THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Page

Minocycline for reduction of radiation therapy treatment-related symptom burden in head and neck cancer: a randomized study.
2010-0096

Core Protocol Information

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Full Title:	Minocycline for reduction of radiation therapy treatment-related symptom burden in head and neck cancer: a randomized study.
Public Description:	N/A
Protocol Type:	Standard Protocol
Protocol Phase:	Phase II
Version Status:	Activated -- Closed to new patient entry as of 08/28/2019
Version:	15
Document Status:	Saved as "Final"
Submitted by:	Angele K. Saleeba--8/28/2019 8:51:48 AM
OPR Action:	Accepted by: Melinda E. Gordon -- 8/28/2019 9:47:45 AM

Which Committee will review this protocol?

◉ The Clinical Research Committee - (CRC)

Protocol Body

1.0 Objectives

The primary objective of this protocol is to test the efficacy of **minocycline** in reducing multiple patient-reported symptoms in patients with oropharyngeal cancer, nasopharyngeal cancer, or unknown primary cancer of head and neck treated with definitive radiation therapy.

2.0 Rationale

The study aims to test a symptom-reduction strategy based on underlying symptom mechanisms associated with cancer treatments. Using a blinded, randomized placebo-controlled trial, we will evaluate **minocycline** safety and ability to reduce the symptom burden of oropharyngeal cancer, nasopharyngeal cancer, or unknown primary cancer of head and neck treated with radiation therapy. The significance of this research is that it (a) evaluates a low-toxicity, low-cost symptom therapy, (b) evaluates a therapy which could reduce multiple commonly reported symptoms in oropharyngeal cancer, nasopharyngeal cancer, or unknown primary cancer of head and neck, and (c) seeks to establish simple medical symptom prevention therapy for a disease site and treatment for which the symptom burden is high and few medical symptom prevention strategies exist.
The agent tested in this trial is **minocycline**. The target of action for the proposed intervention is in reduction of proinflammatory cytokines, specifically IL-1, IL-6, and TNF-alpha, likely mediators of multiple symptom expression. **Minocycline** also crosses the blood-brain barrier, possibly reducing inflammation in the central nervous system, potentially reducing multiple symptom expression at the brain level.

3.0 Background

Cancer was diagnosed in more than 1.4 million people in the United States in 2007 alone — 34,360 with head and neck cancer (HNC) (Jemal et al., 2007). Many of these patients received aggressive therapy and experienced multiple symptoms that cause them significant distress and impair function and rehabilitation. Whereas many of these symptoms are the result of disease, it is increasingly recognized that pain, fatigue, sleep disturbance, cognitive dysfunction, and affective symptoms can also be caused by cancer treatment. Treatment-related symptoms can directly affect survival if they become so severe that patients abandon potentially curative therapies (Borden & Parkinson, 1998; Jeremic et al., 2003). Moreover, treatment-related symptoms may persist for weeks, months, or years and may worsen, even if the cancer improves.
There is growing awareness that common biologic mechanisms may cause or contribute to some of these clusters of symptoms at the same time (Barsevick et al., 2006; Dodd et al., 2005; Wang et al., 2006). The theoretical underpinning for the proposed studies, based on the animal model of inflammation-induced sickness behavior, is that dysregulated inflammation and its downstream toxic effects represent a significant biologic basis for subjectively reported clusters of symptoms (Cleeland et al., 2003; Lee et al., 2004). Based on this model, optimal symptomatic control would attack both underlying symptom mechanisms as well as the end effects of these mechanisms with symptom-focused therapies.

We have reviewed the evidence of the impact of inflammation on several cancer-related symptoms (Lee et al., 2004). The insult of cancer treatment, including radiotherapy and chemotherapy, increases production of inflammatory cytokines, especially interleukin (IL)-6 and tumor necrosis factor (TNF) variants (Linard et al., 2004; Linard et al., 2005). Inflammatory reaction is a classic feature of radiation exposure, and animal models have shown an increase in IL-6 several days after such exposure (Van der Meeren et al., 2003). This increase in inflammation is a prime candidate for the mechanism behind increases in treatment-related symptoms. It has been suggested that reduction of this treatment-induced inflammatory response might significantly reduce the morbidity associated with radiotherapy (Garden, 2003).

3.1 Symptom Management

The control or prevention of cancer-related cytokine dysregulation presents new opportunities for symptom reduction or prevention. Thus, a goal of the proposed study is the development of symptom-management strategy based on underlying symptom mechanisms in combination with empiric treatments. Inflammation can be modulated by a variety of existing pharmaceutical approaches.
Better symptom management, in cancer as well as in other diseases, has *been hampered by the lack of a strong clinical-trial evidence base for guiding symptom management practice.* Several barriers have hindered the development of clinical trials in symptom management. First, the subjective nature of symptoms has limited innovative research into the mechanisms underlying these symptoms and the development of novel ways of treating or preventing them. Special difficulties include the poor fit of current disease models of research for implementing this kind of health-related investigation and lack of statistical models that integrate “rough” self-report data and biologic data (Cleeland, 2001). However, patient-reported outcome research has recently been promoted by the U.S. Food and Drug Administration (FDA) for more accurate therapeutic agent evaluation, and symptom reduction has been recognized as a primary clinical benefit for drug approval (FDA, 2006b).
Other barriers have hindered development of evidence-based methods for controlling treatment-related symptom burden, despite the availability of more adequate symptom measurement methods. Many of the agents that might be effective in the control of treatment-related symptom burden are generic or off-patent drugs that will never receive clinical research support from the pharmaceutical industry because there is no financial incentive to support clinical trials testing their effectiveness for symptom control.
Current practice utilizes randomized clinical trials to manage a single symptom with a single agent, for example, pain controlled with a single analgesic. When clinicians do treat multiple symptoms, they typically prescribe multiple agents based on anecdotal experience or the patient’s perceived needs, rather than on evidence-based research (Foley et al., 2001).

3.2 Head and Neck Cancer Treatment Side-Effects

All cancer therapies, especially multimodality and multiagent treatment programs are associated with a spectrum of early and late adverse effects. Because of the wide variety of symptoms and their severity, toxicity data is a further challenge to evaluate. One recent analysis noted an almost 500% increase in the number of early toxicity events with chemoradiation as compared with standard postoperative radiotherapy for head and neck cancers (Trotti et al., 2007). Chemoradiotherapy for head and neck cancers has consistently shown to yield clinically relevant improvement in locoregional control and overall survival, though at the cost of more severe early toxicity (Pignon et al., 2000). However, many patients treated with radiation therapy alone still report high symptom burden. Early effects are typically expressed during or within a few weeks after the end of therapy, typically in proliferative tissues and organs such as the skin, the mucosal lining of the GI tract and the hematopoietic system. The alterations in swallowing and nutritional intake may cause poor compliance to therapy, may have long-term effects and even cause death of the patient. The burden of treatment- related adverse effects needs to be well documented and controlled to improve both physical and social functioning in these patients. Thus, a goal of the proposed study is to develop symptom management strategy to improve patient outcomes and also to improve compliance to intensive treatment regimen, in this case definitive radiation therapy.

4.0 Background Drug Information

4.1 Minocycline hydrochloride (Minocin®, manufactured by Triaxc Pharmaceuticals, LLC) is a semisynthetic antibiotic derived from tetracycline. It has the unusual side effect of markedly suppressing proinflammatory cytokine release, the primary reason we will include it as an intervention in this study. Preclinical data suggests that minocycline reduces neural inflammation and prevents apoptosis of neural cells. Animal studies have demonstrated that minocycline reduces the levels of the proinflammatory cytokines IL-6, TNF-alpha, IL-1b and interferon (IFN)-g (Ledeboer et al., 2005; Zanjani et al., 2006). Minocycline’s anti-inflammatory effect prevents subacute pathological change in lungs due to inflammation produced by peripheral lipopoly-saccharide administration in animals (Yamaki et al., 1998). Minocycline was found to decrease IL-6 and the acute-phase response protein C-reactive protein (CRP) levels in patients with rheumatoid arthritis (Kloppenburg et al., 1996).

Commonly associated side effects include light-headedness, vestibular symptoms, headache, and nausea (Gump et al., 1977), with no correlation seen between serum concentration and toxicity (Kloppenburg et al., 1995). Minocycline is now widely used in the management of dermatitis associated with targeted therapy in cancer.

4.2 Absolute Contraindications to study symptom intervention agent Minocycline

4.21 hypersensitivity to any tetracyclines;
4.22 pregnancy
4.23 hepatotoxicity (aspartate aminotransferase (AST) or alanine aminotransferase (ALT); 2 times the upper limit of normal)

4.3 Minocycline Common Adverse Reactions

4.31 Minocycline: Dizziness (9%) and vertigo.

4.4 Minocycline Monitoring Parameters

4.41 Minocycline: LFTs, BUN, Sr Cr,
4.42 Signs of acute hepatitis: rash, fever, malaise, abdominal pain, and vomiting

Evidence: Hepatotoxicity (e.g., elevated hepatic enzymes, hyperbilirubinemia, hepatic cholestasis, hepatic failure with some fatalities, hepatitis with autoimmune features, and jaundice) has also been reported. Abdominal complaints may suggest hepatotoxicity; the incidence of this effect is roughly 4.7%. Liver toxicity is possible with excessive accumulation of the drug, which can occur in patients with renal impairment receiving even usual oral or parenteral doses.

4.44 Minocycline Drug Interactions

4.441 Minocycline
4.442 Calcium-, magnesium-, or aluminum-containing antacids, bile acid sequestrants, bismuth, oral contraceptives, iron, zinc, sodium bicarbonate, penicillins, quinapril may decrease absorption of **minocycline: Avoid taking within 2 hours of using this medication.**
4.443 Methoxyflurane anesthesia, when concurrent with minocycline, may cause fatal nephrotoxicity.
4.444 Retinoic acid derivatives: May increase risk of pseudotumor cerebri.
4.445 Warfarin: Hypoprothrombinemic response may be increased with tetracyclines; **monitor INR closely during initiation or discontinuation**

4.45 Storage Information

4.451 Store at 20°C to 25°C (68°F to 77°F)

***References for intervention agent:**
1. MD Anderson Cancer Center Formulary: http://www.crlonline.com/crlsql/servlet/crlonline
2. Micromedex – Healthcare Series: http://www.thomsonhc.com/home/dispatch
3. Micromedex: Minocycline Drugdex Drug Evaluation and Armodafinil Drugdex Drug Evaluation and Turmeric Drug Evaluation by Martindale.
4. Lexi-Comp: Minocycline
5. Clinical Pharmacology: Minocycline

5.0 Study Design

Using a blinded, randomized placebo-controlled trial, we will evaluate **minocycline** safety and ability to reduce the symptom burden of oropharyngeal cancer, nasopharyngeal cancer, or unknown primary cancer of head and neck treated with radiation therapy. This is especially important in trials where symptom reduction is the outcome and where knowledge of the treatment arm might bias assessment staff or patient. The compounding pharmacy will prepare the appropriate active agent and placebo for each patient.

Design: Phase II blinded, randomized placebo-controlled trial
Symptom Intervention Agent: minocycline
Study Period: 15 weeks: intervention agent daily during radiation for 7 weeks (+/- 5 days) + additional follow-up to first follow up (4-8 weeks) for a total of 11-15 weeks.
Primary Outcome Variable: 7-week (+/- 5 days) area under the curve (AUC) for select MDASI-HNC symptoms namely fatigue, pain, sleep disturbance, difficulty swallowing and lack of appetite.
Forty patients will be randomized to either minocycline or placebo, twenty in each arm. AUC values for patients who drop out of the study after entering two weeks of AUC data will be included by carrying their last symptom data forward for the remaining study period under the intent to treat rule (ITT). The carry-forward method of handling drop-outs will be revisited upon completion of the study to determine if adjustments to these values can be made using longitudinal regression models estimated from patients who completed the entire study.
All Grade 3 and 4 toxicities reported by patients in this trial will be evaluated by the principal investigator and treating physician, or other attending physician if PI is not available, to determine if the toxicities were due to study medication. We will use standard 3+3 criteria for determining whether treatment exceeds either grade 3 or 4 toxicities for the first 6 patients assigned to minocycline. That is, if more than 1 symptom intervention related toxicity (grade 3, 4) in the first 6 patients assigned to minocycline is observed, the study will be terminated.
A list of adverse events known to be associated with primary treatment is listed in section 4.0 of the protocol.
The determination of whether a toxicity (grade 3, 4) was due to minocycline received by the patient (rather than the primary radiation) will be performed by the principal investigator in consultation with the treating physician.
The interaction screening will be the responsibility of the research staff. The Research staff will review any current or new medications started with the patient prior to initiating treatment. During the trial, the research staff will capture all drug interactions causing an adverse event on the Adverse Event forms. We plan to document all medications patients will be or have been using during the trial. Medication sheets will be provided to both patients and treating physicians to inform them of the possibility that the patients may be on this drug (see Appendices T and TT).
Minocycline will begin at the start of radiation therapy and continue daily through the final radiation treatment day.

6.0 Administration of Pharmacologic Agent

As stated in section 5, preparation of symptom intervention medication for each patient will be done by the compounding pharmacy. Patients will pick up the assigned study medications at one of the outpatient pharmacy stations in M. D. Anderson. At pickup patients will receive instruction in how to take study medications.

The participants will take study medication twice daily, starting on day one of radiation therapy. The final day of study medication will be the final day of radiation therapy. The participants will take study medications twice daily during entire course of radiation therapy, including weekend days.

Patients will be asked to bring their study medication container to the clinic where study staff will perform a capsule count each week during one of their radiation weekly appointments. Results of the capsule count will be recorded on the Study Medication Accountability form.

Unused drugs will be returned to Investigational Pharmacy Services by the study staff, or destroyed in a red biohazard bag. Once the capsule count is completed, the capsules can be placed into the M. D. Anderson biohazard waste system.

The table below displays the symptom intervention agent and the dosing schedule (Lexi-Comp).

Symptom Intervention Agent	Dosage Forms	Initial Dose (starts on first day of radiation)	Initial Dose (starts on first day of radiation)

Minocycline	100mg capsules	100mg two times a day (200 mg)	Matching placebo

7.0 Data Collection Tools

Patient Reported Outcome (PRO) Measurements

7.11 Symptom Measurement Symptom data will be collected using the **MDASI- HNC** module of the M. D. Anderson Symptom Inventory (see Appendix C and Appendix P). MDASI-HNC items namely fatigue, pain, sleep disturbance, difficulty swallowing and lack of appetite will be used to calculate the symptom AUC. Prior studies (Rosenthal, et al, 2007, 2008) have indicated that a significant proportion of patients reported these symptoms to be moderate to severe. The MDASI-HNC will be collected face to face in the clinic, through an interactive voice response system, through a tablet PC, through phone calls by field coordinators, or by regular mail to measure symptom burden over time of the treatment and post treatment.

7.12 Measure of Quality of Life The EuroQol (EQ-5D) is a standardized instrument for use as a measure of health outcome. (See Appendix D) Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status. EQ-5D was originally designed to complement other instruments but is now increasingly used as a 'stand alone' measure. The EQ-5D descriptive system consists of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three levels, reflecting "no health problems," (level 1) "moderate health problems," (level 2) and "extreme health problems" (level 3). A dimension for which there are no problems is said to be at level 1, while a dimension for which there are extreme problems is said to be at level 3. Each unique health state described by the instrument has an associated 5-digit descriptor ranging from 11111 for perfect health to 33333 for the worst possible state. The resulting descriptive system defines 243 health states. In addition, "unconscious" and "immediate death" are included in the EQ-5D valuation process but are not a part of the descriptive system.

7.13 Measure of Global Quality of Life The Global Quality of Life (GQL) is a single item asking patients to rate their quality of life on a 0 to 10 scale over the past week. (See Appendix DD).

7.14 Measure of Patient Satisfaction with Study Medication Scale The Study Medication Satisfaction Scale is a short, 7-item scale that asks patients about several areas of satisfaction. (See Appendix E) The scale includes questions about ease or difficulty of taking the medication in general and in its current form, convenience of taking the study medication as instructed, and patient confidence that the study medication is of benefit.

7.15 a Tobacco History Form The Tobacco History Form is a short questionnaire that asks about smoking history. (See Appendix F).

7.15 b Follow-Up Smoking Assessment Form The Follow-Up Smoking Assessment Form asks three questions about smoking subsequent to the start of radiation therapy (See Appendix FF).

7.16 Alcohol History Form The Alcohol History Form is a short questionnaire that asks about alcohol history at baseline. (See Appendix G).

7.2 Case Report Forms (CRFs)

7.21 Demographic Form This form includes patient birth date, gender, marital status, race, ethnicity, education, and employment status. (See Appendix H) The Demographic Form will be completed at baseline.

7.22 Charlson Comorbidity Index The Charlson Comorbidity Index yields a comorbidity score, to control for serious concurrent chronic disease conditions (Charlson et al., 1994) (Appendix I).

7.23 On-Study Form The On-Study Form contains data about disease, previous treatment, whether a patient is on concurrent protocols (See Appendix J). This form will be completed at baseline.

7.24 Clinical Monitoring Form The Clinical Monitoring Form contains clinical data including Body Mass Index (BMI), blood pressure, performance status, symptom treatment, and CTC toxicity scores. (See Appendix K).

7.25 Medication Form The Medication Form contains data about types of medications patients have been prescribed. Medication types include pain medications, antiemetics, and psychotropics among others. There is also a general section for other types of medications patients may be taking. (See Appendix L).

7.26 Daily Tracking of Study Medication Taken by Participants Patients will be given a diary and asked to record their doses of study medication (see Appendix M). Each page of the diary contains space to document 7 days of study medication consumption. Patients will be asked to record the number of study capsules they take at one time and also check off the time slot when the capsules are ingested.

7.27 Study Medication Accountability Form This form contains study medication data including the number of capsules dispensed to the patient at the last visit to the outpatient pharmacy, how many capsules were returned from the last visit, and the number of days the pills were taken. (See Appendix N).

7.28 Laboratory Data Form The Laboratory Data Form contains data from blood analysis including C-Reactive Protein (CRP), serum chemistry (albumin, calcium, phosphorous, glucose, BUN, creatinine, total bilirubin, and total protein), electrolytes (sodium, potassium, chloride, carbon dioxide, magnesium), and complete blood count (CBC). (See Appendix W). These values will be recorded if they are available in the patient medical record from a blood draw performed for clinical purposes.
Note: Liver function tests are required at baseline. If they were not performed within the past 3 months prior to starting treatment with the symptom drug/ placebo, they will be drawn for eligibility purposes.

7.29 Treatment Summary Form The Treatment Summary Form contains data about radiation treatment received and induction chemotherapy. (See Appendix O).

7.30 Final Study Status Form The Final Study Status Form contains data about patient disposition at the end of the study (i.e., completed study, withdrew, vital status) and tumor evaluation after treatment. (See Appendix OO).

7.31 CTC Toxicity Form The CTC Toxicity Score Form contains the maximum toxicity score in the last seven days, or since the last assessment. (See Appendix X).

8.0 Patient Eligibility

Patient Eligibility

8.11 Inclusion Criteria

8.111 Patients with a pathologically proven diagnosis of oropharyngeal cancer, nasopharyngeal cancer, or unknown primary cancer of head and neck in MDACC receiving radiation therapy with or without induction chemotherapy.
8.112 Patients ≥ 18 years old.
8.113 Patients with the above cancers, T0, TX, T1 to T3, N any, M0 receiving IMRT (to unilateral or bilateral neck), 64-72 Gy in 6-7 weeks as definitive treatment.
8.114 Patients must have normal renal function test and no prior renal disease: The screening cut off for serum creatinine < upper limit of normal.
8.115 Patients must have normal hepatic function test and no prior liver disease: The screening results for total bilirubin must be < 1.5 times the upper limit of normal. The screening results for the following must be < 2 times the upper limit of normal for patients to be eligible: Alkaline phosphatase (ALP) and Alanine aminotransferase (ALT). The screening results for Aspartate aminotransferase (AST) must be < 2 times the upper limit of normal if available.
8.116 Patients who speak English (due to the novel research and its complexity, we are only accruing English speaking patients to the protocol).
8.117 Patients must be willing to discontinue taking dong quai and/or St John's wort.
8.118 Patients must be willing and able to review, understand, and provide written consent.

8.12 Exclusion Criteria

8.121 Patients receiving concurrent chemotherapy or concurrent biologic agent.
8.122 Patients who are taking medications or have conditions that potentially preclude use of the study medication or intervention as determined by the treating physician.
8.123 Patients who are enrolled in another symptom management trial or receiving active treatment under another clinical trial.
8.124 Bile duct obstruction or cholelithiasis.
8.125 History of clinically significant cutaneous drug reaction, or a history of clinically significant hypersensitivity reaction, including multiple allergies or drug reaction.
8.126 Pre-existing psychosis or bipolar disorder.
8.127 Hypersensitivity to any tetracyclines.
8.128 Patients on anticoagulants (ie warfarin/heparin).
8.129 Patients with INR > 1.5.
8.130 Patients taking any tetracycline within the last 15 days.
8.131 Patients that are pregnant.
8.132 Patients treated with upfront radical surgery at the primary site (other than diagnostic tonsillectomy or excision).

9.0 Patient Enrollment and Registration

Patient Enrollment

Patients will be screened for eligibility and recruited for enrollment in the outpatient Head and Neck Cancer Clinic in Radiation Oncology before their radiation therapy starts. Enrollment will also take place in the outpatient radiation oncology facilities at the MD Anderson regional care centers: Sugar Land, Katy, Bay Area, and the Woodlands.
Research staff will maintain a log of all patients screened, and the reasons that patients do not enter the study will be documented.
Eligible patients who agree to enroll in the study will provide written informed consent/authorization.
Women of child-bearing potential who want to participate will be told that we will perform a mandatory pregnancy screening test through a urine sample at baseline. Study staff will provide the pregnancy kits to these women and make sure the results are known and recorded in the follow-up notes in Clinic Station before additional study drug prescriptions are filled by the Investigational Pharmacy. If the pregnancy test is positive the patient will not be prescribed the symptom drug study.
At enrollment patients will be informed that they will receive a stipend in the total amount of $60 for participation in the pilot study. The stipend will be distributed in $20 increments at three times during the study. Stipends will be distributed to participants at weeks 1, 7 (+/- one week), and at the final study follow up visit.

Enrolled patients will be registered into the Clinical Oncology Research System (CORe), the institutional patient data management system.

Patient Randomization and Assignment to Treatment Arm

The study will accrue a total of 40 patients with 20 patients each in the placebo and minocycline group. Prior to accruing the first patient, a randomization list will be generated by our biostatistician collaborator from the Department of Biostatistics for all 40 patients stating which group a patient was randomized. This list containing the accrual number and treatment group information will be given to Investigational Pharmacy. A sealed backup list will be kept by the assigned data analyst at the Department of Symptom Research. This list will only be opened in case unblinding is needed.

Recruitment efforts will be made such that patients with induction chemotherapy and/or unilateral neck radiation comprised at least 20% of the sample.

Once a patient is enrolled the study staff will contact the Investigational Pharmacy and let them know of the patient's accrual number and patient ID. Investigational Pharmacy retrieves the randomized treatment arm information from the generated randomization list. Once a patient is randomized to a treatment arm, Investigational Pharmacy will relay the information to the dispensing Pharmacy. The patient visits the most convenient outpatient pharmacy to pick up the study medication assigned. Patients will be randomized into one of the 2 possible arms. (See Section 5.0 Study Design).

10.0 Assessment Schedule

Please see Appendix P for an expanded study assessment/evaluation schedule.

Data Confidentiality Plan

All patient-reported outcome, laboratory and clinical data gathered in this protocol will be stored in a password-protected database. All patient information will be handled using anonymous identifiers. Linkage to patient identity is only possible after accessing a password-protected database. Access to the database is only available to individuals directly involved in the study.

When all analysis has been completed and all study results have been reported, the electronic and paper files will be stored in a password-protected MD Anderson secure server. This stored data may be made available to MD Anderson research and clinical faculty for research purposes, with appropriate validation and access controls, so it can facilitate research cross-fertilization and speed insight discovery. Patient data also will be stored and accessible in the MD Anderson Translational Research Accelerator database (TRA; PI: A. Futreal).

11.0 Adverse Event Reporting

11.1 Adverse Events (AE) (See Appendix Q)

All patients will be seen weekly during radiation therapy in the radiation oncology clinics, allowing for close monitoring of potential adverse events by clinic and research staff during treatment.
During the 3 weeks post radiation, patients will be monitored through weekly phone calls by the research staff, and then every other week for another 3 weeks. In addition, patients will be given a contact phone number for treatment-related questions.

Toxicity and other clinical variables will be collected by research staff at weeks 1, 4, 7, and end of study. Treatment-related toxicities (NCI Common Terminology Criteria for Adverse Events, version 4) will be monitored by both clinic and research staff at the patient's regular clinical appointments. (See Appendix R)
Grade 1 and Grade 2 AEs based on radiation treatment and symptom treatment that are expected or unrelated will not be reported. AEs that are Grade 3 and above that are definite, probable, or possible and related will be reported. AEs will be tabulated and reported as a summary on the continuing review report. All Grade 3 and 4 toxicities reported by patients in this trial will be evaluated by the principal investigator and treating physician to determine if the toxicities were due to study medication.

11.2 Serious Adverse Events (SAE) (See Appendix S)

A serious adverse event is any adverse drug experience occurring at any dose that results in any of the following outcomes:

Death

A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.

Inpatient hospitalization or prolongation of existing hospitalization

A persistent or significant disability/incapacity – a substantial disruption of a person's ability to conduct normal life functions.

A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate 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. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the Clinical Research Support Center.

All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy on Reporting Serious Adverse Events". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the Clinical Research Support Center, regardless of attribution (within **5 working days** of knowledge of the event).

All life-threatening or fatal events, expected or unexpected, and regardless of attribution to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the Clinical Research Support Center.

The MDACC "Internal SAE Report Form for Prompt Reporting" will be used for reporting to the Clinical Research Support Center.

Serious adverse events will be captured from the time the patient signs consent until 30 days after the last dose of drug. Serious adverse events must be followed until clinical recovery is complete and laboratory test have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

· **Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the Clinical Research Support Center. This may include the development of a secondary malignancy.**

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

12.0 Criteria for Removal from the Study

12.1 Patients will be taken off study if these values are met or exceeded:

12.11 Alkaline phosphatase (ALP) is >2 times the upper limit of normal

12.12 Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) is >2 times the upper limit of normal

12.13 Total bilirubin > 1.5 times the upper limit of normal

12.14 Monitor for signs and symptoms of severe rash (CTC version 4 $\geq$ grade 3), hypersensitivity, and if appear, need to stop drug immediately and discontinue study.

12.15 Pregnancy during the study period

12.16 INR > 1.5. Treating physician notified so that medical management occurs.

13.0 Statistical Analysis Plan

13.1 Sample Size and Randomization

Forty patients will be randomized equally to the two treatment arms - minocycline and placebo. With 20 patients per treatment arm, we will be able to detect a 0.70 SD effect size on the symptom AUC between the two treatments with 70% power and one-sided 5% significance test. Because this is a pilot study with the intent of providing effect size estimates to inform large clinical trial in the future, we chose a modest statistical power.

13.2 Analysis Plan

Our emphasis is to test the efficacy of minocycline as a potential agent in reducing patient-reported symptoms in cancer patients receiving radiation therapy. The proposed phase II clinical-trial for screening potentially effective symptom intervention agent will provide moderate power in detecting modest intervention effect. If the treatment has a more pronounced effect, then it will be detected with higher power.

This study will allow us to obtain estimates of treatment effect and the variability of these estimates. Estimates of treatment effect will be obtained using standard linear regression techniques in which AUC values (lc(i)) are regressed on indicator variables that represent treatment received. Estimates of treatment effect and between subject variability will then be used to design a more comprehensive study in future clinical trials.
Recruitment efforts will be made such that patients with induction chemotherapy and/or unilateral neck comprised at least 20% of the sample. Indicator variables for the type of treatment (induction chemotherapy vs. radiation therapy alone) and location (unilateral neck vs. bilateral neck) will be created. In addition to the formal evaluation of treatment effects on the primary outcome, we will also examine the prognostic effects of the type of treatment, location, disease stage, ECOG status, age and gender in predicting the outcome variable. Standard exploratory data analysis techniques and descriptive statistics will be used.
We will test minocycline in its ability to reduce values of *5 symptoms*. Assuming that patients accrue at the rate of 4 per month, we anticipate that this pilot study will require approximately 14 months to complete.
We will need at least 2 weeks of treatment with the study drug/placebo for patients to be considered as evaluable. Any patient who drops out prior to this will be replaced.

13.21 Primary Outcome Variable

The primary outcome variable will be the combined AUC for selected symptoms. The value of this variable for patient *i* is denoted *Ic(i)* and is comprised of the **MDASI-HNC scores for fatigue, pain, sleep disturbance, difficulty swallowing and lack of appetite** collected during the 7 weeks of RadTx. Because *Ic(i)* represent the average of a large number of ordinal variables, we assume by the central limit theorem that its value can be considered to be approximately normally distributed.

13.22 Secondary Outcome

In addition to obtaining estimate of treatment effect, this protocol also aims to pilot the procedure used in calculating area under the curve (AUC). Because future clinical trial requires frequent monitoring and updating of symptom data collected using either the interactive voice response system or paper and pencil, the logistics developed here will be useful in ensuring an efficient data collection system.
We are also interested in exploring predictors of survival. Univariate Cox proportional hazards models will be used to screen for potential predictors (demographic and clinical variables) of overall survival. Predictors that are significant with $p<.10$ will be included in the multivariate Cox proportional hazards models. Final predictors will be selected by stepwise regression, with an entry level of 0.1 and a stay level of 0.05. Standard model fitting diagnostics will be performed. Finally, Cox survival curves will be plotted.

13.23 Non-Compliance with Study Agent

Patients who do not comply with study agent dosing requirements will remain in the study under the intent to treat rule.

14.0 References

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