THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Page

A Randomized, Placebo Controlled-Double Blind Study of Minocycline for Reducing the Symptom Burden Produced by Chemoradiation Treatment for Non Small Cell Lung Cancer

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Core Protocol Information

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Which Committee will review this protocol?

(•) The Clinical Research Committee - (CRC)

Protocol Body

1.0 Objectives

1.1 Primary outcome: to test the potential utility of minocycline treatments for symptoms that have been identified as prominent during concurrent chemoradiation (CXRT) for non-small cell lung cancer (NSCLC), including **fatigue, pain, disturbed sleep, lack of appetite, and sore throat**.

1.2 Secondary outcomes

1.21 to examine the effectiveness of minocycline in reducing treatment-induced inflammatory response (serum C-reactive protein (CRP), interleukin (IL)-6, TNF-a, sTNF-R1, sTNF-R2, and activation of indoleamine 2,3-dioxygenase (IDO)).

1.22 to examine the impact of minocycline on patient's quality of life, health status and tumor response to CXRT.

2.0 Rationale

The study aims to develop symptom-management strategies based on underlying symptom mechanisms in combination with empiric treatments. The significance of this research is that it evaluates **minocycline,** a low-toxicity, low-cost, widely used therapy, using a two-arm, placebo-controlled design that will allow us to quickly obtain preliminary estimates of the effects of treatment for reducing the symptom burden of chemoradiation therapy. Our prior longitudinal study of symptom burden in patients with NSCLC indicates that patients receiving CXRT report debilitating fatigue and other symptoms during the therapy and for several weeks afterward (Wang et al., 2006). Figure 1 presents symptom severity reported by patients with NSCLC before, during, and after CXRT, measured by M. D. Anderson Symptom Inventory (MDASI), a multisymptom, patient-reported questionnaire that assesses both symptom severity and the impact of symptoms on patient functioning on a 0-10 numeric scale (Cleeland et al., 2000). Treatment tolerability and patient functioning are often compromised by this therapy-induced severe symptom burden. Few agents have been approved to prevent or treat these side effects, and little is understood about the mechanisms that cause them, except for promising initial studies on inflammation (Wang, et al., 2010).

Clinical studies support the involvement of acute-phase and survival-phase inflammatory response in producing treatment-related symptom burden. Preclinical and clinical work has evidenced the strong anti-inflammatory properties and neuroprotective function of minocycline, whose ability to cross the blood-brain barrier and good safety profile make it desirable for directly testing the role of inflammation in producing symptom burden. The target of action for the proposed intervention is to reduce the expression of inflammatory markers, specifically activation of CRP, IL-6, TNF-a, sTNF-R1, sTNF-R2, and IDO, on the basis of minocycline's broad anti-inflammation properties.

3.0 Background

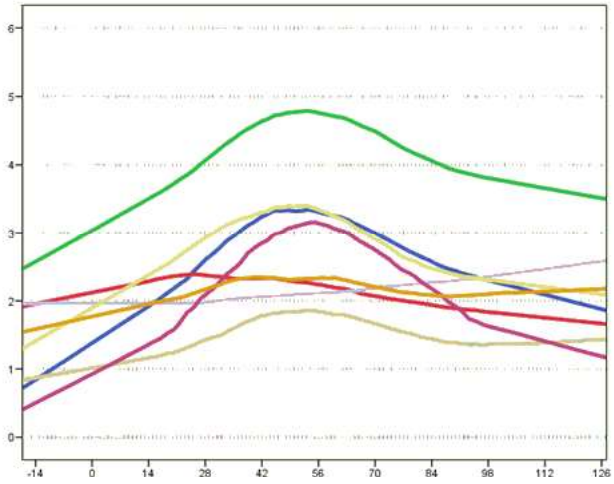
More than 1.5 million new cases of cancer are expected to occur in the United States in 2010, including 222,520 new cases of lung cancer alone (Jemal et al., 2010). Patients with locally advanced lung cancer typically receive aggressive therapy, such as CXRT, and experience multiple symptoms that cause them significant distress and impair function and rehabilitation. Whereas many of these symptoms are the result of disease, it is increasingly recognized that pain, neuropathy, fatigue, disturbed sleep, 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).

An increase in inflammation is a prime candidate for the mechanism behind increases in treatment-related symptoms. 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 IL-6 and tumor necrosis factor (TNF) variants (Linard et al., 2004; Linard et al., 2005). Both paclitaxel and cisplatin are known to cause a rise in the levels of cytokines, especially IL-6, in cancer patients (Endo et al., 2004). High levels of IL-6 have been found in patients with inoperable lung cancer receiving cisplatin along with combination treatment (Mantovani et al., 2000). Reviews have suggested the role of cytokines in initiating and amplifying mucositis in patients receiving chemoradiation (Niscola et al., 2007; Sonis, 1998), increases in IL-6 in response to paclitaxel therapy in breast cancer (Pusztai et al., 2004) and the association of IL-6 with reported symptoms. Further, animal models have shown an increase in IL-6 several days after exposure to radiation (Van der Meeren et al., 2003). It has been suggested that reduction of this treatment-induced inflammatory response might significantly reduce the morbidity associated with radiotherapy (Garden, 2003).

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 biological basis for subjectively reported clusters of symptoms (Cleeland et al., 2003; Lee et al., 2004), in accordance with growing awareness that common biological mechanisms may cause or contribute to some of these symptom clusters at the same time (Barsevick et al., 2006; Dodd et al., 2005; Wang et al., 2006). On the basis of this model, optimal symptomatic control would utilize symptom-focused therapies to attack both underlying symptom mechanisms and the end effects of these mechanisms.

3.1 Symptom Study in NSCLC Patients Undergoing CXRT

Previous symptom study provides the rationale for this intervention study in patients with NSCLC (Wang, et al, 2010). Elevations in cancer treatment-induced circulating inflammatory cytokines may be partially responsible for the development of significant symptom burden (e.g., pain, fatigue, distress, disturbed sleep) during CXRT. Figure 1 depicts Lowess curves representing patient-reported symptom severity on a 0-10 scale, as assessed using the lung-cancer version of the MDASI.



Lowess curves illustrate a gradual increase in symptom severity (on a 0–10 scale) during the accumulated dose of CXRT (Day 0=start of therapy).

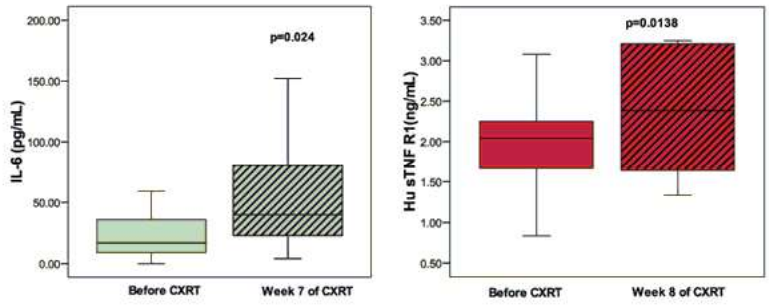
Selected symptoms from MDASI included: Fatigue
Pain Lack of appetite Distress Drowsiness Sleep disturbance
Diarrhea Difficulty swallowing Shortness of breath Coughing

Sixty-two patients undergoing CXRT for locally advanced NSCLC reported symptoms weekly for 15 weeks via the MDASI. Serum inflammatory cytokines were assessed weekly during therapy via enzyme-linked immunosorbent assay. Dynamic changes in cytokines and associated symptom profiles were estimated using mixed-effect models. A component score of mean MDASI symptom severity increased gradually as CXRT dose accumulated, with a significant difference between week 3 and week 4 and the peak at week 8, and symptoms remained high for several more weeks, not returning to baseline severity until week 13. See Table 1 below. The symptom development trend provides the rationale for conducting the proposed study in a 12-week time frame.

Table 1. Mixed-effect Modeling of Weekly Changes in the MDASI 15-Symptom Component Score

Effect	Estimate	SE	df	t	*p**
Intercept	5.8266	2.2260	55	2.62	*0.0114*
Week 0	0	.	.	.	.
Week 1	0.09538	0.1539	569	0.62	*0.5357*
Week 2	0.1042	0.1752	569	0.59	*0.5523*
Week 3	0.3125	0.1859	569	1.68	*0.0933*
Week 4	0.4353	0.1908	569	2.28	***0.0229***
Week 5	0.7248	0.1976	569	3.67	***0.0003***
Week 6	0.9850	0.1973	569	4.99	***<.0001***
Week 7	1.1648	0.1970	569	5.91	***<.0001***
Week 8	1.1956	0.2091	569	5.72	***<.0001***
Week 9	1.0916	0.2069	569	5.28	***<.0001***
Week 10	0.9156	0.2025	569	4.52	***<.0001***
Week 11	0.5016	0.2105	569	2.38	***0.0175***
Week 12	0.4518	0.2134	569	2.12	***0.0347***
Week 13	0.2127	0.2145	569	0.99	*0.3219*
Week 14	0.2248	0.2167	569	1.04	*0.3001*
Week 15	0.1416	0.2239	569	0.63	*0.5276*

Serum concentrations of IL-6, IL-10, and serum soluble receptor 1 for tumor necrosis factor (sTNF-R1) increased significantly by week 8 (all $p < .05$). During CXRT, controlled for age, sex, race, body mass index, cancer recurrence, previous treatment status, total radiotherapy dose, and CXRT delivery technique, an increase in sTNF-R1 was significantly related to an increase in the mean score for all 15 MDASI symptoms (estimate, 1.74; SE, 0.69; $p < .05$) and to a larger radiation dose to normal lung volume (estimate, 1.77; SE, 0.71; $p < .01$); an increase in serum IL-6 was significantly related to increased mean severity for the **five most severe symptoms (pain, fatigue, disturbed sleep, lack of appetite, sore throat)** (estimate, 0.32; SE, 0.16; $p < .05$). These results suggest a role for overexpressed proinflammatory cytokines in significant worsening of symptoms in NSCLC patients undergoing CXRT, and warrant further study to identify biological targets for ameliorating treatment-related symptom burden. See Figure 2 below for a comparison of serum IL-6 and sTNF-R1 before and after CXRT.



Depressive symptoms frequently develop in patients undergoing cytokine immunotherapy for the treatment of viral diseases and certain cancers (Capuron & Dantzer, 2003; Capuron et al., 2002). In most of these conditions, clinical reports have revealed an increase in the ratio of plasma kynurenine to tryptophan. This increase in the kynurenine/tryptophan ratio is associated with increased plasma levels of neopterin, a marker of macrophage activation, which points to activation of the tryptophan-catabolizing enzyme IDO (Widner et al., 2002). IDO is an extrahepatic enzyme that is present in macrophages and other cells that degrades the essential amino acid tryptophan along the kynurenine pathway. This enzyme is induced by proinflammatory cytokines, mainly interferon (IFN)-g (Takikawa et al., 1999) and TNF-a. (Popov et al., 2006; Fujigaki et al., 2006). When IDO is activated in conditions of chronic inflammation, its degree of activation is correlated to the intensity of depressive symptoms, as observed in cancer patients chronically treated with IFN-a (Capuron et al, 2002). Animal studies also have identified IDO as a critical molecular mediator of inflammation-induced depressive-like behavior (O'Connor et al, 2009). Inhibition of IDO by targeting proinflammatory cytokine expression (via minocycline) or IDO itself (via 1-MT) blocks development of depressive-like behaviors in mice in response to LPS.

Although IDO activation has often been proposed to mediate the relationship between inflammation and depression, this mechanism has not been examined in cancer treatment-induced fatigue and other major physical symptoms in NSCLC patients. CXRT provides a window of expected symptom development to test our primary and secondary outcomes, and the preclinical data on the impact of minocycline on IDO and clinical data on depressed symptoms provide the rationale for the effects of minocycline in reducing IDO activation to reduce symptom development.

3.2 Symptom Management

The control or prevention of cancer-related cytokine dysregulation presents new opportunities for symptom reduction or prevention. Just as with optimal curative cancer treatments, optimal symptom management is highly likely to be dependent on combinations of treatments with different targets of action (mechanistic, empiric, behavioral) (Miller, 2003).Thus, a goal of the proposed study is the development of symptom-management strategies 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. 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. However, patient-reported outcomes research has recently been promoted by the U.S. Food and Drug Administration (FDA) for more accurate evaluation of therapeutic agents, and symptom reduction has been recognized as a primary clinical benefit for drug approval (FDA, 2009).

Other barriers have hindered development of evidence-based methods for controlling treatment-related symptom burden, despite the availability of 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. Additionally, the control of treatment-related symptoms almost always involves the use of combined treatment modalities, which are difficult to evaluate using traditional clinical trial methods.

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 have few options in agents to prescribe on the basis of evidence-based research that would address multiple symptoms. The proposed study aims to investigate the effects of treatment on multiple symptoms and on inflammation mechanisms using one agent, minocycline.

4.0 Symptom Intervention Agent Minocycline

Minocycline hydrochloride (Minocin®, manufactured by Triax Pharmaceuticals, LLC, Cranford, NJ) is an inexpensive, widely used, semisynthetic antibiotic derived from tetracycline that has strong preclinical and clinical evidence of anti-inflammatory effects. Minocycline 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 suggest 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-a, IL-1b and IFN-g (Ledeboer et al., 2005; Zanjani et al., 2006). This effect, along with the inhibition of microglial activation due to the damaged nerves, has been shown to have neuroprotective action in animal models of a number of diseases, including stroke, multiple sclerosis, and Parkinson's disease, with the potential to be used in preventing and reducing chemotherapy-induced neuropathic pain (Raghavendra et al., 2003). Minocycline's anti-inflammatory effect prevents subacute pathological change in lungs due to inflammation produced by peripheral lipopolysaccharide administration (Yamaki et al., 1998). It effectively modulated mechanical hyperalgesia in newly developed animal models and prevented loss of intraepidermal nerve-fiber density in oxaliplatin-treated rats (Boyette-Davis & Dougherty, 2011). In a rat model of neuropathy, minocycline affected the development of hypersensitivity (Raghavendra et al., 2003).

The therapeutic effects of minocycline have been investigated in a number of pathological domains, including dermatological and autoimmune disorders (Sapadin & Fleischmajer, 2006). Minocycline's long-lasting effects in preventing neuropathic pain (Padi & Kulkarni, 2008; Raghavendra et al., 2003) and as a potential remedy for human inflammatory bowel disease (Huang et al., 2009), neurodegenerative disorders (Noble et al., 2009), and HIV (Zink et al., 2005) have been reported. Minocycline was safe and effective for patients with rheumatoid arthritis in a 48-week double-blind placebo-controlled trial (Tilley et al., 1995). Recent clinical trials for Fragile X Syndrome (Paribello et al., 2010), vitiligo (Parsad & Kanwar, 2010), and schizophrenia, in which minocycline was used to block nitric oxide-induced neurotoxicity (Levkovitz et al., 2010), have shown a significant benefit from this well-tolerated agent. Minocycline was found to decrease levels of IL-6 and the acute-phase response protein CRP in patients with rheumatoid arthritis (Kloppenburg et al., 1996), and it is now widely used in the management of dermatitis associated with targeted therapy in cancer (Appendix D).

Commonly associated side effects of minocycline include light-headedness, vestibular symptoms (such as dizziness and vertigo), headache, and nausea (Case, 2001; Gump et al., 1977), with no correlation seen between serum concentration and toxicity (Kloppenburg et al., 1995). Another side effect is photosensitization.

4.1 Absolute Contraindications to Study Symptom Intervention Agent Minocycline

4.11 Hypersensitivity to any tetracyclines

4.12 Pregnancy

4.13 Hepatotoxicity (=aspartate aminotransferase (AST) or alanine aminotransferase (ALT); 2 times, or greater than, the upper limit of normal)

4.2 Minocycline Common Adverse Reactions

4.21 Minocycline: dizziness (9%) and vertigo

4.3 Minocycline Monitoring Parameters

4.31 Minocycline: LFTs, BUN, Sr Cr

4.32 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.

4.4 Minocycline Drug Interactions

4.41 Antacids containing calcium, magnesium, or aluminum, bile acid sequestrants, bismuth, oral contraceptives, iron, zinc, sodium bicarbonate, penicillins, and quinapril: may decrease absorption of minocycline; **avoid taking within 2 hours of using this medication**
4.42 Methoxyflurane anesthesia: when concurrent with minocycline, may cause fatal nephrotoxicity
4.43 Retinoic acid derivatives: may increase risk of pseudotumor cerebri
4.44 Warfarin: hypoprothrombinemic response may be increased with tetracyclines; **monitor INR closely during initiation or discontinuation**
4.45 Storage information: at 20°C to 25°C (68°F to 77°F)

References for intervention agents:

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
4. Lexi-Comp: Minocycline. http://www.lexi.com/
5. Clinical Pharmacology: Minocycline
6. http://medicine.iupui.edu/flockhart/clinlist.htm: Abbreviated Clinical Drug Interactions Table (Appendix E)

5.0 Study Design

We will conduct **a two-arm, placebo-controlled phase II study** to obtain preliminary estimates of the treatment effects of minocycline in patients with NSCLC who are qualified for and are being consented for CXRT (see Appendix F).

Study Period: 12 weeks: intervention from start to end of CXRT +/-2 days, plus additional follow-up for a total of 12 weeks on study.
Primary Outcome Variable: Minocycline will be tested for its ability to reduce the value of patient 12-week (+/- 2 days) area under the curve (AUC) for 5 targeted symptoms: fatigue, pain, disturbed sleep, lack of appetite, and sore throat, either as a combination or individually.
Baseline assessments are to occur prior to start of CXRT. Administration of the symptom intervention agent will start the day CXRT commences or within 2 days of the start of CXRT.
The phase II study will be **placebo controlled and double blinded**. This is especially important in trials where symptom reduction is the outcome and where knowledge of the treatment arm might bias assessment staff.
All grade 3 and 4 toxicities observed during the trial will be evaluated by the principal investigator (PI) in consultation with the treating physician, or by another attending physician if the PI is not available, to determine if the toxicities were caused by minocycline (rather than the primary chemotherapy agent) and to decide whether to remove the patient from the trial (see 10.1 for unblinding procedure).
Table 3 below displays the symptom intervention agent and the dosing schedule (Lexi-Comp).
Table 3. Dosing Schedule

Symptom Intervention Agent	Dosage Forms	Initial Dose (starts on first day of CXRT)	Initial Dose (starts on first day of CXRT)
Minocycline	100 mg capsules	100 mg two times a day (200 mg/day)	Matching placebo

6.0 Patient Eligibility

6.1 Inclusion Criteria

6.11 Patients with a pathologically proven diagnosis of NSCLC and consented to receive CXRT at MD Anderson
6.12 Patients ≥ 18 years old
6.13 Patients who will receive CXRT with platinum/taxane-based-chemotherapy and with a total radiation dose of ≥ 50 Gy, per treating physician's assessment
6.14 Patients who speak English or Spanish (due to MDASI language options, we are only accruing English-speaking or Spanish-speaking patients to the protocol)
6.15 Patients willing and able to review, understand, and provide written consent before starting therapy
6.16 Patients with normal renal function according to MD Anderson testing standards and no prior renal disease [screening cut off for serum creatinine < 1.5 times ULN]
6.17 Patients must have the following screening results for hepatic function according to MD Anderson testing standards: total bilirubin < 1.5 times the upper limit of normal; alkaline phosphatase (ALP)**,** alanine aminotransferase (ALT)**,** and aspartate aminotransferase (AST **-** if available) must be < 2 times the upper limit of normal

6.2 Exclusion Criteria

6.21 Patients with a history of clinically significant cutaneous drug reaction to minocycline, as documented in the patient medical records
6.22 Patients who are enrolled in other symptom management or symptom clinical trials
6.23 Patients who currently have bile duct obstruction or cholelithiasis
6.24 Patients with hypersensitivity to any tetracyclines
6.25 Patients who are pregnant; pregnancy will be confirmed by negative urine test
6.26 Patients on vitamin K antagonist warfarin

7.0 Study Procedures

7.1 Patient Enrollment and Registration

Patients will be screened for eligibility and recruited for enrollment in the outpatient Thoracic Cancer Clinic in Radiation Oncology before their radiation therapy starts. 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.
At enrollment, patients will be informed that they will receive a stipend in the total amount of $60 for participation in the phase II study. The stipend will be distributed in $20 increments three times during the study. Stipends will be distributed to participants at study enrollment, at the end of the study intervention, 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.

The study will accrue a total of 40 patients. Once a patient is enrolled and registered in CORe, the Investigational Pharmacy retrieves the randomized treatment arm information from the Clinical Trial Conduct website. 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).

7.2 Patient Randomization and Assignment to Treatment Arm

The study will accrue a total of 40 patients with 20 patients each in the intervention and placebo arms. Prior to accruing the first patient, a randomization list for the entire sample will be generated by our biostatistician collaborator from the Department of Biostatistics, stating into which group a patient will be randomized . This list containing the accrual number and treatment group information will be set up in the Clinical Trial Conduct website.

Once a patient is enrolled on the study, the Investigational Pharmacy retrieves the randomized treatment arm information from the Clinical Trial Conduct website. 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.

7.3 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.
Information gathered for this study will not be reused or disclosed to any other person or entity, or for other research. Once the research has been completed, identifiers will be retained for as long as is required by law and by institutional regulations, and at that point will be destroyed.

8.0 Data Collection

Baseline assessments are to occur prior to start of CXRT. The symptom intervention agents (minocycline or placebo) will start the day of CXRT or within 2 days of the start of CXRT and continue for the duration of CXRT +/2 days. Patients will continue in follow up after completion of CXRT and symptom intervention agents for a total of 12 weeks on study to observe treatment effects.

Patients will pick up the assigned study medications at one of the outpatient pharmacy stations in MD Anderson. At pickup, patients will receive instruction in how to take study medications. The participants will take study medication enterally, once daily, in the morning, after study entry. The final day of study medication is the last day of CXRT. Total daily doses will be dispensed.

Study medication use will be reviewed by study staff weekly during administration of study intervention agent. While on study intervention agent, patients will be asked to bring their capsules to the clinic at the end of the first week, every 3 weeks thereafter, and at the end of the study intervention medication administration period. At those times, study staff will perform a capsule count and record the results.

Study staff will contact patients weekly to check for adverse events. Study staff will make weekly phone calls after completion of CXRT and study medication.

8.1 Patient-Reported Outcome (PRO) Measurements

8.11 Symptom Measurement (Appendix H)

Symptom data will be collected using the MDASI-Lung-Plus module at baseline and during the 12 weeks of the study. The MDASI-Lung-Plus will be administered face-to-face in the clinic, and through phone calls by field coordinators or by regular mail to measure symptom burden during and after treatment (Cleeland, et al, 2000; Mendoza, et al, 2011).

8.12 Measure of Quality of Life (Appendix I)

The EuroQol (EQ-5D) is a standardized instrument used as a measure of health outcome (EuroQol Group, 1990). Applicable to a wide range of health conditions and treatments, the EQ-5D provides a simple descriptive profile and a single index value for health status. It 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. The EQ-5D is a secondary outcome variable where each of the EQ-5D dimensions will be used as a dependent variable to explore whether health status differ between patients treated with minocycline or placebo and to estimate these effects.

Reporting Requirement

If in the course of assessing symptoms the patient reports severe levels of sadness (7 or above on the MDASI-Lung-Plus) or extreme anxiety or depression ("I am extremely anxious or depressed" on the EQ-5D), the clinical data coordinator will send a memo or notify the patient's treating physician immediately, to make him/her aware of the patient's condition.

8.13 Measure of Global Quality-of-Life Rating (GQL) (Appendix J)

The reporting of symptom severity has been shown to be correlated with other self-report measures, especially quality-of-life ratings, including a single-item global quality of life (GQL) rating (Mendoza et al., 2002). This single-item rating of current quality of life is measured on a 0-10 scale, bounded by worst ever and best ever (Sloan et al., 1998). The GQL baseline will be used as a covariate in assessing changes in symptoms and longitudinally for secondary exploratory analyses of the effects of interventions on patients' overall impression of quality of life.

8.14 Measure of Patient Satisfaction with Study Medication (Appendix K)

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

8.15 Tobacco History Form (Appendix L)

The Tobacco History Form is a short questionnaire that asks about smoking history at baseline and at the end of study.

8.2 Other Data to be Collected

Research staff will collect demographic and clinical information from the patient's medical record. Demographic data to be collected may include such items as birth date, marital status, race/ethnicity, education, and employment status. Examples of clinical information that may be collected at one or more timepoints during the study include height and weight, disease information (eg, cancer diagnosis/stage), treatment information (eg, radiotherapy, chemotherapy agents, current medications), comorbidities, and performance status.

Laboratory values from blood analysis**,** such a**s** 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)**,** will be recorded if they are available in the patient medical record from a blood draw performed for clinical purposes.

Note: Liver function tests, renal function tests, INR tests, and urine pregnancy tests are required at baseline. If the liver, renal, or INR tests were not performed within the past 3 months prior to starting treatment with the symptom drug/placebo, they will be drawn for eligibility purposes. The study coordinator will perform the urine pregnancy tests.

8.3 Cytokine Data Collection

In addition to routine blood testing, and if possible, **4 serum samples** will be measured for inflammatory markers: at baseline upon enrollment into the study (before minocycline treatment), at the end of week 1 of the intervention, at end of treatment +/- 1 week, and at the end of the study period at about week 12, +/-1 week. In animal models, minocycline acts very early in a chain of events that leads from Toll-like receptor 4 activation by LPS to IDO activation and depressive-like behavior. Therefore, it will be important to collect samples before and after the first week of intervention in this human study. The end-of-intervention sample will provide information about any differences in treatment effects between the two arms.
Serum samples (one 10 cc red top tube) will be obtained from each patient, usually in the morning or early afternoon and preferably within 1 or 2 days of MDASI administration. The blood samples will be centrifuged to separate serum and blood cells. The serum and blood cells will be stored at -80C for batch analyses of serum markers CRP, IL-6, TNF-a, sTNF-R1, sTNF-R2, and IDO activation, respectively. The investigators retain the right to adjust this list if any technical laboratory issues arise or if relevant new data are published. Cytokine levels will be determined using ELISA or Multiplex kits, with duplicate measures for each patient.

8.4 Assessment Schedule

Table 4. Clinical and Laboratory Monitoring Schedule

	Base-line	*Wk 1 +/- 1wk*	*Wk 2*	*Wk 3*	*Wk 4 +/- 1wk*	*Wk 5*	*Wk 6*	*Wk 7***** +/- 1wk*	*Wk 8*	*Wk 9*	*Wk 10*	*Wk 11*	*Wk 12 +/- 1 wk*
Demographic information	x												
Disease history, current disease status	x												
Other clinical information*		x			x			x					x
Laboratory information**	x	x			x			x					x
Medication information	x	x			x			x					x
Comorbidity information	x												
Study medication accountability		x			x			x					
Treatment summary information								x					
Final status information													x
MDASI-Lung-Plus***	x	x	x	x	x	x	x	x	x	x	x	x	x
EQ-5D	x				x			x					x
GQL	x				x			x					x
Tobacco History	x												x
Study Medication Satisfaction Scale								x					
Patient-Reported Information Checklist	x	x	x	x	x	x	x	x	x	x	x	x	x
Research blood draw****	x	x						x					x

* For example, ECOG performance status, height, weight.
** Laboratory values are recorded when available
*** Each designated MDASI collection (phone call or in clinic) requires 3 attempts.
****Biomarker testing at baseline, week 1, end of CXRT and symptom intervention agent regardless of week (Week 7 is used only as an estimate of when this assessment will be done), and week 12 after start of treatment.
*****Assessments to occur at week 7, or at end of CXRT and symptom intervention agent.
Baseline assessments to occur before start of CXRT, while the symptom intervention agent starts the day of CXRT or within 2 days of the start of CXRT and continues through the end of CXRT (+/- 2 days).

9.0 Adverse Events (AE) Reporting

9.1 Adverse Events (AE)

All patients will be seen weekly in the radiation oncology clinics, allowing clinic and research staff to closely monitor potential adverse events during treatment. Patients will continue to complete the MDASI-Lung-Plus for an additional 5 weeks after therapy is completed (when study treatment-related symptoms are at their peak). By that time, adverse reactions to interventions should have declared themselves. During these 5 weeks post-CXRT, patients will be monitored by phone calls once a week by the research staff. 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 (+/- 1 week), 7 (+/- 1 week), 12 (+/- 1 week). 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 or by phone call. (See Appendix C)

Grade 1 and Grade 2 AEs based on chemoradiation 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 resulted from study medications.

The PI or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial.

9.2 Serious Adverse Events (SAE)

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

- Grade 3 or above AE per CTC
- 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; 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).

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 "The University of Texas MD 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 University of Texas MD Anderson Cancer Center Institutional Review Board (U.T. MDACC IRB), regardless of attribution (within **5 working days** of knowledge of the event).

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 values have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

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.

10.0 Unblinding and Criteria for Removal

10.1 Unblinding Procedure

In the event of an SAE (as defined above) or an emergency situation that is likely due to the symptom trial agents as determined by the treating physician or PI, a request for unblinding the symptom trial agents for the affected study subject will be sent via email to invdrugs@mdanderson.org or phoned into the Investigational Pharmacy Services at 713-792-2848. The pharmacy staff will proceed with unblinding and will contact the PI with the symptom trial agent information so that the treating clinicians can appropriately manage the SAE and confirm the specific source of the SAE. All incidents of unblinding will be documented by the Study Team and will also be maintained on file in the Investigational Pharmacy Services for reference. The Investigator must notify The University of Texas MD Anderson Cancer Center Institutional Review Board system (UTMDACC IRB) when unblinding occurs.

10.2 Criteria for Removal from the Study

Patients will be taken off symptom study drug/s if these values are met or exceeded:

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

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

10.23 Total bilirubin > 1.5 times the upper limit of normal

10.24 Signs and symptoms of severe rash (CTC v. 4 $\geq$ grade 3) and hypersensitivity; if these appear, the study drug must be stopped immediately and the patient must be removed from the study

10.25 Pregnancy during the study period

10.26 The patient is taken off chemoradiation treatment for any reason

10.27 INR > 1.5; treating physician notified so that medical management occurs

11.0 Statistical Considerations

11.1 Primary Analyses and Sample Size Justification

The primary outcome variable for this trial will be the mean difference between AUC values recorded for patients assigned to the treatment and control arms. We will enroll 20 patients in each arm, and will test whether the patients in the treatment arm report significantly lower symptom severity. AUC values will be calculated for the five MDASI items corresponding to fatigue, pain, disturbed sleep, lack of appetite, and sore throat. AUC is calculated using a trapezoidal approximation. The area of a trapezoid is derived by multiplying half of the base with the sum of the two heights. The base is the number of days in between two administration of the M.D. Anderson Symptom Inventory (MDASI). The two heights correspond to the two mean symptom scores of the five MDASI items computed at each of those assessments. AUC is the sum of the area of the trapezoids that can be fitted during the 12 week period and is measured in units of mean MDASI score in days. For patients who fail to provide a MDASI response during the study, the missing MDASI value(s) will be obtained by assuming that the missing value is equal to the average of the preceding and subsequent MDASI values. If the preceding (subsequent) value is missing, then the subsequent (preceding) value will be used. A t-test that assumes equal variance between treatment arms will be used to assess statistical significance. With 40 patients, 20 per treatment arm, we will be able to detect a 0.80 standardized effect size on the symptom AUC between the two treatments with 80% power in a one-sided 5% significance test.

11.2 Secondary Analyses

In addition to testing the ability of minocycline to reduce the AUC of the five selected symptoms, we will also perform a number of regression analyses to examine the relationship between AUC values/MDASI values and CRP, IL-6 TNF-a, sTNF-R1, sTNF-R2, and IDO values. These analyses will include linear regression analyses of AUC values on the measured CRP, IL-6, TNF-a, sTNF-R1, sTNF-R2,and IDO values, as well as longitudinal analyses of the relationship between individual symptom scores as measured by MDASI and CRP, IL-6, TNF-a, sTNF-R1, sTNF-R2, and IDO variables. Using linear regression analyses, we will also examine the effects of minocycline treatment on each of the serum markers.

11.3 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 except for those patients who do not complete the initial 2 weeks of symptom intervention drugs. Those patients will be replaced with other participants receiving the same symptom intervention drug combination.

11.4 Failure to Complete Chemoradiation Therapy

Patients who do not complete 2 weeks of chemoradiation therapy will be excluded from the trial analysis. These participants will be replaced with another participant receiving the same treatment.

11. 5 Failure to Contribute Outcome Measurement

Patients who do not complete 5 consecutive MDASI data during the study drug/placebo treatment will be excluded from the trial. These participants will be replaced with another participant receiving the same treatment (Dworkin et al., 2010).

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