A221304

A Phase III Placebo-Controlled, Randomized Three-Arm Study of Doxepin and a Topical Rinse in the Treatment of Acute Oral Mucositis Pain in Patients Receiving Radiotherapy With or Without Chemotherapy

ClinicalTrial.gov Identifier: NCT02229539

Study Background

Trial Description

The purpose of this study is to test whether a mouthwash made with a drug called doxepin can reduce the pain caused by mouth sores resulting from radiation therapy. A number of mouth rinse preparations exist for patients with treatment-related oral mucositis pain such as the DLA rinse, an over-the-counter medication. This study will evaluate the effects of doxepin compared to DLA (diphenhydramine, lidocaine and antacids) and placebo. Doxepin is approved by the Food and Drug Administration (FDA) for the treatment of depression, anxiety, long-term pain management, as well as management of rash.

Arms:

Doxepin rinse: (Experimental): Patients receive 2.5 mL (25 mg) doxepin and 2.5 mL water orally, swish and gargle for 1 minute then spit. Doxepin rinse is administered in the clinic on Day 1 (Cycle 1). The patient will remain at the treating location for the first hour and complete the Oral Symptoms booklet at time zero (prior to the oral swish, gargle and spit), and at 5, 15, 30 and 60 minutes post-administration. After completing the booklet at 60 minutes, patients may then leave the clinic and complete the 2- and 4-hour assessments at home. There is an optional continuation phase within seven days following Day 1 (Cycle 1), patients will be encouraged to continue treatment with the study agent for an additional week (Cycle 2) where the patient takes the rinse at home every 4 hours. Chemotherapy is allowed during the continuation phase. Patients randomized to doxepin or placebo, they and their caregivers will continue to be blinded to the treatment. Patients will complete the Oral Symptoms booklet per the protocol.

DLA (diphenhydramine, lidocaine and antacid) rinse: (Active Comparator): Patients receive 5.0 mL DLA orally, swish and gargle for 1 minute then spit. DLA is administered in the clinic on Day 1 (Cycle 1). The patient will remain at the treating location for the first hour and complete the Oral Symptoms booklet at time zero (prior to the oral swish, gargle and spit), and at 5, 15, 30 and 60 minutes post-administration. After completing the booklet at 60 minutes, patients may then leave

the clinic and complete the 2- and 4-hour assessments at home. There is an optional continuation phase within seven days following Day 1 (Cycle 1), patients will be encouraged to continue treatment with the study agent for an additional week (Cycle 2) where the patient takes the rinse at home every 4 hours. Chemotherapy is allowed during the continuation phase. Patients receiving DLA during the continuation phase of the study, they and/or caregivers may be aware that they are receiving DLA. Patients will complete the Oral Symptoms booklet per the protocol.

Placebo rinse: (Placebo Comparator): Patients receive 2.5 mL placebo and 2.5 mL water orally, swish and gargle for 1 minute then spit. The placebo rinse is administered in the clinic on Day 1 (Cycle 1). The patient will remain at the treating location for the first hour and complete the Oral Symptoms booklet at time zero (prior to the oral swish, gargle and spit), and at 5, 15, 30 and 60 minutes post-administration. After completing the booklet at 60 minutes, patients may then leave the clinic and complete the 2- and 4-hour assessments at home. There is an optional continuation phase within seven days following Day 1 (Cycle 1), patients will be encouraged to continue treatment with the study agent for an additional week (Cycle 2) where the patient takes the rinse at home every 4 hours. Chemotherapy is allowed during the continuation phase. Patients randomized to doxepin or placebo, they and their caregivers will continue to be blinded to the treatment. Patients will complete the Oral Symptoms booklet per the protocol.

Objectives:

Patients are stratified according to sex (male vs. female), concurrent use of chemotherapy (no vs. yes), patient age at registration (< 60 years old vs. ≥ 60 years old and RTOG acute radiation morbidity criteria (1 vs. 2 vs 3 or more). Protocol therapy will consist of 2 cycles. Patients are randomized to one of three treatment regimens, which include doxepin, DLA and placebo. Cycle One will consist of one day. The care provider or nurse will confirm that the oral pain is at least 4 out of 10 severity level at the time of the rinse on the first day of the study. If the pain score is less than 4 then administration will be delayed until the pain is at least 4. Patient will be asked to complete the Oral Symptoms booklet at baseline (prior to the oral swish, gargle and spit), and at 5, 15, 30 and 60 minutes post-administration. After completing the booklet at 60 minutes, patients may then leave the clinic and complete the 2- and 4-hour assessments at home. Cycle Two will consist of an optional continuation phase lasting up to 7 days. Initiation of the Cycle 2/Continuation Phase may be delayed up to one week after Cycle 1/Day 1.

Primary Objective:

1. Determine whether the doxepin rinse or DLA rinse is more effective than placebo in reducing OM-related pain in patients undergoing RT to the oral cavity, as measured by a patient-reported questionnaire at baseline, 5 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, and 4 hours.

Secondary Objectives:

1. Assess the adverse event profile of the doxepin rinse, the DLA rinse agent, and the placebo using a patient-reported questionnaire at 5 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, and 4 hours for domains of unpleasant taste, burning or stinging discomfort, and drowsiness.

2. Compare the incidence of using additional analgesics between 1 and 4 hours after the initial mouthwash, between the doxepin oral rinse, the DLA rinse agent, and the placebo arms.

3. Compare the length of time that each study product is used by patients in the one-week continuation phase.

4. Compare the daily pain scores in the one-week continuation phase for the three study arms.

5. Compare the 24-hour morphine equivalent dose used in the continuation phase for the three study arms.

Study Milestones:

Start date: November 2014

Primary Completion Date: May 2016

Publication Information:

Analysis Type: Primary

Pubmed ID: 30990550

Citation: JAMA. 2019 Apr 16;321(15):1481-1490. doi: 10.1001/jama.2019.3504.

Associated Datasets: NCT02229539-D1.csv (Fig1_allptchar), NCT02229539-D2.csv (Anlypt), NCT02229539-D3.csv (c1ctcae), NCT02229539-D4.csv (c2ctcae)

Dataset Information:

Dataset Name: NCT02229539-D1.csv (Fig1_allptchar)

Description: Dataset NCT02229539-D1.csv (Fig1_allptchar) is one of 4 datasets associated with PubMed ID 30990550. This dataset contains information that will allow you to reproduce the Table 1, the baseline characteristics.

NCT02229539-D1.csv (Fig1_allptchar) Data Dictionary:

LABEL	NAME	elements	comments
Patient Reference	PATREF		
Arm	ARM	Doxepin, Placebo, DLA	
Age (years)	AGE		
Race	RACE1	White, Asian, Black or African American, American Indian or Alaska Native, Not reported: patient refused or not available	
Gender	GENDERC	Female, Male	
Concurrent chemotherapy	CHEMUSE	Yes, No	
Mucous membrane score	MMSCORE	3 or more, 2, 1	
ECOG performance status	ECOGPS	1, 0, 2	
Oral pain score at registration	PAIN_SC	10, 6, 7, 8, 5, 4, 9	0-10 scale with 0=No pain; 10= Worst pain imaginable or possible
Baseline: Currently Smoke Cigarettes	c1v0_SMOKE	No, Yes	Missing indicates the data was not collected
Baseline: Drink Alcohol	c1v0_DRINK	No, Yes	Missing indicates the data was not collected
Protocol Treatment Status as Randomized	rcvd_prot_rx	Received protocol treatment as randomized,	

		Did not receive protocol treatment as randomized	
Reason Per-Protocol Treatment Ended or Did not Receive Treatment	offreas_primary	Completed treatment per protocol, Treatment cancelled, Mouth pain score <4 before treatment, Discontinued: Mouth pain score <4 before treatment, Withdrew 2-4 h after treatment, Discontinued: Did not return questionnaire booklet, Ill and admitted to the hospital, Received alternate therapy 2-4 h after treatment, Discontinued: Inadvertent unblinding by study team, Ineligible	
Continuation Phase Treatment Status	cont_phase_status	Available for continuation phase analysis, Discontinued at end of chemotherapy cycle 1	Missing indicates patients were excluded in primary and per-protocol analysis.
Reason Treatment Ended on Continuation Phase	offreas_contphase	Completed continuation phase, Received alternate therapy, Withdrew or dropped out, Adverse events	Missing indicates the patient did not participate in continuation phase
Included in Primary and Per-Protocol Analysis	inclu_primary	Yes, No	
Total Pain AUC (All Randomized Patients)	c1pain_area_itt		Cycle 1 Day 1 Total pain score during the first 4 hours after treatment

			(using the mean score as measured by the area under the curve and adjusted for the baseline pain score) for All Randomized Patients