IRB Protocol

Randomized Trial of Duloxetine Versus Placebo for the Treatment of Taxane Induced Neuropathy

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Study Purpose and Rationale:

Peripheral neuropathy is a common side effect of several chemotherapeutic agents. In particular, taxanes, a class of chemotherapeutic agents, cause a peripheral sensory neuropathy in up to 50-60% of its recipients, and 20-30% develop moderate to severe acute neuropathy.(1)(2) This neuropathy manifests as a feeling of pain, numbness, and tingling in the extremities and a reduced ability for the extremities to function properly.

Traditionally, this adverse effect of taxane-based drugs is managed by a reduction in exposure to the offending agent. Yet, taxanes are the standard of care for breast, ovarian, and other solid tumors and have been shown to improve survival in these diseases. Thus, the current management of peripheral neuropathy in this setting may lead to suboptimal cancer treatment.

The purpose of this study is to determine what effect duloxetine (Cymbalta) has on peripheral neuropathy attributed to taxane-based chemotherapy. Duloxetine is a dual reuptake inhibitor of both serotonin and norepinephrine. It has been approved by the FDA for diabetic neuropathy, generalized anxiety disorder, major depressive disorder, and urinary incontinence. There have been several double-blinded randomized controlled trials that have shown duloxetine to be both safe and efficacious in treating neuropathy from diabetes mellitus.(3)(4)(5)(6) However, the efficacy of duloxetine has not been studied, as of yet, in neuropathies of other etiologies.

Study Design and Statistical Analysis:

This will be a prospective, randomized, interventional, placebo-controlled, double-blinded, and parallel arm study. At the onset of neuropathy of any gradation (see Appendix A for the National Cancer Institute Common Terminology Criteria for Adverse Events), subjects will be randomized to duloxetine 60 mg orally daily or placebo. This randomization will be stratified by the type of taxol-based regimen being received. The FACT-Taxane 11-item neurotoxicity questionnaire (Appendix B) will be completed by participants at the time of randomization and then subsequently at 12 weeks after randomization. Scores on this questionnaire, which measures the severity of neurotoxicity, will be the primary end-point. Studies have documented the validity of this questionnaire.(7) Additionally, on average the change in score from week 0 to week 12 was a decrease of 7.0 points, with a standard deviation of 9.4.(7) On this scale, a decrease in score is associated with a worsening of symptoms. The distribution of change resembled a normal distribution curve. As such, an unpaired t-test will be used to analyze the data and a sample size of 158 in each arm is sufficient for 80% power testing at a p-value of 0.05 to detect a decrease of 3 points between baseline and follow up at 12 weeks. A change of 3 points has been proposed as the minimal change that is of clinical importance.(7) All eligible randomized patients will be included in the analysis under the intention-to-treat and, assuming 10% loss to follow up, 175 participants will be recruited for each arm.

Secondary outcomes that will be investigated include deviations from planned treatment regimens and toxicities likely attributable to the study drug.

Study Procedure:

The study will involve taking the study medication, duloxetine 60 mg, or placebo daily. At the time of randomization and 12 weeks later, participants will be asked to complete the FACT-taxane 11-item neurotoxicity questionnaire. Participants and clinicians will be blinded to the receipt of experimental drug or placebo. Clinicians will report any toxicity likely or definitely related to the study drug. Additionally, all deviations from planned treatment regimens will be reported. No invasive monitoring will be performed unless clinically indicated.

Study Drugs:

Duloxetine (Cymbalta) is an oral medication approved for use for diabetic neuropathy, generalized anxiety disorder, major depressive disorder, and urinary incontinence. Its effects on peripheral neuropathy from taxane-based drugs has not been studied. However, its efficacy in diabetic neuropathy is its rationale for study. Previously, randomized controlled trials have found duloxetine both safe and efficacious in treating symptomatic diabetic neuropathy.

Standard dosing varies by indication: diabetic neuropathy 60 mg orally once daily; generalized anxiety disorder 60 mg orally once daily; major depressive disorder 20 mg orally twice daily; and urinary incontinence 40 mg orally twice daily. Here, the 60 mg oral once daily dosing for diabetic neuropathy will be used. An Investigational New Drug (IND) approval will be obtained from the FDA for this study.

Serious side effects include hepatotoxicity and suicidal thoughts (4%). Other side effects occurring in >15% include anorexia, nausea, dizziness, and somnolence. Side effects occurring in <15% include palpitations, diaphoresis, constipation, diarrhea, xerostomia, asthenia, insomnia, vertigo, blurry vision, increased frequency of urination, cough, nasopharyngitis, and fatigue. The syndrome of inappropriate antidiuretic hormone secretion has occurred during treatment with duloxetine in volume-depleted elderly or those concurrently on diuretic therapy.

Medical Device: Not applicable

Study Questionnaires:

A copy of the FACT-Taxane 11-item neurotoxicity questionnaire has been included as Appendix B.

Study Subjects:

Inclusion criteria are:

1) women age 18 and over

2) histologically confirmed primary invasive adenocarcinoma of the breast at stage I, IIA, IIB, or IIIA (see Appendix C for staging criteria)

3) completion of primary treatment (modified radical mastectomy or breast sparing surgery plus radiation) and resolution of any side effects

4) receiving one of five standard taxane-based regimens: (a) paclitaxel at 80 mg/m2 weekly x 12 weeks; (b) paclitaxel at 175 mg/m2 every other week x 4 cycles; (c) paclitaxel at 175 mg/m2 every other week x 6 cycles; (d) docetaxel 75

mg/m2 every three weeks x 4 cycles; (e) docetaxel 75mg/m2 every three weeks x 6 cycles

4) adequate renal function (creatinine <2.5 times the upper limits of normal within 30 days of randomization)

5) Zubrod performance status of 0-2 (see Appendix D)

6) English literacy and ability to complete questionnaire

Exclusion criteria are:

1) evidence of metastatic disease
2) prior receipt of taxane-base drug
3) history of diabetes
4) history of neuropathy
5) pregnancy or breast feeding
6) prior malignancy
7) concomitant use of MAOIs
8) concomitant use of diuretics
9) narrow-angle glaucoma

Recruitment of Subjects:

Subjects will be identified by medical oncologists at breast clinics within the Southwest Oncology Group at the onset of peripheral neuropathy while receiving taxane-based chemotherapy. If the patient is willing to discuss the study, the site study administrator will be notified and then approach the patient to solicit her participation in the study. Informed consent will be obtained by the study administrator.

Confidentiality of Study Data:

All patients will be assigned a random, numerical, unique identifier to help safeguard the privacy of their information. If information from this study is published or presented at scientific meetings, names and other personal information will not be used. Only researchers and government agencies such as the Food and Drug Administration or the National Cancer Institute will have access to this information.

Potential Conflict of Interest:

None of the investigators has a proprietary interest in duloxetine.

Location of the Study:

This study will be conducted in the office space of the medical oncology clinics at Columbia Presbyterian Medical Center as well as at other hospital centers affiliated with the Southwest Oncology Group, a regional oncology consortium. Each site will obtain its own IRB approval.

Potential Risks:

Everyone participating in this study will be carefully monitored for any side effects. Common side effects include anorexia, nausea, dizziness, and somnolence. Less likely are diaphoresis, constipation, diarrhea, insomnia, and fatigue. Unlikely are palpitations and blurry vision. Additionally, only half of the participants in the study will

be receiving duloxetine while the other half receive a placebo. The placebo consists of inactive ingredients and no adverse effects are expected.

The risks of duloxetine to an unborn fetus in humans is unknown but animal studies have shown an adverse effect on the fetus. Women should not become pregnant or breastfeed while participating in this study. Contraception should be used while participating in this study. Participants should check with their physician about what methods to use and for how long to use them.

Potential Benefits:

Taking part in this study may or may not improve the health of the participant. While doctors hope that duloxetine will be helpful in reducing neuropathy, there is, as of yet, no proof of this. The information from this study will help doctors learn more about duloxetine as a drug for treatment of neuropathy, which might help future cancer patients who are receiving chemotherapy that causes neuropathy.

Alternative Therapies:

Currently, there are no approved treatments for neuropathy due to taxane-based chemotherapy. Usual care has traditionally included discontinuation of taxane-based drug, decrease of taxane-based drug dose, or changing to another drug. The advantage of changing treatment is that the cause of neuropathy is removed or reduced. The limitation of this approach is that potentially curative treatment is cut short or altered.

Compensation to Subjects:

Participants will not be paid for taking part in this study.

Costs to Subjects:

Participants and/or their health insurance companies will need to pay for some or all of the costs of cancer treatment in this study. Some health insurance companies will not pay these costs for people taking part in studies. Potential participants should check with their specific health insurance provider to determine applicable insurance benefits. Furthermore, taking part in this study may or may not cost more than the cost of usual cancer care. Those organizing and conducting the research will pay for the study drug as well as the cost of maintaining research records.

Minors as Research Subjects: Not applicable

Radiation or Radioactive Substances: Not applicable

Appendix A

National Cancer Institute Common Terminology Criteria 3.0 for Neuropathy

Adverse Event	1	2	3	4	5
Neuropathy: Motor	Asymptomatic, weakness	Symptomatic, weakness interfering with function but not ADLs	Weakness interfering with ADLs, bracing or assistance to walk	Life-threatening	Death
Neuropathy: Sensory	Asymptomatic, loss of deep tendon reflex, not interfering with function	Sensory alteration or parasthesia, interfering with function but no ADLs	Sensory alteration or paresthesia interfering with ADL	Disabling	Death

Appendix B

Functional Assessment of Cancer Therapy-Taxane, Neurotoxicity Component (7)

Concern	Not at All	A Little Bit	Somewhat	Quite a Bit	Very Much
I have numbness or tingling in my hands					
I have numbness or tingling in my feet					
I feel discomfort in my hands					
I feel discomfort in my feet					
I have joint pain or muscle cramps					
I feel weak all over					
I have trouble hearing					
I get a ringing or buzzing in my ears					
I have trouble buttoning buttons					
I have trouble feeling the shape of small objects when they are in my hands					
I have trouble walking					

Appendix C

Staging of Breast Cancer (8)

Primary Tumor (T)

T1	tumor 2 cm or less in greatest dimension
T2	tumor more than 2 cm but not more than 5 cm in greatest dimension
T3	tumor more than 5 cm in greatest dimension

Regional Lymph Nodes (N)

N0	no regional lymph node metastasis
N1	metastasis to movable ipsilateral axillary lymph node(s)
N2	metastasis to ipsilateral axillary lymph nodes fixed to one another or to other structures

Distant Metastasis (M)

M0	No distant metastasis

Stage grouping

STAGE	T	N	M
I	1	0	0
IIA	0	1	0
	1	1	0
	2	0	0
IIB	2	1	0
	3	0	0
IIIA	0	2	0
	1	2	0
	2	2	0
	3	1	0
	3	2	0

Appendix D

Zubrod Performance Status Scale

Point	**Description**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair

References:

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2) Hilkens PH, Verweij J, Stoter G, et al. Peripheral neurotoxicity induced by docetaxel. Neurology 46: 104-108, 1996.
3) Raskin J, Wang F, Pritchett YL, et al. Duloxetine for patients with diabetic peripheral neuropathic pain: a 6-month open-label safety study. Pain Medicine 7(5): 373-385, 2006.
4) Goldstein DJ, Lu Y, Detke MJ, et al. Duloxetine vs. placebo in patients with painful diabetic neuropathy. Pain 116: 109-118, 2005.
5) Raskin J, Pritchett YL, Wang F, et al. A double-blind, randomized multicenter trial comparing duloxetine with placebo in the management of diabetic peripheral neuropathic pain. Pain Medicine 6(5): 347-356, 2005.
6) Wernicke JF, Pritchett YL, D'Souza DN, et al. A randomized controlled trial of duloxetine in diabetic peripheral neuropathic pain. Neurology 67: 1411-1420, 2006.
7) Cella D, Peterman A, Hudgens S, et al. Measuring the side effects of taxane therapy in oncology: the functional assessment of cancer therapy-taxane (FACT-taxane). Cancer 98: 822-831, 2003.
8) Greene FL, et al. AJCC Cancer Staging Manual. 6th edition, 2002.