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Protocol Page

A Phase II Randomized Study of the Efficacy of Minocycline vs. Placebo to Reduce Symptom Burden during Maintenance Therapy for Multiple Myeloma
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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 ameliorating symptoms that have been identified as prominent during maintenance therapy for multiple myeloma, including **fatigue, pain, bone aches, muscle weakness, and numbness**.

1.2 Secondary outcomes: (1) To evaluate the effect of minocycline vs. placebo on serum and cell inflammatory markers in this patient cohort. (2) To examine the association between inflammatory markers and symptom expression.

2.0 Background

2.1 Multiple Myeloma and Maintenance Therapy

Multiple myeloma (MM) is a plasma cell neoplasm that accounts for approximately 14% of hematological malignancies. More than 15,000 cases of MM are diagnosed in the United States each year. Multiple myeloma is twice as common in African Americans as in white persons, and is slightly more common in men than in women (Rajkumar & Kyle, 2005). The median age at onset is 66 years, and only 2% of patients are younger than 40 years at diagnosis (Sirohi & Powles, 2004).

High-dose chemotherapy supported by autologous hematopoietic stem cell transplantation (AuHSCT) is a standard treatment for MM. Transplant-eligible patients usually receive 2-4 cycles of thalidomide-based or bortezomib-based induction therapy, followed by AuHSCT. Thalidomide (Barlogie et al., 2001; Rajkumar et al., 2002; Singhal et al., 1999; Weber et al., 2003), bortezomib (Jagannath et al., 2005; Richardson et al., 2003, 2004), and lenalidomide (a thalidomide analog) (Dimopoulos et al., 2005; Richardson et al., 2002; Weber et al., 2005) have emerged as effective induction-therapy agents, dramatically altering the way the disease is treated. Disease relapse or progression is the primary reason that MM treatment fails. Patients who do not achieve complete response after induction therapy and/or AuHSCT are likely to receive some form of maintenance chemotherapy, which has been shown to increase the mean progression-free survival (PFS) interval (Boccadoro et al., 2005; Stewart et al., 2004).

Maintenance therapy in MM has been under investigation for more than three decades, but only recently has evidence of clear benefit become apparent. Interferon-based maintenance, which has been associated with minimal improvement in clinical outcomes, is poorly tolerated. Results of corticosteroid maintenance studies have been conflicting, although at least one randomized trial showed improved survival with prednisone maintenance after conventional chemotherapy.

Ongoing randomized trials are evaluating the efficacy of lenalidomide maintenance therapy for MM (Badros, 2010). Recent studies of lenalidomide in the posttransplant setting have established the dosage and timing for the start of lenalidomide after AuHSCT and have shown better PFS. Results from a French multicenter study of lenalidomide maintenance after transplantation for MM indicated that maintenance with lenalidomide improved the three-year PFS from 35% for a placebo group to 68% for a lenalidomide intervention group (N=614, HR=0.46, p<0.001) (Attal et al, 2010). This benefit was observed whether or not patients achieved a complete response after AuHSCT. In multivariate analysis, PFS was related to response after consolidation, beta-2 microglobulin at diagnosis, and treatment arm. The investigators concluded that lenalidomide is an effective maintenance treatment that prolongs PFS after AuHSCT. As a result of this and other studies, **lenalidomide has become a new standard maintenance therapy for patients with MM.**

2.2 Lenalidomide: Safety and Dosing

Lenalidomide is a 4-amino-glutamyl analogue of thalidomide that lacks thalidomide's neurological side effects of sedation and neuropathy, and it has emerged as a drug with activity against various hematological and solid-tumor malignancies. It is approved by the US Food & Drug Administration (FDA) for clinical use in MM. Lenalidomide has been shown to be an immunomodulator, affecting both cellular and humoral branches of the immune system. It has also been shown to have antiangiogenic properties.

The **safety** of lenalidomide was reported in a newly published multicenter Phase I study of patients with relapsed and relapsed/refractory MM receiving maintenance therapy of lenalidomide plus bortezomib (Richardson et al., 2009). The sample included patients previously treated with lenalidomide, bortezomib, and/or thalidomide. The maximum tolerated dose (MTD) was lenalidomide 15 mg/day plus bortezomib 1.0 mg/m^2. The most common treatment-related grade 3–4 toxicities included reversible neutropenia thrombocytopenia, anemia, and leukopenia. Dose-limiting toxicities were grade 3 hyponatremia and herpes zoster reactivation (n=1) and grade 4 neutropenia (n=1). The authors concluded that lenalidomide plus bortezomib was well tolerated and showed promising activity with durable response.

A pooled update of two large, multicenter placebo-controlled randomized Phase III trials (MM-009 and MM-010) (Dimopoulos et al, 2009) assessed lenalidomide plus dexamethasone versus placebo plus dexamethasone in 704 patients with relapsed or refractory MM. Among the patients treated with lenalidomide plus dexamethasone, 38.8% had at least one dose reduction of lenalidomide and 30.9% had at least one dose reduction of dexamethasone due to chemotherapy intolerance. Grade 3 or 4 hyperglycemia was the most common event noted among those treated with placebo-dexamethasone (**Table 1**). Patients treated with lenalidomide -dexamethasone experienced grade 2 (1.4%) and grade 3 (1.4%) peripheral neuropathy. Patients in the placebo-dexamethasone group experienced grade 2 (1.7%) and grade 3 (0.6%) peripheral neuropathy; there were no grade 4 events in either group. Results from this pooled analysis of data from the MM-009 and MM-010 trials, with a median extended follow-up of 48 months, confirm significant response outcomes and significant overall-survival benefits with manageable toxicities for patients treated with lenalidomide and dexamethasone in relapsed or refractory MM.

Table 1. Grade 3 Adverse Events Occurring in More Than 5% of patients

Adverse event, n (%)	Lenalidomide+ dexamethasone (n=353)	placebo + dexamethasone (n=351)
Neutropenia	125 (35.4)**	12 (3.4)
Thrombocytopenia	46 (13.0)**	22 (6.3)
Anemia	38 (10.8)*	21 (6.0)
Pneumonia	32 (9.1)	19 (5.4)
All thromboembolic events	56 (15.9)**	19 (5.4)
Hyperglycemia	27 (7.6)	27 (7.7)
Fatigue	23 (6.5)	17 (4.9)

Muscle weakness	20 (5.7)	11 (3.1)
Hypokalemia	20 (5.7)	5 (1.4)
Asthenia	17 (4.8)	18 (5.1)

* p<0.001; ** p<0.05.

2.3 Symptom Burden During Maintenance Therapy in MM Patients

The expression of multiple concurrent symptoms is often observed in clinical practice. Poor tolerance of maintenance chemotherapy almost always requires patients to undergo dose reduction during treatment. Prompt dose reduction and accurate management of treatment-related toxicity can greatly reduce early discontinuation rates and significantly improve treatment efficacy. Thus, the efficacy of maintenance drugs must always be balanced against their toxicity, even while better symptom management strategies are needed.

Effective symptom management, in cancer as well as in other diseases, has been hampered by the lack of a strong clinical-trial evidence base to guide symptom management practice. Currently, randomized clinical trials manage a single symptom with a single agent (e.g., pain controlled with an analgesic); few evidence-based options are available to clinicians treating multiple symptoms. Further, 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. Notwithstanding, patient-reported outcomes research has recently been promoted by the FDA for more accurate evaluation of therapeutic agents, and symptom reduction has been recognized as a primary clinical benefit for drug approval (US Food and Drug Administration, 2009).

Just as with optimal curative cancer treatments, optimal symptom management is highly likely to be dependent on target of action (mechanistic, empiric, behavioral) (Miller, 2003). Thus, the **overarching goal of the proposed study** is the development of a symptom-management strategy based on underlying symptom mechanism(s) in combination with empiric treatments.

The control or prevention of cancer-related inflammation presents new opportunities for symptom reduction or prevention. To that end, the proposed study aims to investigate the effects of a single agent, minocycline, on multiple symptoms and on inflammation mechanisms. Minocycline is a semisynthetic antibiotic derived from tetracycline that has strong preclinical and clinical evidence of anti-inflammatory effects. The **primary objective** of this randomized Phase II clinical trial is to explore broad proinflammatory cytokine blockade by minocycline, as a rationale for managing the **general symptoms** of MM (fatigue, muscle weakness, and bone aches) and the **neuropathy** (pain and numbness/tingling) induced by novel induction and maintenance therapies. The **secondary objectives** of the study are to evaluate the effect of minocycline on inflammatory markers and to examine the associations between inflammation and symptom expression. Although clinical outcomes have been explored, to our knowledge no study has examined whether downregulating a network of cytokines would be helpful for symptom reduction during maintenance therapy for MM.

2.31 Preliminary study on symptom burden

In our ongoing descriptive symptom study during maintenance therapy for MM (protocol 2007-0612, unpublished data from P01-supported study), we observed the trajectory of symptom development based on patient report from the M. D. Anderson Symptom Inventory for multiple myeloma (MDASI-MM), a validated multisymptom assessment tool. Our results show that three months post-AuHSCT, patients often still suffer from some residual symptom burden related to previous therapy, with pain being the most severe symptom, followed by fatigue, numbness, bone aches, muscle weakness, and disturbed sleep. About one third of patients (32%) reported either pain or fatigue at 4 or greater on the MDASI-MM's 0-10 scale.

Table 2 presents the mean severity of the most severe patient-reported symptoms during the three to six months post-AuHSCT. These data provide the rationale for the symptom intervention target chosen for this study. Pain, fatigue, muscle weakness, and bone aches were consistently the worst symptoms over time. Numbness, indicative of chemotherapy-induced peripheral neuropathy, remained a significant issue for these patients in the three to six months post-AuHSCT. Appetite recovered after a nadir within 3 months of AuHSCT.

Table 2. Descriptive Statistics of MDASI-MM Symptom Severity (N=Number of Observations)

	N	Mean (Std. Deviation)	Patient Reported Moderate to Severe Symptoms on MDASI
Pain	400	2.86 (2.69)	32.5%
Fatigue	399	2.85 (2.43)	34%
Numbness	398	2.80 (3.04)	36%
Muscle weakness	398	2.43 (2.41)	27%
Bone aches	398	2.36 (2.71)	27%
Disturbed sleep	399	1.84 (2.11)	21%
Drowsiness	398	1.64 (1.95)	18%
Lack of appetite	398	0.59 (1.44)	6%

2.32 Inflammation and Symptom Burden

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 interleukin (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).

Exposure of peripheral nerves to inflammatory cytokines results in extirpation of myelin and perineural swelling like that observed in the early stages of Wallerian degeneration as well as that observed in neural biopsies from chemotherapy-treated animals and humans. While the specific causes of chemotherapy-induced peripheral neuropathy remain to be fully elucidated, the severity of such neuropathy may be reduced by inhibition of proinflammatory cytokines.

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 MM patients. Post AuSCT patients 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.
Interim results from the ongoing study described above (protocol 2007-0612) provided preliminary results that frequent assessment can document the longitudinal course of multiple symptoms during induction therapy for MM and provides opportunity to evaluate systemic inflammation as a potential source of symptom burden during induction (Cleeland et al., 2012, unpublished data). Bortezomib-based induction therapy was received by 89% of the sample. Fatigue was persistently the most severe symptom during induction therapy, followed by disturbed sleep, muscle weakness, pain, drowsiness, and bone aches. Numbness, which is representative of chemotherapy-induced peripheral neuropathy, significantly worsened from baseline ($p=0.01$). We observed significant longitudinal associations between sIL-1R1 and distress and sadness (both $p=0.02$); between sIL-6R and disturbed sleep ($p=0.001$), poor appetite ($p=0.04$), and sore mouth ($p=0.006$). IL-6 was significantly associated with pain, fatigue, nausea, and sore mouth (all $p<.05$). A negative association between sTNF-R2 and pain, sleep, distress, remembering, poor appetite, and nausea (all $p<0.05$) was also observed. MCP-1 was positively associated with numbness ($p=0.04$), while MIP-1a was negatively associated with sleep, numbness, constipation, poor attention (all $p<0.01$), and bone aches ($p=0.0006$). IL-10 was negatively associated with mood interference ($p=0.04$).

To this end, the **primary objective** of this randomized Phase II clinical trial is to explore broad pro-inflammatory cytokine blockade by minocycline, as a rationale for **managing the general symptoms of MM** (fatigue, muscle weakness, and bone aches) and treatment-induced neuropathy (pain and numbness/tingling) by novel agents from previous induction therapy and from maintenance therapy in patients with myeloma. **Effects of minocycline on inflammatory markers as the rationale for the secondary objective of the trial.**

Although inflammatory mechanisms have been investigated with clinical outcomes in MM, to our knowledge, no study has examined whether downregulating a network of cytokines would be helpful for **symptom reduction**, this is our objective for this proposed study. On the basis of strong evidence that minocycline has a wide range of anti-inflammatory effects in the brain and peripheral system, which it accomplishes by inhibiting microglial activation and proliferation through inhibition of the p38 MAKP pathway, we propose a Phase II, 2-arm, double-blind, placebo-controlled randomized study in MM patients undergoing maintenance therapy. Minocycline's capacity to cross the blood-brain barrier makes it desirable for testing the role of inflammatory cytokines in producing symptom burden. The positive results may immediately help patients with MM live with fewer symptoms during survival and will support a mechanism-driven approach to managing cancer-related symptoms with this low-toxicity drug. Finally, positive results in humans would set the stage for a future proposal with phase III trial in this cohort of patients to confirm that the manipulation of peripheral and central inflammation by anti-inflammatory agents such as minocycline will relieve multiple symptoms.

3.0 Background Drug Information

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 to effect broad cytokine blockade.

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 interleukin (IL)-6, tumor necrosis factor (TNF)-α, IL-1β and interferon-γ (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 prevented 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). In addition, minocycline reduces activation of caspases including caspase-1 and caspase-3 which may further limit neural cell death (Stirling et al., 2005).
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 C-reactive 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.
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. Other adverse effects reported include serum sickness-like reactions, ototoxicity, azotemia, pulmonary infiltrate formation with associated eosinophilia, and discoloration of the sclera or teeth. A rare but serious reported side effect is pseudo-tumor cerebri.

3.1 Absolute Contraindications to Study Symptom Intervention Agent Minocycline

3.11 Hypersensitivity to any tetracycline

3.12 Pregnancy

3.13 Hepatotoxicity (aspartate aminotransferase (AST) or alanine aminotransferase (ALT); 2 times the upper limit of normal)

3.2 Minocycline Clinical Pharmacology

3.21 Metabolism

Minocycline is metabolized to a significant degree; however, the nature of the metabolic products or sites of metabolism have not been elucidated with certainty (Allen, 1976b)

3.22 Pharmacokinetics

Minocycline has a long serum half-life and can be administered at 12-hour intervals

3.23 Time to Peak Concentration

Oral: 1 to 4 hours (Prod Info Dynacin®,2011); (Prod Info Minocin®, 2008)(Simon et al, 1976; MacDonald et al, 1973).

- One to four hours after a single dose of two 100-mg minocycline pellet-filled minocycline capsules were given to 18 healthy fasting adults, the Cmax ranged from 2.1 to 5.1 micrograms per milliliter (mcg/mL) (Prod Info Minocin®, 2008)(Simon et al, 1976)
- One hour after a single dose of two 100-mg minocycline capsules was given to 10 normal adult volunteers, the Cmax ranged from 0.74 mcg/mL to 4.45 mcg/mL (Prod Info Minocin®, 2008)

3.3 Minocycline Common Adverse Reactions

3.31 Minocycline: dizziness (9%) and vertigo

3.4 Minocycline Monitoring Parameters

3.41 Minocycline: LFTs, BUN, Sr Cr
3.42 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.

3.5 Minocycline Drug Interactions

3.51 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 two hours of using this medication**
3.52 Methoxyflurane anesthesia: when concurrent with minocycline, may cause fatal nephrotoxicity
3.53 Retinoic acid derivatives: May increase risk of pseudotumor cerebri
3.54 Warfarin: hypoprothrombinemic response may be increased with tetracyclines; **monitor INR closely during initiation or discontinuation**
3.55 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

3.6 Serious Adverse Events for Minocycline

No serious adverse events (SAEs) have been reported for this trial agent.

References:

1. www.fda.gov, drug information
2. National Committee for Clinical Laboratory Standards, Performance Standards for Antimicrobial Susceptibility Tests—Eighth Edition; Approved Standard. NCCLS Document M100-S8, Vol.18, No.1, NCCLS, 940 West Valley Road, Suite 1400, Wayne PA, January 1998.
3. http://www.drugs.com/pro/minocycline.html

4.0 Treatment Plan

We will conduct a **double-blind, placebo-controlled Phase II study** of minocycline vs. placebo in patients receiving a maintenance regimen containing lenalidomide. The placebo controlled, double blinded design is especially important in trials where symptom reduction is the outcome and where knowledge of the treatment arm might bias assessment staff.
Patients will be randomized between two treatment arms:

- **Arm A (Group 1):** will receive a placebo 200 mg orally for the first day of maintenance therapy for MM, then 100 mg doses every 12 hours for three months (three cycles of maintenance chemotherapy).
- **Arm B (Group 2):** will receive minocycline 200 mg orally for the first dose, then 100 mg orally every 12 hours for three months beginning at initiation of maintenance therapy for MM.

Minocycline is currently approved by the FDA for the treatment of bacterial infections. The dose and schedule of minocycline chosen for this study (**Table 3;** Lexi-Comp) follows that used for this approved indication.
Table 3. Dosing Schedule

Symptom Intervention Agent	Dosage Forms	Initial Dose (first day of lenalidomide therapy)	Subsequent Doses (second day of lenalidomide therapy

			and thereafter)
Minocycline or matching placebo	100 mg capsules	200 mg (two 100-mg capsules)	100 mg two times a day (200 mg/day)

Study Period: three months, to begin concurrently with the start of maintenance therapy. This time frame will be long enough to allow for the evaluation of the impact of minocycline on symptom reduction and serum cytokine levels in patients with MM after AuHSCT, but most likely before occurrence of relapse.
Disease progression and survival data will be tracked during the study.
Primary Outcome Variable: Minocycline will be tested for its ability to reduce the value of a patient's three-month (± two days) area under the curve (AUC) for five symptoms: fatigue, pain, muscle weakness, numbness, and bone aches, either in combination or individually.

The 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 computed at each of these assessments. The AUC is measured in units of mean MDASI score in days. The area for the subsequent trapezoid can be calculated in the same way. Given a baseline, weekly assessment schedule over a three month period and end of trial assessment, there will be a total of 14 trapezoids. The AUC is the sum of the area of the 14 trapezoids.

Baseline assessments are to occur prior to start of maintenance therapy. Administration of the symptom intervention agent will start the day maintenance therapy commences or within two days.
Chemotherapy Regimen: The chemotherapy agent is lenalidomide, because it was the standard of care suggested by MM experts at both ASH 2009 (McCarthy, et al., 2009) and ASCO 2011 (Dimopoulos, et al., 2011). All patients in both study arms will receive standard instructions from their treating physicians and/or designees about the risk of development of peripheral neuropathy with lenalidomide therapy, about the signs and symptoms of peripheral neuropathy, and about reporting signs and symptoms of peripheral neuropathy to their treating physicians. Symptomatic management of CTC $\geq$ grade 2 painful neuropathy (e.g. duloxetine hydrochloride, gabapentin, pregabalin) will be allowed on both arms of the study. As there are no standardized treatment guidelines for chemotherapy-induced peripheral neuropathy, the choice of treatment will be made at the discretion of the treating physician. However, a list of medications given for treatment of peripheral neuropathy, and the date each medication was started and stopped, will be collected by the clinical study coordinator at each clinic visit.
Serum/Plasma Inflammatory Markers: Markers of inflammation are selected from among the effector components of the inflammatory response (cytokines and their soluble receptors) or their target molecules (e.g., CRP). Circulating cytokines to be measured include proinflammatory and anti-inflammatory cytokines and receptors (IL-1RA, IL-6, IL-8, sIL-6R, IL-10, MCP-1, sTNF-R1, and sTNF-R2). Transcriptional factor (p50/p65 of nuclear factor [NF]-κB) that was appreciated as a factor regulating IL-6 expression *in vivo* in an MM cell line study and p38 MARK that been considered the mechanism underlying minocycline's anti-inflammatory effect, will be tested. As IL-6 can induce the production of IL-1RA and sTNF-R1 to block the action of IL-1 and TNF-α, both of which play a major role in disease progression, we will also assess the biological activity of IL-6 by measuring soluble IL-1RA and sTNF-R1. In general, if IL-6 activity is strongly inhibited, it will be indicated by reduced CRP levels, which we have included in the panel of biomarkers to be tested. We will also test the kynurenine/tryptophan ratio that associated with increased plasma levels of neopterin, a marker of macrophage activation, which points to activation of the tryptophan-catabolizing enzyme IDO.

5.0 Patient Eligibility

5.1 Inclusion Criteria:

5.11 Patients with pathologically diagnosed who have received induction chemotherapy, with or without AuSCT, and who have qualified to receive lenalidomide-based maintenance therapy for their MM.
5.12 Patients $\geq$ 18 years old.
5.13 Patients able to render informed consent and to follow protocol requirements.
5.14 Patients who speak English (due to PRO language options, we are only accruing English-speaking patients to the protocol).
5.15 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 the upper limit of normal].
5.16 Patients with normal hepatic function according to MD Anderson testing standards and no prior liver disease [screening results for total bilirubin must be < 1.5 times the upper limit of normal; screening results for alkaline phosphatase (ALP) and alanine aminotransferase (ALT) must be < 2 times the upper limit of normal; if available, screening results for aspartate aminotransferase (AST) must be < 2 times the upper limit of normal].

5.2 Exclusion Criteria

5.21 Patients who are taking minocycline for other conditions, as determined by the treating physician
5.22 Patients with hypersensitivity to tetracyclines
5.23 Women who are pregnant or nursing; pregnancy will be confirmed by urine test
5.24 Patients who are enrolled in other clinical trials that have symptom management as primary outcome
5.25 Patients who are not able to use telephone-based interactive voice response software due to physical limitations (e.g., impaired hearing)
5.26 Patients taking tetracycline within the last 15 days
5.27 Patients on vitamin K antagonist warfarin

6.0 Pretreatment evaluation

6.1 Patient Enrollment and Registration

Patients will be screened for eligibility and recruited for enrollment in the outpatient clinic approximately three months post-AuHSCT, during a regularly scheduled follow-up clinic visit. 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 study. The stipend will be distributed in $20 increments three times during the study, at start of each cycle of therapy at the clinic visit.
Enrolled patients will be registered into the Clinical Oncology Research System (CORe), the institutional patient data management system.

6.2 Patient Randomization and Assignment to Treatment Arm

The study will accrue a total of 88 patients, with 44 patients randomized to each of the two arms (minocycline and placebo). Prior to accrual of the first patient, a randomization list matched to accrual numbers will be generated for all 88 patients by our biostatistician collaborator from the Department of Biostatistics. This list, containing the accrual number and treatment group information, will be set up in the Clinical Trial Conduct website.
When a patient is registered on study the Investigational Pharmacy will retrieve the randomization assignment information from Clinical Trial Conduct website.
Once a patient is randomized to a treatment arm, the Investigational Pharmacy will relay the information to the dispensing pharmacy. The patient will visit the most convenient outpatient pharmacy to pick up the study medication assigned.
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 Section 10.1 for unblinding procedures). In the event of a grade 3-4 SAE that may be related to the study medication, the treating clinician will contact the Investigational Pharmacy to determine the patient's randomization group.

6.3 Pretreatment Evaluation

6.31 In order for study staff to determine patient eligibility, patients must have the following tests **prior to initiating maintenance** chemotherapy and the study trial agent. These tests will be completed by their treating physician, as part of their pretreatment evaluation for lenalidomide therapy.
6.311 Blood chemistries (albumin, creatinine, SGOT**,** total bilirubin, ALT, and ALP) and complete blood count (WBC, Hgb, platelets) will be reviewed; we will also document other lab data if available in the patient medical records (Appendix D)
6.312 Pregnancy test, if the patient is a female of childbearing potential
6.313 History and physical examination (including documentation of current medications and Eastern Cooperative Oncology Group performance status (ECOG PS)
6.32 **After consent but prior to initiating chemotherapy** and the study trial agent, patients will complete the following baseline assessments, which will require approximately 20 minutes.
6.321 Assessment of cancer-related symptoms via the paper-and-pencil version of the MDASI-MM or by tablet PC; demonstration of the interactive voice response (IVR) system will be conducted at enrollment and an instructional brochure will be given to patients
6.322 Assessment of neuropathic pain (Chemotherapy-Induced Peripheral Neuropathy [CIPN]-20)
6.323 ID Pain and Treatment-Related Neuropathy Assessment Scale
6.324 Beck Depression Inventory
6.325 Blood collection for serum cytokine analysis

7.0 Evaluation During Study

Baseline assessments are to occur prior to start of lenalidomide maintenance therapy. The symptom intervention agents (minocycline or placebo) will start the day of or within two days of the start of lenalidomide therapy and continue for three cycles (approximately three months). Assessments made every cycle may be completed within +/- three days of the cycle start date.

Patients will pick up the assigned study medications at one of the outpatient pharmacy stations within MD Anderson. At pickup, patients will receive instruction in how to take study medications. The participants will take study medication enterally, twice daily, in the morning and evening. The final day of study medication is three months after medication is started.
Study medication use will be reviewed by study staff. Study staff will contact patients weekly to check for adverse events during therapy either in routinely scheduled clinic visits or via telephone calls. Study staff will make weekly phone calls for 30 days after completion of the study medication.
Patients and family members will be asked to notify the research team if the patient is hospitalized or moves to another location. Patients hospitalized because of complications will be identified and tracked by the research coordinator. Tracking of patient hospital admissions will be conducted either through (1) checking admissions through the institutional database; (2) contacting the closest relative; (3) follow-up calls after no IVR contact for two weeks, and/or (4) follow-up with the outpatient clinic nurse in the clinic. The reason for hospital admission will be recorded on the checklist. When a family member or health care provider notifies the research coordinator of the death of a patient, the date of death will be recorded.

7.1 Patient-Reported Outcome (PRO) Measures
7.11 Symptom Assessment (Appendix E)

Symptoms will be measured by the MDASI-MM (Appendix E). The core M. D. Anderson Symptom Inventory (MDASI) is a multiple-symptom measure of the severity of cancer-related symptoms and the functional interference caused by symptoms (Cleeland et al., 2000) that is sensitive to disease and treatment changes (Cleeland et al., 2004). This instrument is brief, easily understood, and validated in the cancer population. Patients rate the severity of 13 physical, affective, and cognitive symptoms on 0–10 numeric scales, ranging from "not present" to "as bad as you can imagine." The MDASI also assesses 6 items related to symptom interference with functioning, also on a 0–10 numeric scale ranging from "did not interfere" to "interfered completely."
The MDASI-MM includes the 13 symptoms and 6 interference items from the core MDASI, along with seven additional symptoms known to be important in assessing patients with MM (constipation, muscle weakness, diarrhea, sore mouth or throat, rash, difficulty concentrating, and bone aches). The MDASI-MM takes less than five minutes to complete and will be administered at baseline and weekly during the study. The MDASI-MM will be collected either face to face in the clinic, through phone calls by field coordinators, or through the IVR system described in the next section.

7.12 Delivery of Repeated Multiple-Symptom Assessments

The longitudinal tracking of symptoms in patients can be greatly facilitated by using an Interactive Voice Response System (IVR) system, which is programmed to call patients at home for symptom assessment. The IVR system asks patients to rate each symptom and interference item on the MDASI-MM's 0 to 10 numeric scales using the keypad of a touchtone telephone. We will use the IVR weekly to administer the MDASI-MM.
Participants will be provided with an informational brochure outlining the steps to complete an IVR call. A telephone number will be provided in the event of questions or problems. Patients will also be given a Patient Identification Number (PIN) for access to the system (Appendix F). IVR calls will be scheduled at a time that is convenient for the patient.
Patients will be instructed by the research team to report severe symptoms to their physician or go to the emergency room. The research staff will notify the clinical service should patients report a high symptom-severity level. These patients will receive standard care at MD Anderson.

Missed Calls: Completion or failure of calls will be monitored by the research staff. In the event of missed calls, a notification screen will appear in the IVR system to alert the research staff. The research staff will then contact the patient, check on their status and, if possible, complete the assessment with the patient during the telephone interview. The system will continue calling the patient at the preset schedule.
Data Security: The IVR symptom and interference data will be available on an MD Anderson intranet site with access limited to authorized project staff only. Patient data will be identified by subject study number.

7.13 Measure of Neuropathic Pain (Appendix G)

The Chemotherapy-Induced Peripheral Neuropathy (CIPN)-20 is a 20-item patient self-report questionnaire that provides valuable information on CIPN-related symptoms and functional limitations of patients exposed to potentially neurotoxic chemotherapeutic and/or neuroprotective agents (Postma et al., 2005). This tool will be administered to the patients at baseline, at the start of each cycle, and at end of study.

7.14 Neuropathic Pain Screening Tool (Appendix I)

The ID Pain questionnaire is a short six-item self-report screening tool designed to help differentiate nociceptive and neuropathic pain (Portenoy, 2006). This tool will be administered to patients at baseline, at the start of each cycle, and at end of study, to aid in the identification of patients with neuropathic pain.

7.15 Measure of Neuropathic Pain (Appendix J)

The Treatment-Related Neuropathy Assessment Scale is an 11-item patient reported outcome measure that provides an additional opportunity to capture the chemotherapy-induced neurosensory changes that were not captured on the ID Pain or MDASI-MM. This tool will be administered to patients at baseline, at the start of each cycle and at end of study, to aid in the identification of patients with neuropathic pain.

7.16 Measure of Mood (Appendix K)

The Beck Depression Inventory-II (Beck et al., 1996) is a 21-question multiple choice survey that asks questions about depression symptoms, including emotions such as hopelessness and irritability, cognitions such as guilt or feelings of being punished, and physical symptoms such as fatigue, weight loss, and lack of interest in sex. Participants are asked to rate how they have been feeling for the past two weeks. Each answer is given a value of 0 to 3. The scoring is as follows: 0-13 = minimal depression; 14-19 = mild depression; 20-28 = moderate depression; and 29-63 = severe depression. Higher total scores indicate more severe depressive symptoms. This tool is to be administered at baseline, and at end of study.

7.2 Case Report Forms

Case report forms (CRFs) include information that will be collected for the study. MM therapy and toxicity, comorbidity, ECOG PS, and other medications will be documented. Tumor evaluation is not required but will be collected when data are available in the patient medical records.

7.21 Case Report Form Checklist (Appendix L)

The Case Report Form Checklist is to be completed at the time that patient-reported outcome measures (section 7.1 above) are completed, either by paper and pencil or tablet PC.

7.22 Demographic Form (Appendix M)

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

7.23 On-Study Form (Appendix N)

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

7.24 Charlson Comorbidity Index (Appendix O)

The Charlson Comorbidity Index yields a comorbidity score, to control for serious concurrent chronic disease conditions (Charlson et al., 1994). The Charlson Index will be used as a covariate in the analyses. This form will be completed at baseline.

7.25 Clinical Monitoring Form (Appendix P)

The Clinical Monitoring Form contains clinical data including body mass index (BMI), blood pressure, pulse rate, performance status, symptom treatment. It also includes data about types of medication patients have been prescribed, such as pain medications and adjuvant analgesics, as well as other types of medications patients may be taking. This form will be completed at each clinic visit. If no clinic visit is scheduled until the study is over, this information, if available, will be obtained from the local treating facility.

7.26 Laboratory Data Form (Appendix D)

The lab values from standard care will be collected at baseline and each cycle if they are available in the medical record. If the research blood sample was collected, this will be recorded. This form will be completed at each clinic visit. If no clinic visit is scheduled until the study is over, this information, if available, will be obtained from the local treating facility.

7.27 Myeloma Protein Data Form (Appendix R)

The Myeloma Protein Data form collects information derived from serum and urine protein electrophoresis. This information will be collected each cycle and at end of study. If no clinic visit is scheduled until the study is over, this information, if available, will be obtained from the local treating facility.

7.28 Study Medication Accountability (Appendix S)

The Study Medication Accountability Form contains study medication data from the research staff capsule count. Data includes the number of capsules dispensed to the patient at the last visit to the outpatient pharmacy, the number of days the pills were taken, the number of capsules returned at the last visit, and the number of capsules dispensed during the current visit. This information will be collected each cycle and at end of study.

7.29 Treatment Summary Form (Appendix T)

The Treatment Summary Form contains data about treatment received and tumor evaluation after treatment. This information will be collected at end of study only if available in the patient medical records.

7.30 Final Study Status Form (Appendix U)

The Final Study Status Form contains data about patient disposition at the end of the study (i.e., completed study, withdrew, vital status). This information will be collected at end of study.

7.3 Data Collection for Inflammatory Marker Assay

If possible, research samples will be collected at baseline, at cycle start date, and at end of trial. IL-6, sTNF-R1 and other serum cytokines have a great ability to discriminate between subjects in responding to therapy, but a discrimination ratio can only be calculated with repeated sampling of the population under study because it corresponds to the ratio of the between-subject to within-subject variance. Serum/plasma cytokines will be measured at clinic visits. A 7-mL blood sample will be collected from patients in a tube without anticoagulant (red top tube) to obtain serum for the detection of cytokines. The Luminex Multiplex Cytometric Bead Array (Multiplex) assay or enzyme-linked immunosorbent assay (ELISA) will be used to measure cytokines.
Cellular sample collection: A 10-mL peripheral blood sample will be collected in Vacutainer tubes with heparin (green top tube). Peripheral blood mononuclear cells (PBMC) will be isolated using density gradient centrifugation (Ficoll-Hypaque) separation. The PBMC pellet will be lysed for assessment of active NF-κB using the ELISA-based TransAM assay (Active Motif, Carlsbad, CA).

7.4 Assessment Schedule

Patient-reported outcome measurements and case report forms listed here are located in the appendices of this protocol as indicated by the letters in brackets.

Table 4. Clinical and Laboratory Monitoring Schedule

Form [Appendix]	Baseline	During Trial	End of Trial
MDASI-MM [E]	X	weekly	X
CIPN 20 [G]	X	every cycle	X
ID Pain Questionnaire [I]	X	every cycle	X
Treatment-Related Neuropathy Assessment Scale [J]	X	every cycle	X
Beck Depression Inventory II [K]	X		X
Case Report Form Checklist [L]	X	every cycle	X
Demographic Form [M]	X		
On-Study Form [N]	X		
Charlson Comorbidity Index [O]	X		
Clinical Monitoring Form [P]	X	every cycle	X
Laboratory Data Form [D]	X	every cycle	X
Myeloma Protein Data Form [R]	X	every cycle	X
Study Medication Accountability Form [S]	-	every cycle	X
Treatment Summary Form [T]	-	-	X
Final Study Status Form [U]	-	-	X
Research blood sample for biomarkers (If possible)	X	every cycle	X

Baseline: before the first dose of maintenance treatment is administrated.

End of trial: completion of three cycles of maintenance chemotherapy, or upon patient withdrawal

Assessments may be completed within +/- three days of the cycle start date.

8.0 Data Monitoring Plan

8.1 Data Confidentiality

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.
Patient folders containing CRFs are marked with patient initials, CORe accession number, and the protocol number. These patient folders are kept in locked cabinets in the Department of Symptom Research.
Once the research has been completed, patient data will be stored in an institutional big data warehouse and made available to all research and clinical faculty, with appropriate validation and access controls, so it can facilitate research cross-fertilization and speed insight discovery.
Data is collected either (1) on scannable paper-and-pencil Teleforms that can be administered face-to-face in the clinic, through phone calls by field coordinators, or by regular mail, or (2) via Health Insurance Portability and Accountability Act (HIPAA)-compliant, institutionally approved, secure electronic data-capture methods (eg, tablet PCs in the clinic; the telephone-based, computerized interactive voice response system (IVR); or the web-based REDCap application hosted by MD Anderson). Electronic capture eliminates the need for

manual data entry. All data resides in a relational database with audit tracking for efficient data retrieval. All data and software related to the patient data are password protected with controlled access.

A custom software application performs protocol tracking. The software monitors patients as they progress through the protocol from screening to off-study and informs the data coordinators of protocol events and what CRFs to administer.

Data management and quality assurance is conducted using REDCap. REDCap (Research Electronic Data Capture) electronic data capture tools (www.project-redcap.org) is a secure, web-based application hosted at MD Anderson with controlled access designed to support data capture for research studies (Harris et al., 2009). REDCap provides: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless downloads to common statistical packages; and 4) procedures for importing data from external sources. In the case of multi-center studies REDCap uses Data Access Groups (DAGs) to ensure that personnel at each institution are blinded to the data from other institutions. REDCap (https://redcap.mdanderson.org) is hosted on a secure server by MD Anderson's Department of Research Information Systems & Technology Services. REDCap has undergone a Governance Risk & Compliance Assessment (05/14/14) by MD Anderson's Information Security Office and found to be compliant with HIPAA, Texas Administrative Codes 202-203, University of Texas Policy 165, federal regulations outlined in 21CFR Part 11, and MD Anderson's Institutional Policy #ADM0335. Those having access to the data file include the study PI and research team personnel. Users are authenticated against MD Anderson's Active Directory system. External collaborators are given access to projects once approved by the project sponsor. The application is accessed through Secure Socket Layer (SSL). All protected health information (PHI) will be removed from the data when it is exported from REDCap for analysis. All dates for a given patient will be shifted by a randomly generated number between 0 and 364, thus preserving the distance between dates. Dates for each patient will be shifted by a different randomly generated number. After publication, study data will be archived in REDCap.

8.2 Data Monitoring

The Department of Symptom Research has a comprehensive data monitoring process in place. This system ensures compliance with regulatory agencies and the accuracy and timeliness of data from the point of consenting a patient to having a completed data set ready for analysis.
Patient consents are reviewed to ensure patient and data coordinator signatures are legible and correctly located. The dates of the consent are reviewed for accuracy and to determine that all pages of the consent are available. Progress notes developed by the PI state that the inclusion and exclusion criteria were discussed with the patient and the patient understood the consent form. The age of the patient and the date of consent are included in the progress notes.
Patient-reported outcomes data are collected by paper and pencil administration, IVR, or tablet PCs. CRFs may be completed in paper format or with the tablet PC. Paper forms are designed in Teleform (a paper document data capture system that electronically scans the data on a page, thereby eliminating the need for manual data entry). The tablet PC and IVR are electronic data capture systems. All data resides in a relational database for efficient data retrieval. A protocol tracking software system monitors the patient as s/he progresses through the protocol from screening to off study, and it informs the data coordinators of protocol events and which CRFs to administer at a given time point. The software also tracks when patient data is collected, scanned, and monitored. All data and software related to the patient data is password protected with controlled access.
Patient-reported assessments and CRFs are organized into packets based on the time point of delivery to the patient, for ease of administration and accuracy. Source documents on all clinical variables in the protocol are obtained and printed from Clinic Station. Patient folders contain patient data along with the source documents.
Data management and quality assurance for symptom outcome data are performed using a custom software application developed by the Department of Symptom Research. This powerful tool expedites routine data processing by simplifying the creation of custom algorithms and storing them for future use. These algorithms check the data for potentially erroneous values, and then automatically write them to an error log for later review. Dataset review also consists of reviewing labels, value codes of the data, and logic checks. Should the data require correction, the changes are made to the data themselves, and the description of those changes are documented in the error log. The data management application also allows for easy dataset construction using several preloaded architectural paradigms.

9.0 Reporting Requirements

9.1 Adverse Events

Patients will be seen in the outpatient clinics for each chemotherapy cycle, allowing for close monitoring of potential adverse events (AEs) by clinic and research staff. 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.
Grade 1 and Grade 2 AEs will not be reported. AEs that are Grade 3 and above are considered to be serious adverse events (SAEs) and will be reported. SAEs that are **unexpected and related** (definitely, probably, or possibly related) to the study medication will be reported promptly according to institutional policies (see Section 9.2 below). SAEs that are either (1) **expected** or (2) **unexpected but unrelated** (unrelated or unlikely to be related) to the study medication will be summarized on the continuing review report. The principal investigator and the treating physician will determine whether or not an AE is related to the study medication.
The PI or physician designee is responsible for verifying and providing source documentation for all AEs and assigning the attribution for each event for all subjects enrolled on the trial.

9.2 Serious Adverse Events

9.21 Definition

A serious adverse event (SAE) 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 (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 or 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 an SAE when, based upon appropriate medical judgment, they may jeopardize the patient 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).

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

9.22 Reporting Serious Adverse Events

It is the responsibility of the PI and the research team to ensure SAEs are reported according to the Code of Federal Regulations, Good Clinical Practices, protocol guidelines, the sponsor's guidelines, and MD Anderson Institutional Review Board (IRB) policy.
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 University of Texas MD Anderson Cancer Center (UTMDACC) IRB **within five working days** of knowledge of the event, regardless of attribution.
All **life-threatening or fatal events**, regardless of attribution to the study drug, must be reported to UTMDACC IRB **in writing within 24 hours** (next working day) of knowledge of the event.
Additionally, any SAEs that occur more than 30 days after the last dose of study drug that are related to the study treatment must be reported to the UTMDACC IRB Office. This may include the development of a secondary malignancy.
The MD Anderson "Internal SAE Report Form for Prompt Reporting" will be used for reporting to UTMDACC IRB. (See Appendices V and W for CRFs to be included in the study database).

10.0 Criteria for Removal from the Study

10.1 Unblinding Procedure

In the event of an SAE as defined above or an emergency situation that is likely caused by the symptom trial agents as determined by the treating physician or PI, a request for unblinding the symptom trial agents for the affected patient will be sent via e-mail (Invdrugs@mdanderson.org) or phoned into the Investigational Pharmacy at 713-792-2848. Investigational 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 Investigational Pharmacy Services for reference.

10.2 Criteria for Removal from the Study

10.21 Development of an SAE related to the study drug
10.22 Inability to comply with protocol requirements (See sections 11.3 to 11.5)
10.23 Discontinuation of treatment with lenalidomide
10.24 Pregnancy during the study period
10.25 Any of these values are met or exceeded:

10.251 Alkaline phosphatase (ALP) > 2 times the upper limit of normal
10.252 Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2 times the upper limit of normal
10.253 Total bilirubin > 1.5 times the upper limit of normal
10.254 Signs and symptoms of severe rash (CTC $\geq$ grade 3) and hypersensitivity; if these appear, the study drug must be stopped immediately and the patient must be removed from the study
10.257 INR > 1.5; treating physician notified so that medical management occurs

10.26 Completion of study

11.0 Statistics consideration

11.1 Sample Size

We hypothesize that, compared with a placebo group, patients with MM undergoing lenalidomide maintenance therapy who are randomized to receive 200 mg minocycline will exhibit reduced severity in a cluster of symptoms, such as fatigue, pain, muscle weakness, bone aches, and neuropathy (numbness). **Our primary outcome variable is the daily area under the curve (AUC) calculated from three months posttransplantation (beginning of study) to six months posttransplantation.** The AUC is based on the average of the five most-severe symptoms (pain, fatigue, bone aches, numbness, muscle weakness) reported by MM patients in our previous studies. On the basis of our pilot data, we estimate a standard deviation for this AUC measurement of 304.2. We will be able to detect a difference of 182.8 (a moderately large effect size of 0.6*SD) on the symptom AUC between the two treatments with 80% power in a one-sided 5% significance test using 35 patient per treatment arm. We expect to enroll three patients per month. Allowing for an attrition rate of 20%, we will need a total of 88 patients. No interim analysis is planned.
Missing MDASI-MM value(s) will be obtained by using **LOCF (last observation carried forward). To assess the effect of early dropout on the study results, we will perform sensitivity analyses.**

11.2 Analysis Plan

The primary analysis will be based on a two-sample t-test or its nonparametric counterpart to test the null hypothesis that the mean AUC score for patients in the two arms are equal against the alternative that the minocycline group has smaller AUC compared to the placebo group.

Statistical analyses employed in support of the secondary objective will focus on longitudinal modeling of MDASI-MM scores. Regression functions to predict these scores will include predictors derived from cytokine and other serum markers measured at the four clinic visits scheduled for patients during the maintenance phase of treatment. More specifically, we will fit ordinal probit models to individual MDASI-MM symptom items. Random patient effects will be included in these regression analyses, as will the primary independent variable of interest (whether or not the patient received minocycline). Global effects of treatment on MDASI-MM symptom measures will similarly be estimated by fitting generalized estimating equation (GEE) regression models to the AUC area measured for the component score for the most severe symptoms (which will be generated from the trial results; expected to be pain, fatigue, numbness, muscle weakness, and bone aches); these models are expected to include patient baseline measures of these symptoms and treatment dose as explanatory variables. Conclusions from these analyses will be based on the magnitudes of estimated regression coefficients relative to their standard error of estimation. In addition, we will fit longitudinal models that treat patient baseline measurements, treatment time, and other covariates (such as age, sex, BMI, comorbidity, standard symptom control) as explanatory variables.

Change in neuropathy scores will also be calculated and a linear model similar to that described above will be used to test the effect of treatments on the MDASI-MM scores. The same set of covariates will be used in this model.

Secondary Analyses: In addition to testing the ability of minocycline to reduce the AUC of the five most-severe symptoms, we will also perform a number of regression analyses to examine the relationship between AUC values/MDASI-MM values and CRP, IL-6, and IDO values. These analyses will include linear regression analyses of the effect of AUC values on CRP, IL-6, and IDO values, as well as longitudinal analyses of the relationship between individual MDASI-MM symptom scores and CRP, IL-6, and IDO variables. Using linear regression analyses, we will also examine the effects of minocycline treatment on each of the serum markers.

Scatterplots will be created to visually examine the relationship between each MDASI-MM measurement and NF-κB, IL-6, TNF-α and other serum proinflammatory cytokines. If the data are normally distributed, Pearson's correlation coefficient will be used to assess the association between the MDASI-MM measures and inflammatory marker levels. Spearman's correlation coefficient will be used if the data are not approximately normally distributed. These analyses will be repeated for each inflammatory marker at each collection time point.

To assess the effect of early dropout on the study results, we will perform sensitivity analyses and will consider statistical methods such as LOCF (last observation carried forward) to model outcomes over time.

11.3 Noncompliance 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 4 weeks of symptom intervention drug. Those patients will be replaced with other participants receiving the same symptom study treatment (minocycline or placebo).

11.4 Failure to Complete Chemotherapy

Patients who do not complete two weeks of chemotherapy will be excluded from the trial analysis. These participants will be replaced with another participant receiving the same treatment (intervention or placebo).

11.5 Failure to Contribute Outcome Measurement

Patients who do not complete five MDASI-MM assessments during chemotherapy will be excluded from the trial analysis. These participants will be replaced with other participants receiving the same study treatment (intervention or placebo).

11.6 Futility Monitoring

A predictive probability calculation will be performed after evaluable information (i.e., at least 5 MDASI-MM assessments) has been obtained for 64 patients; which is the number of patients halfway between 40 (number of patients in the interim analysis) and 88 (total target accrual). Based on results from this analysis, the study will stop for futility if the predictive probability is deemed too low by the DSMB committee.

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