THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Page

A Randomized, Placebo Controlled-double Blind Study of Minocycline for Reducing the Symptom Burden for Pancreatic Cancer Patients
2012-0587

Core Protocol Information

Short Title	Minocycline randomized study in pancreatic cancer patients
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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 establish the efficacy of minocycline in reducing symptoms during a cycle (14 days) of FOLFIRINOX* or gemcitabine-based chemotherapy in patients with pancreatic cancer. Our working hypothesis is that patients randomized to receive 200mg/day minocycline will report less severe **fatigue, pain, disturbed sleep, lack of appetite, and drowsiness**, compared with a placebo group.

* References to FOLFIRINOX in this protocol include modified versions of the treatment, such as FOLFOX. Treating oncologists may alter the FOLFIRINOX combination depending on the patient's condition.

1.2 Secondary outcomes:

1.21: To establish the efficacy of minocycline in reducing symptoms beyond the first cycle of FOLFIRINOX or gemcitabine-based chemotherapy in patients with pancreatic cancer. Our working hypothesis is that patients who receive up to 4 cycles of chemotherapy and who are randomized to receive 200 mg/day minocycline will report less severe fatigue, pain, disturbed sleep, lack of appetite, and drowsiness compared with a placebo group.

1.22: To characterize the effect of minocycline on modulating inflammatory biomarkers and their possible association with dynamic changes in symptom burden in patients diagnosed with pancreatic cancer. Our working hypothesis is that patients undergoing chemotherapy who receive minocycline will exhibit reduction in concentrations of circulating inflammatory markers, compared with a placebo group.

1.23: To examine the potential effects of minocycline on preventing rapid increase of cytokine release in patients with mild baseline symptoms. Our working hypothesis is that patients receiving minocycline will exhibit a slower rate of increase in biomarkers (IL-6 and sTNF-R1), compared with a placebo group.

1.24: To examine the effect of minocycline on muscle and fat mass and wasting: We will compare CT images pre and post treatment to measure changes in fat and muscle mass. We will then compare these measurements with baseline symptoms and cytokines and changes in these measures.

1.25: To examine the effect of minocycline on managing disease-driven symptoms for about 2 weeks before the start of chemotherapy. Our working hypothesis is that patients who have 2 weeks (+/- 2 weeks) as a run-in phase intervention with minocycline will benefit from reduced baseline symptom severity and reduced inflammatory activity before chemotherapy.

1.26: To characterize the effect of FOLFIRINOX and disease progression on the development of high symptom burden in patients diagnosed with pancreatic cancer.

2.0 Rationale

Nearly 75% of patients with pancreatic cancer experience a rapid and merciless course of intractable pain, fatigue, poor appetite, distress, and death within the first 12 months of diagnosis. Over the past 30 years, extensive clinical research has focused on reversing cachexia and wasting by using growth factors, anabolic steroids, and food supplements. Other researchers have worked to identify prognostic factors from inflammation biomarkers and tumor markers. However, this paradigm has not been a great help for reducing the high symptom burden produced by this very lethal cancer, especially when the disease is not resectable (Yip et al., 2006).

The recent randomized phase III trial reported by Conroy et al (NEJM, 2011) is a major therapeutic advance in the management of patients with a confirmed metastatic pancreatic cancer. A combination chemotherapy regimen consisting of oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX) improved overall survival as compared with gemcitabine as first-line therapy in selected patients with metastatic pancreatic cancer. This study indirectly suggests new insights for patients with unresectable locally advanced, but nonmetastatic, pancreatic carcinoma (LAPC). Recent studies examined this regimen used as neoadjuvant therapy for newly diagnosed unresectable locally advanced pancreatic cancer patients (Levy A, et al, 2012; Hosein et al., 2012). In the era of new effective cytotoxic agents (platinum compounds, taxanes, and other third-generation chemotherapies), targeting the subclinical disease or the early metastatic step of pancreatic cancer could be the cornerstone of new advances in curative-intended strategy. In the Conroy et al study, quality of life at 6 months was significantly higher in the FOLFIRINOX arm, with twice fewer patients having a definitive degradation of their quality of life than that in the gemcitabine group (31% vs 66%; hazard ratio, 0.47; 95% confidence interval, 0.30–0.70; $P < 0.001$). However, acute toxicity was increased significantly in the experimental arm versus the gemcitabine arm of this Phase III trial, with symptoms ranging from fatigue, vomiting, and diarrhea to sensory neuropathy. In some cases, treating oncologists modify the FOLFIRINOX regimen for sicker patients in order to reduce toxicity and improve tolerability, and studies have shown that such modifications do not adversely impact the efficacy of the treatment (Gunturu et al, 2013; Mahaseth et al, 2013). Nonetheless, FOLFIRINOX is an aggressive therapy, and a strategy to reduce symptom burden during the acute treatment phase may help patients remain in treatment for their cancer.

Typically diagnosed with advanced disease, patients with pancreatic cancer suffer from high symptom burden during their limited survival period. Their most disturbing symptoms—often fatigue, poor appetite, drowsiness, disturbed sleep, pain, and distress—present a serious challenge for patient care. The underlying mechanisms and signaling pathways involved in human symptom experiences are not yet well understood. The role of peripheral inflammation in producing a number of centrally mediated physiological and behavioral changes has been widely studied across many chronic diseases; however, for cancer specifically, the effect of peripheral and central inflammation as a common mechanism underlying the development of multiple symptoms due to disease/therapy has only been hypothesized. Lack of confirmative evidence of such association becomes a key problem for providing effective, mechanism-driven symptom control for patients with cancer.

Based on animal studies of sickness behavior (Dantzer, 2001), we theorize that many of the symptoms of cancer and its treatment are related to cytokine dysregulation (Cleeland et al., 2003; Lee et al., 2004). The fluctuations in inflammatory cytokines, primarily interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-a, are related to fluctuations in components of sickness in

animals (anorexia, disturbed sleep, hyperalgesia, disrupted learning). It is well recognized that p38 mitogen-activated protein kinase (MAPK) enhances the access of inflammatory cytokines to the brain via leaky regions in the blood-brain barrier. Active transport molecules and afferent nerve fibers may also activate sickness behavior (Maier et al., 1998; Raison et al., 2006). Microglia-dependent TNF-a–mediated increase in CNS excitability provides further insight into potential mechanisms underlying disparate neurological and behavioral changes associated with chronic inflammation.

Although inflammatory mechanisms have been investigated with clinical outcomes in pancreatic cancer, to our knowledge, no study has examined whether downregulating a network of cytokines would be helpful for **symptom reduction**, especially for the most severe symptom, fatigue; this is our primary 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 MAPK pathway, we propose a Phase II, 2-arm, double-blind, placebo-controlled randomized study in patients with newly diagnosed pancreatic cancer.

Our proposed study is innovative because minocycline, although used widely as an anti-inflammatory agent in other chronic conditions, has never been tested for improving symptoms in pancreatic cancer to confirm the central hypothesis of inflammation as a mechanism for cancer-related symptom development. 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 pancreatic cancer live with fewer symptoms during limited 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 R01 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

3.1 Pancreatic Cancer, High Symptom Burden, and Inflammation

Pancreatic cancer is the fourth leading cause of cancer-related deaths in the United States, where an estimated 42,500 Americans were diagnosed with pancreatic cancer in 2009 and more than 35,000 were expected to die from the disease (Jemal et al., 2009). Survival for regional pancreatic cancer has improved in the past decade, most strikingly for patients undergoing neoadjuvant chemotherapy and resection (Riall et al., 2006), while overall survival has increased only a few months for patients with metastatic disease, at the cost of significant toxicity (Moore et al., 2007; Conroy 2011).

Patients living with unresectable pancreatic cancer suffer from multiple severe symptoms, including pain, fatigue, cachexia, depression, bowel dysfunction, and infection. The “symptom burden” produced by these multiple symptoms reduces functioning and quality of life (Kelsen et al., 1997). The most disturbing symptoms of patients with advanced pancreatic cancer—fatigue, loss of appetite, and impaired sense of well-being—were reported in a recent prospective study (Labori et al., 2006). Nonetheless, MacDonald (2007) subsequently pointed out that “lack of emphasis on symptom studies is disproportionate to their importance to patients and their families” for advanced cancer. Despite the assistance of nutrition and pain management consultants (Wong et al., 2004), the methods for effective symptom control are limited, especially for some of the most distressing symptoms that this disease produces, such as those related to fatigue.

3.2 Inflammatory Cytokines, Sickness Behavior, and Cancer-Related Symptoms

Multiple cancer symptoms closely parallel the sickness behaviors observed in animals after administration of inflammatory agents (Dantzer, 2009; Hart, 1988; Kent et al., 1992; Lee et al., 2004; Miller et al., 2008). Laboratory studies have identified certain inflammatory cytokines (tumor necrosis factor [TNF]-a, interferon (IFN)-g, interleukin [IL]-1, and IL-6) as central mediators of sickness behavior resulting from infections (Kelley et al., 2003). Somewhat independently, researchers have proposed inflammation as a candidate mechanism for expression of cancer-related symptoms, and modulation of this inflammation as representing a potential pathway for the clinical prevention and treatment of these symptoms (Miller, 2003; Wang et al., 2010a; Wood et al., 2006).

In both advanced and inoperable pancreatic cancer there is evidence for the role of the inflammatory response in the development of cachexia and in determining prognosis (McKay et al., 2008; Seruga et al., 2008). A high level of IL-6 is an independent predictor of shorter overall survival in patients with pancreatic cancer (Ebrahimi et al., 2004). Serum IL-6 is correlated with staging and size of pancreatic cancer (Chen & Huang, 2009; Talar-Wojnarowska et al., 2009). As long as a decade ago, researchers reported that a set of inflammatory cytokines, rather than a single cytokine, work in concert in cachexia (Matthys & Billiau, 1997).

3.3 Basic and Clinical Studies for Palliative and Supportive Care in Pancreatic Cancer

Research suggests that even when cancer has not metastasized extensively, metabolic changes, including alterations in resting energy expenditure, are occurring. Although the mechanisms remain unknown, corticosteroids and megestrol acetate are widely used for palliating anorexia. Murine and human research has evidenced a stereotypical set of pathological changes that occur as pancreatic cancer develops, and whereas weight loss generally tracks disease progression, there is a significant lag between behaviors indicative of pancreatic cancer pain and disease progression (Lindsay et al., 2005). This evidence suggests that early mechanism-driven symptom prevention might reduce symptom burden in pancreatic cancer.

3.4 Assessing the Symptoms of Pancreatic Cancer

Symptoms and health-related quality-of-life assessments are gradually being integrated into oncology clinical research and practice, including pain management. For more than a decade, systematic assessment via patient-reported outcomes (PROs) has been used to evaluate the clinical impact of new therapies for pancreatic cancer. The US Food and Drug Administration has promoted the use of PRO measures in clinical trials (US Food and Drug Administration et al., 2009), and there is a dawning recognition that asking patients directly about their cancer-related symptom burden using the same scientific rigor required of other clinical outcomes can provide valuable data for prognosis, treatment, symptom management, and supportive care (Cleeland, 2007; Müller-Nordhorn et al., 2006). Clinical studies have challenged the assumption that response rate and survival are the only appropriate endpoints for clinical trials in measures of treatment efficacy.

3.5 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 (US Food and Drug Administration et al., 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.

This study is a minocycline intervention during 3-4 cycles of FOLFIRINOX or gemcitabine-based chemotherapy. The primary outcome will be the first cycle (2 weeks) of intervention. The short, 2-week intervention period is based on research in which symptom reduction was the primary outcome of intervention trials in patients with advanced cancer (Bruera et al, 2013; Yennurajalinggam et al, 2013). This strategy is designed to investigate the effectiveness of a trial agent on symptom reduction due to both disease and chemotherapy while avoiding the confounding issues of patient drop-off and increase in symptom burden induced by disease progression. The secondary outcomes of the trial will include continued study during the intervention for 3-4 cycles chemotherapy. Continued observation of the effect of minocycline in responders who are in good compliance with their chemotherapy will provide further evidence of symptom reduction related to accumulated anti-inflammatory effect.

4.0 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. See Appendix D.

4.1 Minocycline: Inhibiting Activation and Proliferation of Microglia

Minocycline is a synthetic antibiotic tetracycline that has been shown to possess anti-inflammatory, antiviral, and antioxidant properties (Mishra & Basu, 2008). It is a lipophilic molecule readily absorbed across the blood-brain barrier (Aronson, 1980). In pure microglia cultures, glutamate-induced transient activation of p38 mitogen-activated protein kinase (MAPK) was inhibited by minocycline (Tikka et al., 2001). Inhibition of p38 MAPK is considered to be the mechanism underlying minocycline's anti-inflammatory, non-antibiotic effects (Sapadin & Fleischmajer, 2006). 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 shown that minocycline reduces the levels of the proinflammatory cytokines IL-6, TNF-a, IL-1β and IFN-γ (Ledeboer et al., 2005). This effect, along with the inhibition of microglial activation caused by nerve damage, has been shown to have neuroprotective action in animal models of a number of diseases, including stroke, diabetic retinopathy, multiple sclerosis, and Parkinson's disease. 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).

Common side effects of minocycline include light-headedness, vestibular symptoms, headache, and nausea (Gump et al., 1977), without correlation between serum concentration and toxicity. Another side effect is photosensitization.

4.2 Minocycline: clinical studies

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 to managed dermatitis associated with targeted therapy in cancer. Minocycline was safe and effective for patients with rheumatoid arthritis in a 48-week double-blind placebo-controlled trial, with no serious toxicities and similar side effects in both groups (Tilley et al., 1995). Its long-lasting effects for 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.

4.3 Absolute Contraindications to Study Symptom Intervention Agent Minocycline

4.31 Hypersensitivity to any tetracyclines

4.32 Pregnancy

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

4.4 Minocycline Common Adverse Reactions

4.41 Minocycline: dizziness (9%) and vertigo

4.5 Minocycline Monitoring Parameters

4.51 Minocycline: LFTs, BUN, Sr Cr

4.52 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.

4.6 Minocycline Drug Interactions

4.61 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**

4.62 Methoxyflurane anesthesia, when concurrent with minocycline, may cause fatal nephrotoxicity

4.63 Retinoic acid derivatives: may increase risk of pseudotumor cerebri

4.64 Warfarin: hypoprothrombinemic response may be increased with tetracyclines; **monitor INR closely during initiation or discontinuation**

4.65 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

4.7 Serious Adverse Events for Symptom Drugs

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. http://www.drugs.com/pro/minocycline.html

5.0 Study design

5.1 Randomized Controlled Trial of Minocycline vs. Placebo

We will conduct **a two-arm, placebo-controlled randomized study, with a run-in phase,** to obtain preliminary estimates of the treatment effects of minocycline in patients (N=76) diagnosed with pancreatic cancer, who are beginning or have begun chemotherapy. We will also assess the safety of minocycline, and the results from this pilot study will inform subsequent symptom-management clinical trials. **Overall Objective:** To develop evidence-based strategies for preventing or ameliorating symptoms produced by aggressive cancer and chemotherapy.

Study Period:

1. Run-in pilot phase: 2 weeks (+/- 2 weeks) prior to initiation of chemotherapy (e.g. during patients waiting time for biopsy or placement of central lines for chemotherapy). This run-in phase is not mandatory.

2. Minocycline intervention during a minimum of 1 and maximum of 4 cycles of FOLFIRINOX or gemcitabine-based chemotherapy (up to 8 weeks). The primary outcome will be assessed from the first cycle (2 weeks) of intervention. The secondary outcomes of the trial will include continued study during the intervention for a minimum of 1 and maximum of 4 cycles chemotherapy (up to 8 weeks).

Primary Outcome Variable: Average area under the curve (AUC) using the average of five targeted symptoms (fatigue, pain, disturbed sleep, lack of appetite, and drowsiness) and divided by the number of weeks of therapy received. This measurement does not include the run-in phase.

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 2 heights. The base is the number of days in between 2 administrations of the M. D. Anderson Symptom Inventory (MDASI). The 2 heights correspond to the 2 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 weekly assessment schedule, there will be approximately 5 trapezoids during the first cycle (baseline plus twice-a-week data for 2 weeks). The AUC is the sum of the area of the 5 trapezoids. The averaged AUC will be the total AUC divided by the number of data time points.

Baseline assessments are to occur prior to start of study drug. Administration of the symptom intervention agent will commence within 2 days of the start of the next chemotherapy cycle after study enrollment.

The pilot 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).

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

Symptom Intervention Agent	Dosage Forms	Initial Dose (starts on first day of run-in phase or chemotherapy)	Initial Dose (starts on first day of run-in phase or chemotherapy)
Minocycline	100 mg capsules	100 mg two times a day (200 mg/day)	Matching placebo

Minocycline is commercially available as 50 mg, 75 mg, and 100 mg capsule or tablet. It can be taken with or without food and should be stored (packaged) protected from light.

5.2 Observational Arm

Because symptom profile information on patients with pancreatic cancer treated with FOLFIRINOX is lacking, an observational study of these patients will provide valuable information to patients and clinicians about the high symptom burden associated with the interaction between this aggressive therapy and rapid disease progression. We will enroll patients who receive FOLFIRINOX chemotherapy but who either do not qualify for the minocycline intervention study or elect not to participate in it. **Overall objective:** To characterize the effect of FOLFIRINOX and disease progression on the development of symptom burden in patients diagnosed with pancreatic cancer.

Study Period:
1. Run-in pilot phase: 2 weeks (+/- 2 weeks) prior to initiation of chemotherapy (e.g. while patient is waiting for biopsy or placement of central lines for chemotherapy). This run-in phase is not mandatory.
2. Symptom assessment during a minimum of 1 and a maximum of 4 cycles of FOLFIRINOX chemotherapy (up to 8 weeks).

Primary Outcome Variable:
Severity of MDASI symptoms at baseline and follow-up assessments.

6.0 Patient Eligibility

6.1 Inclusion Criteria

6.11 Minocycline Trial only: Patients with a pathological or clinical diagnosis of pancreatic cancer and beginning or continuing FOLFIRINOX or gemcitabine-based chemotherapy.

6.12 Observational Arm only: Patients with a pathological or clinical diagnosis of pancreatic cancer and beginning or continuing FOLFIRINOX chemotherapy.

6.13 Patients > 18 years old.

6.14 Minocycline Trial only: Patients with ECOG PS = 0-2.

6.15 Patients who speak English or Spanish (due to MDASI language options, we are only accruing English-speaking or Spanish-speaking patients to the protocol).

6.16 Patients willing and able to review, understand, and provide written consent before starting therapy.

6.17 Minocycline Trial only: Patients with adequate renal function according to MD Anderson testing standards (screening cut off for serum creatinine < 2 times the upper limit of normal).

6.18 Minocycline Trial only: Patients with adequate hepatic function according to MD Anderson testing standards (screening results for total bilirubin must be < 2 times the upper limit of normal; screening results for alanine aminotransferase (ALT) must be < 3 times the upper limit of normal; screening results for aspartate aminotransferase (AST), if available, must be < 3 times the upper limit of normal).

6.2 Exclusion Criteria

6.21 Minocycline Trial only: Patients who are taking medication or have conditions that potentially preclude use of minocycline, as determined by the treating physician.

6.22 Patients who are enrolled in other symptom management clinical trials.

6.23 Minocycline Trial only: Patients who currently have bile duct obstruction or cholelithiasis.

6.24 Minocycline Trial only: Patients with hypersensitivity to any tetracyclines.

6.25 Minocycline Trial only: Patients who are pregnant. Pregnancy will be confirmed by negative urine test; patients with a positive urine test will be retested for doubling of HCG 48 hours after the first test, because of beta-HCG's role as a tumor marker. Patients without such a rise will be eligible for the study and will be enrolled at the investigator's discretion.

6.26 Minocycline Trial only: Patients who are under treatment of warfarin with INR > 1.5.

6.27 Patients who, in the judgment of the investigator, may be unable to participate in the required study procedures.

6.28 Minocycline Trial only: Patients who have had prior treatment for pancreatic cancer within the past six months may be excluded at the discretion of the investigator.

7.0 Study Procedures

7.1 Patient Enrollment and Registration

Patients will be screened for eligibility and recruited for enrollment in the outpatient GI Medical Oncology Clinic. The opportunity to participate in the minocycline trial will be presented to eligible patients. Those who opt not to enroll in the minocycline study, along with those who do not qualify for the minocycline study, will be approached about participating in the observational arm. 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.

Enrolled patients will be registered into the institutional patient data management system.

7.2 Randomized Controlled Trial of Minocycline vs. Placebo

7.21 Patient Randomization and Assignment to Treatment Arm

The minocycline study will accrue a total of 76 patients, with 38 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.

Patients will pick up the assigned study medications at one of the outpatient pharmacy stations in MD Anderson, or study medication will be mailed to the patient by the MD Anderson pharmacy. Patients will be given instruction in how to take study medications. The participants will take study medication enterally, twice daily, after study entry. The final day of study medication is the final day of the chemotherapy cycle after a maximum of 4 cycles after medication is started or at the time of discontinuation of FOLFIRINOX or gemcitabine-based chemotherapy, whichever is earlier; this does not count the optional run-in period. Total daily doses will be dispensed. Study medication use will be reviewed by study staff.

Study staff will contact patients every two weeks to check for adverse events

during routinely scheduled clinic visits or via telephone calls.

At enrollment, patients will be informed that they will receive a stipend in the maximum total amount of $60 for participation in the study. The stipend will be distributed in $20 increments three times during the study. Stipends will be distributed to participants at the first 3 cycle start dates after they are enrolled in the study and if they remain on study.

7.22 Potential Confounding Impact from Palliative Care

Because of the high level of symptom burden typically experienced by this cohort of patients, both new and widely adapted supportive care other than the agent to be tested may emerge over the time of the study and might affect symptom burden. Agents that could modify inflammation, such as the nutritional supplements curcumin and fish oil, and megestrol (an FDA-approved agent) for managing cachexia, will be allowed for both groups of patients. We expect that changes in symptom severity that can be attributed to changes in primary treatment regimen or other covariates can be incorporated into study at any point during the trial's conduct, and that documented data can be incorporated into this regression equation in a straightforward manner.

7.3 Observational Arm

A total of 45 patients will be accrued for the observational arm. Patients will be under the same assessment schedule as patients in the minocycline trial.

8.0 Data Collection

With a few exceptions as noted below, data collection will be the same for both the minocycline trial and the observational study. Multiple symptoms will be monitored weekly using the gastrointestinal cancer module of the MDASI (MDASI-GI; Wang et al., 2010b) to simultaneously document symptom prevalence, severity, and interference. We will concurrently track markers of inflammation to establish correlations with symptom development.

Research staff will collect other data for all patients: demographics, co-morbidities, cancer therapy and tumor response, ECOG PS, weight changes, infections, routine lab results, symptom-control and palliative care.

8.1 Patient-Reported Outcome (PRO) Measurements

8.11 Symptom Measurement (Appendix G)

Symptom data will be collected using the MDASI GI module prior to the start of the first chemotherapy cycle after the patient is enrolled in the study, twice a week during the first chemotherapy cycle, and weekly during the 2-week run-in phase and subsequent chemotherapy cycles for a maximum of 12 weeks.

8.12 Measure of Global Quality-of-Life Rating (QoL) (Appendix H)

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 will be administered prior to the start of the first chemotherapy cycle after the patient is enrolled on the study and weekly thereafter. It will be used as a time-varying 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.

8.13 Measure of Patient Satisfaction with Study Medication Satisfaction Scale (Appendix I) - Minocycline Trial Only

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.

8.14 Remote PRO Data Capture

PRO questionnaires can be administered in several formats, including paper-and-pencil (both in the clinic and by mail), face-to-face or telephone interview, and secure, institutionally approved electronic means (such as tablet PC or REDCap).

Study data may be collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at MD Anderson (Harris et al, 2009. REDCap (www.project-redcap.org) is a secure, web-based application with controlled access designed to support data capture for research studies, providing: 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 Cancer Center'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 was 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 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. Following publication, study data will be archived in REDCap.

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, chemotherapy agents, current medications), comorbidities, and performance status.

Laboratory values from blood analysis, such as 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.

8.3 Cytokine Data Collection

We will concurrently track the serum concentrations of a panel of inflammatory markers (e.g. IL-1RA, IL-6, IL 8, IL-10, sTNF-R1, MCP-1, midkine, CRP, CXCL16).

In addition to routine blood testing, **up to 5 blood samples** (if the patient will have a run-in phase) **or up to 4 blood samples** (if the patient will start the chemotherapy immediately) will be assayed for inflammatory markers: (1) at baseline, upon enrollment into the study (before intervention treatment begins); (2) at the start of the 2nd, 3rd, and 4th chemotherapy cycles**, if applicable**; and (3) at the end of the last chemotherapy cycle (end of study). The end-of-intervention sample, if available, will provide information about any differences in treatment effects between the two arms.

During the patient's routine clinic visits, 10 mL of blood will be drawn in a red stopper. The tube will be placed at 4°C within 15 minutes of phlebotomy and transferred to the research laboratory within a maximum period of 2 hours. The sample will be processed immediately once received by the research lab. Briefly, dispensed in 0.5 mL cryopreservation tubes labeled with the subject's study number and date of collection, samples will be stored at -80°C until the cytokine assays. Blood samples will be delivered to MD Anderson's Laboratory of Neuroimmunology of Cancer-Related Symptoms (NICRS) for processing and cytokine assay. Cytokine levels will be measured using Multiplex and ELISA methods.

8.4 Assessment Schedules

8.41 Randomized Controlled Trial of Minocycline vs. Placebo

	Run-in or chemotherapy + minocycline start*	***Study Cycle 1****	***Study Cycle 2 (if applicable) *****	***Study Cycle 3 (if applicable)****	***Study Cycle 4 (if applicable)****	***End of study (last day of last cycle)***
MDASI-GI[1]	X	X	X	X	X	X

QoL[1]	X	X	X	X	X	X
Study Medication Satisfaction Scale[2]				X	X	
Patient-Reported information checklist	X	X	X	X	X	X
Demographic Information	X					
Disease history, current disease status	X					
CTC Toxicity information		X	X	X	X	
Other clinical information		X	X	X	X	X
Laboratory Information	X	X	X	X	X	X
Research Blood Sample Collection* **	X		X	X	X	X
Medication information	X		X	X	X	
Study Medication Accountability	X	X	X	X	X	
Final Status information						X

1. Collected weekly (twice a week during the first cycle), either in the clinic or by phone call or other institutionally approved electronic means. Run-in or chemotherapy + minocycline start assessments to occur no more than 12 days before start of study cycle 1 of chemotherapy. If patient will participate in the run-in phase, the intervention will be administrated for 2 weeks before chemotherapy begins.
2. If the patient withdraws before completing the trial, staff will make an effort to collect this form as soon as possible.

* Baseline and Cycle 1 may coincide if no run-in period is completed. In this case, forms are completed only once.

** Some patients will receive less than 4 cycles of chemotherapy while on the study. These procedures will be performed only at the end of intervention (i.e. at the end of study cycle 2, 3 or 4 depending on the total number of cycles completed while on study).

*** Blood for biomarkers will be collected if possible and if the patient is having routine blood draws at MD Anderson main campus.

8.42 Observational Arm

	Baseline	***Study Cycle 1***	***Study Cycle 2****	***Study Cycle 3****	***Cycle 4 (if applicable)****	***End of study (end of last cycle)***
MDASI-GI[1]	X	X	X	X	X	X
QoL[1]	X	X	X	X	X	X
Patient-Reported information checklist	X	X	X	X	X	X
Demographic information	X					
Disease history, current disease status	X					
Other clinical information		X	X	X	X	X
Laboratory Data information	X	X	X	X	X	X
Research Blood						

Sample Collection**	X		X	X	X	X
Final Status information						X

1. Collected weekly (twice a week during the first cycle), either in the clinic or by phone call or other institutionally approved electronic means. Run-in or chemotherapy + minocycline assessments to occur no more than 12 days before start of study cycle 1 of chemotherapy.
   * Some patients will receive less than 4 cycles of chemotherapy while on study. These procedures will be performed only at the end of intervention (i.e. at the end of study cycle 2, 3 or 4 depending on the total number of cycles completed while on study).
   ** Blood for biomarkers will be collected if possible and if the patient is having routine blood draws at MD Anderson main campus.

8.5 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.

9.0 Adverse Events Reporting

9.1 Adverse Events (AE) - Minocycline Trial Only

All patients will be contacted weekly by research staff either in person or by telephone to closely monitor potential adverse events during treatment. 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 baseline, every cycle and end of treatment. 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). 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.

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) 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.

9.2 Serious Adverse Events (SAE) - Minocycline Trial Only

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. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity – a substantial disruption of a person's ability to conduct normal life functions
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

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 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 system (UTMDACC 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 Criteria for Removal from the Study

10.1 Unblinding Procedure - Minocycline Trial Only

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 UTMDACC IRB when unblinding occurs.

10.2 Criteria for Removal from the Study - Minocycline Trial Only

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

10.21 Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 5 times the upper limit of normal.

10.22 Total bilirubin > 3 times the upper limit of normal.

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

10.24 Pregnancy during the study period.

10.25 The patient is permanently taken off chemotherapy treatment for any reason.

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

Symptom assessment measures will continue to be administered to patients taken off the study drugs until all planned assessments are completed.

11.0 Statistical considerations

11.1 Primary Analyses and Sample Size Justification

The primary outcome variable for the study is the average area under the curve (AUC) value of 5 symptoms: fatigue, drowsiness, pain, disturbed sleep, and lack of appetite over 2 weeks. These were the most prevalent and severe symptoms identified in our pilot studies of patients with pancreatic cancer.

Seventy-six patients will be randomized equally to the 2 treatment arms (minocycline

and placebo). To ensure that we have the same number of patients randomized between the treatment arms within chemotherapy treatment, the randomization will be stratified by chemotherapy treatment (i.e., FOLFIRINOX or gemcitabine-based chemotherapy). Note that this stratification allows for unequal numbers of patients being treated within each chemotherapy type. Taking into account a 10% attrition rate, we expect 68 evaluable patients. With 34 **evaluable** patients per treatment arm for 2 weeks, we will be able to detect a 0.53 SD effect size on the average symptom AUC between the 2 treatments with 70% power and a one-tailed 5% significance test for primary outcome 1.1.

Because this is a Phase II study with the intent of determining effect size estimates to inform a large clinical trial in the future, we chose a modest statistical power to detect a modest intervention effect of minocycline as a potential agent for reducing symptoms in cancer patients receiving chemotherapy. If the treatment has a more pronounced effect, it will be detected with higher power.

This study will allow us to obtain estimates of treatment effect and the variability of these estimates. We will test minocycline's ability to reduce the severity of 5 symptoms. Estimates of treatment effect will be obtained using standard linear regression techniques in which AUC values are regressed on indicator variables that represent treatment received, controlling for type of chemotherapy treatment. Estimates of treatment effect and between-subject variability will then be used to design a more comprehensive study for future clinical trials. We will also fit mixed models using the average of the 5 symptoms as the dependent variable, with time (week), group (minocycline vs. placebo), type of chemotherapy treatment, and other covariates as independent variables. In addition, we will consider the subset of patients that have mild baseline symptoms and fit a linear regression model to compare the AUC values between minocycline and placebo. Further, we will fit a linear mixed model to the symptom scores to assess the effect of time, treatment, and other covariates. 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. Finally, because the number of assessment time points during the first cycle was increased after we had already enrolled patients, we will verify that the comparative results are similar for patients accrued before and after this change before combining the data for analysis.

Non-Compliance with Study Agent: Patients who randomly do not comply with study agent dosing requirements will remain in the study under the intent-to-treat rule.

11.2 Secondary Analyses

To determine whether there was significant symptom reduction between symptom intervention arms after the first study chemotherapy cycle, we will compare the placebo and minocycline groups in terms of their change scores from the end of the first study cycle to the end of the last study cycle. We will also report the number of patients who have available symptom data at the end of cycle 2, cycle 3, and cycle 4, and account for drop-off driven by disease progression in the analysis. We expect to see better palliative effect in the minocycline group than in the placebo group, even in patients who remain in chemotherapy and are likely to be responders to disease control.

To address secondary objectives related to both the minocycline trial and the observational study, we will examine the relationship between dynamic changes in inflammation biomarkers and symptom outcomes, controlling for the grouping variable, disease progression (tumor markers, weight loss), evidence of infection, ECOG PS, age, and gender. Standard exploratory data analysis and descriptive statistics will be used.

Minocycline trial: In addition to testing the ability of minocycline to reduce the average AUC of the 5 selected symptoms, we will also perform a number of regression analyses to examine the relationship between AUC values/MDASI values and concentration serum of inflammatory markers. These analyses will include linear regression analyses of AUC values on the two measured CRP and IL-6 intensity values, as well as longitudinal analyses of the relationship between individual symptom scores as measured by MDASI, and CRP and IL-6 intensity variables. Using linear regression analyses, we will also examine the effects of minocycline treatment on each of the serum markers.

Observational arm: To understand the symptom profiles of these patients, we will produce Lowess curves for each symptom over time. We will fit mixed models using individual symptoms as dependent variables with patients treated as a random effect, and variables such as cancer stage, age, and gender as potential covariates. Also, with 45 patients in this group, we will be able to estimate the prevalence of moderate to severe fatigue, a well-known symptom associated with FOLFIRINOX treatment (Conroy et al, 2011) within +/- 15% of the true fatigue prevalence with 95% confidence. This assumes a worst-case scenario in terms of largest variance possible for a proportion of 50%.

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