otherwise stated in the table below:

System Organ Class (SOC)	Adverse event/Symptoms	Baseline	Each evaluation
None			

- 10.52 Submit via appropriate Academic and Community Cancer Research United (ACCRU) Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.5:

10.521 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.522 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.523 Grade 5 AEs (Deaths)

10.5231 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.5232 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

11.0 Treatment Evaluation Using RECIST Guideline: None**12.0 Descriptive Factors: None****13.0 Treatment/Follow-up Decision at Evaluation of Patient**

- 13.1 A patient is deemed *ineligible* if at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. *The patient will go directly off of the study.*
- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted
 - If the patient never received treatment, on-study material must be submitted.
- 13.2 A patient is deemed a *major violation* if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered.
- 13.3 A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted.
- 13.4 If the patient starts any additional neurotoxic chemotherapy, or changes to a different paclitaxel treatment regimen, the patient should be taken off study. All protocol procedures should be stopped.
- 13.5 If the patient stops topical cryotherapy but continues paclitaxel, the patient should continue to fill out weekly questionnaires on-study as long as the patient is on the paclitaxel.
- 13.6 At the end of paclitaxel chemotherapy treatment, the patient will continue to be followed on study as part of the observation phase. Monthly questionnaires will be completed for 6 months from the completion of paclitaxel treatment.
- 13.7 If the paclitaxel dose is delayed, missed, or skipped the patient should continue to fill out weekly questionnaires.

14.0 Body Fluid Biospecimens: None**15.0 Drug Information: N/A****15.1 Nursing Guidelines:**

Educate the patient regarding the cryotherapy procedure.

If a patient's hand(s) or foot/feet become painful while receiving cryotherapy, then examine them to make sure that color is good. If there is concern about frostbite or pain, then you can remove part (e.g., top bag) or all of the ice, temporarily or permanently, as clinically indicated.

16.0 Statistical Considerations and Methodology

16.1 Study Design

This study is a prospective, randomized pilot study comparing topical cryotherapy to control in patients receiving paclitaxel given every week for a planned course of 12 weeks. The purpose of this pilot is to estimate the treatment effects of topical cryotherapy and control arms using patient-reported outcome assessment tools, to provide preliminary efficacy information to warrant a large scale randomized phase III clinical trial. The focus of this pilot study is more on estimation rather than hypothesis testing.

16.2 Statistical Endpoints and Analyses

The primary goals of this trial are to obtain pilot data regarding the possible effect of topical cryotherapy on the prevention of paclitaxel-induced CIPN and the P-APS. An additional goal is to look at the potential toxicities of topical cryotherapy in this study.

We hypothesize that we will not see any differences in the paclitaxel acute pain syndrome results between the two study arms, because these problems are usually more central and would not be expected to be altered with peripheral extremity cryotherapy. This will serve as a good control.

We also hypothesize that differences will occur between the cryotherapy and control groups for peripheral chemotherapy-induced neuropathy symptoms. The primary measurement of this will be with the use of the EORTC CIPN-20 instrument, sensory scale. While we will have little power to detect a small difference between the two study arms, given the small patient numbers in this pilot trial, if the true response is large, there is a high likelihood that we will observe a statistically significant difference (see Section 16.3).

Due to the nature of pilot study, descriptive statistics and statistical plots will be mainly utilized. Statistical hypothesis testings will be used in an exploratory manner and shall be interpreted accordingly. The difference between the topical cryotherapy and control arms will be compared in an exploratory fashion to determine if the difference, if any, is clinically meaningful and important, and worthy of further studies.

Statistical endpoints for goals 2.1, 2.2, and 2.3 will be analyzed in similar manners, where means and 95% CIs will be produced for continuous data for both the topical cryotherapy arm and the control arm. For categorical/discrete data, frequency counts and percentage will be produced. The mean estimates will be compared and differences in frequency distributions noted.

The endpoints for these goals are listed in the following table.

Goal	Endpoint
2.1: To estimate whether topical cryotherapy can alleviate paclitaxel-induced peripheral neuropathy.	<ol style="list-style-type: none"> 1. Subscales of the EORTC CIPN-20 (sensory, motor, and autonomic) (Appendix VIII). 2. Individual items of the EORTC CIPN-20 instrument (Appendix VIII) 3. Maximum of each EORTC CIPN-20 variable. 4. Area under the curve (AUC) of each EORTC CIPN-20 variable. 5. The worst pain scores in the first cycle of therapy (question 1 from Appendix IV and question 2 from Appendix V) and the subsequent neuropathy scores as judged from the daily questions. 6. Individual items from the monthly follow-up questionnaire (Appendix VI).
2.2 To estimate whether topical cryotherapy can alleviate P-APS.	<p>Cycle 1 data:</p> <ol style="list-style-type: none"> 1. Maximum of the worst pain scores (item 1, Appendix IV) over the period from treatment initiation to day 7 (for cycle 1). 2. Maximum of the average pain score (item 3, Appendix IV). 3. Area under the curve (AUC) of worst, average and least pain (items 1-3, Appendix IV). 4. The proportion of patients who use non-prescription pain medications (item 4, Appendix IV). 5. The proportion of patients who use opioids (item 7, Appendix IV). 6. The proportion of patients who report the development of new aches/pains that they attribute to paclitaxel (item 1, Appendix V). 7. The worst pain reported at the end of the week for the overall week (item 2, Appendix V). 8. The proportion of patients who report, at week's end, using non-prescription pain medications (item 3, Appendix V). 9. The proportion of patients who report, at week's end, using opioids (item 6, Appendix V). <p>Cycles 2-12 data: Secondary endpoints for each subsequent cycle will be summarized in a similar fashion to the data from cycle 1.</p>
2.3: To examine the possible relative toxicities related to topical cryotherapy therapy in this study situation.	<ol style="list-style-type: none"> 1. The proportion of patients who report the toxicity as determined by nurses report (Appendix IX), by patient reports (question 11, Appendix V) and by CTCAE reported events.

16.3 Sample Size, Power, Accrual time, and Study Duration (primary endpoint completion time)

Due to the exploratory nature of this pilot study, the sample size of 46 (23 patients per arm) is determined by logistical and financial considerations, rather than based on a formal hypothesis testing of the primary endpoint. However, in terms of the primary endpoint of the CIPN-20 sensory subscale, converted into a 0-100 scale, the following table provides some power analysis for various effect size based on a two-sided two-sample t test at the $\alpha = 0.05$ for a fixed sample size of 46 patients.

Two sample <i>t</i> -test of equal means (equal n's)					
Effect size, $\Delta = \mu_1 - \mu_2 / \sigma$	0.500	0.750	0.850	0.950	1.000
Power (%)	38	70	80	88	91

For example, we will have 80% power to detect an effect size of 0.85 in CIPN-20 sensory score with a sample size of 46 patients.

Based on past experience of patient accrual in previous trials and the frequency of weekly paclitaxel treatment in oncology practice, we estimate an accrual rate of approximately 5 patients per month and thus expect to complete accrual of 46 patients in approximately 10 months.

16.4 Adverse Event stopping rule

The stopping rule specified below is based on the knowledge available at study development. We do note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe events that the study team considers to be at least possibly related to study treatment (i.e., an adverse event with attribute specified as “possible,” “probable,” or “definite”) that satisfy the following:

If there are 10 or more patients on the topical cryotherapy arm and a 50% increase in grade 4 or higher non-hematologic adverse events (compared to the control arm) in the first 20 treated patients; or a 25% increase in grade 4 or higher nonhematologic adverse events on the topical cryotherapy arm compared to the control arm after 20 patients total are accrued.

We note that we will review grade 4 and 5 adverse events deemed “unrelated” or “unlikely to be related” to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

16.5 Study monitoring

The efficacy and toxicity data for this study will be reviewed semiannually by the Mayo Clinic Data Safety Monitoring Board (DSMB). Early termination of accrual will be considered if there is evidence of unacceptable toxicity.

17.0 Pathology Considerations/Tissue Biospecimens: None

18.0 Records and Data Collection Procedures

18.1 Submission Timetables

Initial Material(s)

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)
On-Study	≤2 weeks after registration
End of Active Treatment/Cancel Notification	Submit ≤2 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy
Patient Questionnaire Booklet(Baseline Pre-Paclitaxel Questionnaire, EORTC QLQ-CIPN20) ¹	≤ 28 days after registration – Patient questionnaire booklet must be used; copies are not acceptable for this submission.
Booklet Compliance	≤ 28 days after registration – This form must be completed only if the booklet/s contains absolutely NO patient provided assessment information.
Neurotoxicity Evaluation	≤ 28 days prior to registration
Deviation	Submit only if applicable during <u>all</u> phases of the study (initial, active and observation)

1. Patient questionnaire booklet must be used; copies are not acceptable for this submission.

Test Schedule Material(s)

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)		
	At each evaluation during treatment	At end of treatment	Observation
Nurse/CRA Evaluation	X	X	
Nurse Evaluation of Cryotherapy Tolerance	X		
Nurse/CRA Evaluation/Observation			X ²
Neurotoxicity Evaluation	X		
Other Adverse Event	X		
Patient Questionnaire Booklets: ¹ <ul style="list-style-type: none"> • Daily Post-Paclitaxel Questionnaire • Acute Pain Syndrome Symptom Summary Questionnaire • EORTC QLQ-CIPN20 Questionnaire • Monthly Questionnaire 	X X X		X ² X ²
Booklet Compliance ³	X ³		X ³
End of Active Treatment/Cancel Notification		X	
ADR/AER	At each occurrence (see Section 10.0)		

1. Patient questionnaire booklet **must** be used; copies are not acceptable for this submission.
2. Complete at each evaluation during Observation (see Section 4.0).
3. This form **must** be completed only if the booklet/s contains absolutely **NO** patient provided assessment information.
4. Submit only if applicable.

19.0 Budget

19.1 Each site should review the test schedule (Section 4.0), taking into account local and regional coverage policies, to determine which items are standard of care and which are research at their site. Refer to the payment synopsis for funding provided per accrual for covering study costs, as well as any additional invoiceables that may be allowed.

19.2 Tests to be research funded: N/A

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