Original Article

Minocycline for Symptom Reduction During Oxaliplatin-Based Chemotherapy for Colorectal Cancer: A Phase II Randomized Clinical Trial

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Abstract

Context. The most debilitating symptoms during oxaliplatin-based chemotherapy in patients with colorectal cancer (CRC) are neuropathy and fatigue. Inflammation has been suggested to contribute to these symptoms, and the anti-inflammatory agent minocycline is safe and readily available.

Objectives. This proof-of-concept study investigated minocycline's capacity to reduce treatment-related neuropathy and fatigue and its impact on inflammatory markers during chemotherapy in a Phase II randomized, double-blind, placebo-controlled clinical trial.

Methods. Patients with locally advanced or metastatic CRC who were scheduled for oxaliplatin-based chemotherapy were randomly assigned to receive either minocycline (100 mg twice daily) or placebo over four months from started chemotherapy. Toxicity assessments and blood samples were prospectively collected monthly. The severity of fatigue and numbness/tingling was assessed weekly using the MD Anderson Symptom Inventory. The primary endpoint, area under the curve for numbness/tingling and fatigue over approximately four months, was compared between the two arms.

Results. Of 66 evaluable participants, 32 received minocycline and 34 placebo. There was no observed significant symptom reduction on both fatigue and numbness/tingling in either arm, nor was there a difference in levels of serum proinflammatory and anti-inflammatory markers between arms. No Grade 3 adverse events nor disparity mediating effects on intervention were observed.

Conclusion. Minocycline treatment is feasible and has a low-toxicity profile. However, with 200 mg/day, it did not reduce numbness/tingling or fatigue nor moderate inflammatory biomarkers from this Phase II randomized study. Our results do not support further exploration of minocycline for fatigue or neuropathy symptom intervention in patients treated for CRC. J Pain Symptom Manage 2019;58:662–671. © *2019 American Academy of Hospice and Palliative Medicine. Published by Elsevier Inc. All rights reserved.*

Key Words

Minocycline, colorectal cancer, chemotherapy-induced symptoms, neuropathy, fatigue, patient-reported outcomes

Introduction

Patients with advanced colorectal cancer (CRC) may experience substantial symptom burden that is often exacerbated by standard chemotherapy. The most bothersome symptom related to oxaliplatin-based chemotherapy for CRC is dose-dependent chemotherapy-induced peripheral neuropathy (CIPN),

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which often manifests as numbness and/or tingling in the hands and feet[1]; fatigue is the most prevalent symptom related to both disease and therapy in these patients.[2] Oxaliplatin-induced neuropathy and fatigue may interfere with daily functioning and can persist into survivorship, becoming a significant burden for both patients with early-stage or metastatic CRC,[3] and effective management of CIPN and fatigue is still very challenging. Thus, it is critical to develop an effective intervention that would allow patients to continue their cancer treatment without diminishing their quality of life during or after treatment.

Conceptually, modulation of inflammatory activity presents a potential mechanism for reducing treatment-induced symptoms.[4–7] The anti-inflammatory effects of minocycline, a widely used second-generation tetracycline derivative, inexpensive antibiotic, manifest in both the peripheral and central nervous systems.[8] Preclinical animal modeling has provided strong evidence that minocycline has a neuroprotective effect on oxaliplatin-induced[9] and taxane-induced hyperalgesia.[10] Minocycline may also have long-lasting effects in preventing neuropathic pain[11,12] and neurodegenerative disorders.[13] Finally, a recent randomized placebo-controlled pilot study reported that minocycline reduced paclitaxel-related pain and fatigue over a 12-week period, although no effect on CIPN was noted[14] and a Phase II trial reported a positive effect of symptom reduction in head and neck cancer patients undergoing radiotherapy/chemoradiation.[15] Based on this evidence, we proposed a proof-of-concept study to investigate minocycline's capacity to reduce symptoms and their impact on biobehavioral mechanisms during oxaliplatin-based chemotherapy in a Phase II randomized, double-blind, placebo-controlled clinical trial in patients with CRC. Our goal was to identify a signal of effective intervention and/or prevention of both CIPN and fatigue.

We previously showed that patients with advanced non–small cell lung cancer treated at a public hospital reported a significantly more severe treatment-related symptom burden than patients treated with the same standard chemotherapy at The University of Texas MD Anderson Cancer Center.[16] Therefore, we were also interested in examining possible disparities in outcomes between medically underserved patients with CRC treated in a public hospital and patients treated in a tertiary cancer center.

Methods

Patients

Eligible patients for this prospective, double-blind, placebo-controlled Phase II randomized trial were adults who 1) had early-stage or metastatic CRC and were scheduled for oxaliplatin-based chemotherapy (either FOLFOX or CAPOX) lasting at least four months and 2) were being treated either at MD Anderson, a tertiary academic hospital in Houston, Texas, or Lyndon B. Johnson Hospital (LBJ), a public hospital in Harris County, Texas, that primarily treats underserved patients.

Patients were recruited between April 2013 and May 2018. All participants were required to have no baseline peripheral neuropathy (a clinician-rated sensory score of 0 assessed using the National Cancer Institute's Common Terminology Criteria for Adverse Events v4), adequate renal and hepatic function, and the ability to read and understand English. To select a more homogenous sample, we excluded patients who were using tetracycline (the same category of the trial agent, within two weeks) and patients potentially with high inflammatory status due to obesity (BMI > 40). Pregnant patients or patients with resectable metastatic disease for which metastasectomy was planned within four months of starting chemotherapy were excluded.

Baseline patient demographic and clinical variables were collected. Patient performance status before treatment was rated by the research staff according to the Eastern Cooperative Oncology Group scale. This study was approved by the MD Anderson and LBJ Institutional Review Boards, and all patients provided study-specific written informed consent to participate. The trial is registered at ClinicalTrials.gov: NCT01906008.

Randomization and Intervention

Participants were randomly assigned equally using a permuted block design to receive either minocycline capsules or matching placebo capsules in size and color during four months of chemotherapy. Patients were advised by the pharmacy to take the capsules with food in the morning and evening. The minocycline dose in 200 mg per day was based on the previous clinical trials with majority of the studies using this dose with an excellent safety profile.[17] The four-month intervention period for the primary endpoint was chosen because at four months, patients would be receiving the minimum dosage of oxaliplatin chemotherapy that would be expected to reach a cumulative oxaliplatin dose (780 mg/m^2) considered sufficient to produce CIPN.

Assessment of Patient-Reported Outcomes

Patients rated their symptoms and the subsequent interference with activities of daily living using the MD Anderson Symptom Inventory gastrointestinal cancer module (MDASI-GI), a psychometrically validated, 24-item questionnaire containing 13 core symptom items common to all cancer types and six interference items[18]; both "numbness/tingling" and "fatigue" are among the core items. MDASI-GI symptom items are rated on a numeric scale ranging from 0 or "not present" to 10 or "as bad as you can imagine."

Participants self-administered and completed the MDASI-GI before starting therapy (baseline, week 0) and then weekly during the trial by patient preferred time of the day. The MDASI-GI was completed on paper when participants were evaluated in the clinic areas; otherwise, assessments were done using a computerized, telephone-based interactive voice response system or via telephone interview when patients did not respond to the automated system.

The European Organization for Research and Treatment of Cancer CIPN20 questionnaire[19] was assessed each month during treatment to characterize three subscales of patient-reported neuropathy information.

Other Study Assessments

Toxic effects and any adverse events (AEs) were prospectively assessed every cycle during the study period and were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4. Attribution and severity of AEs were determined by the treating oncologist and further categorized as potentially related to study medication or chemotherapy. Safety and futility monitoring for both sites was overseen by MD Anderson's Data Safety and Monitoring Board.

Inflammatory Marker Assay

Serum was prepared from blood samples to test cytokine and chemokine levels. Specifically, leukocytes isolated from peripheral blood were stimulated *ex vivo* with the T cell–stimulating antibodies anti-CD2/CD28, and their supernatants after centrifugation were analyzed to determine cytokine and chemokine production as we described before.[20] Samples were collected at baseline, two months, and four months (the end of the trial). We assessed serum inflammatory markers that had been identified as potentially relevant to symptom development in animal and human studies: interleukin (IL)-1 receptor antagonist, IL-5, IL-6, IL-6 receptor, tumor necrosis factor-α (TNF-α) receptors 1 and 2, and C-reactive protein. The *ex vivo* stimulated leukocyte supernatants were analyzed for interferon (IFN)-γ, IL-10, IL-17A, chemokine monocyte chemoattractant protein-1, and IFN-γ–induced protein-10.[21,22]

Blood sampling was scheduled for the morning of the patient's routine clinic visit, concurrent with the patient's MDASI-GI assessment. After serum isolation by centrifugation, samples were stored at −80°C for batch analysis. All serum proteins were measured in 25 μL of serum using MILLIPLEX map assays (EMD Millipore Corporation, Billerica, MA, USA), and data were acquired using a Luminex 100 analyzer (Luminex Corporation, Austin, TX, USA). The Millipore nonmagnetic Human Soluble Cytokine Receptor Panel was used to measure soluble IL-1 receptors 1 and 2, soluble IL-2 receptor antagonist, soluble IL-6 receptor, and soluble TNF-α receptors 1 and 2. C-reactive protein was measured in 1:27,000 diluted serum sample before analysis using the Millipore Human Cardiovascular Disease Panel 2. IL-1 receptor antagonist was measured in 100 μL of serum by enzyme-linked immunosorbent assay (R&D Systems, Inc., Minneapolis, MN, USA).

Statistical Methods

The overall goal of this study was to generate estimates of the clinical efficacy of minocycline in reducing symptom burden during oxaliplatin-based chemotherapy in patients with CRC to inform future clinical trials. The primary outcome variable, the area under the curve (AUC) for numbness/tingling and fatigue over approximately four months, were compared between the two arms. The AUC was calculated using trapezoidal approximation.[23] All patients who completed the intervention were included in the analysis. The missing of outcome variables were imputed via Last Observation Carried Forward for AUC calculation. Our preliminary data on CRC patients undergoing chemotherapy yielded an average

Table 1

Baseline Patient, Tumor, and Treatment Characteristics of Evaluable Patients, by Treatment Arm (n = 66)

	Minocycline (n = 32)	Placebo (n = 34)	P-value
Mean age, yrs (SD)	53.4 (10.1)	51.4 (10.1)	0.43
Median age, yrs (range)	52 (33–76)	54 (31–69)	
Educational level, n (%)			0.14
12th grade and below	17 (53.1)	24 (70.6)	
Beyond 12th grade	15 (46.9)	10 (29.4)	
Race, n (%)			0.66
White non-Hispanic	13 (40.6)	12 (35.3)	
Hispanic	19 (59.4)	22 (64.7)	
Sex, n (%)			0.57
Female	11 (34.4)	14 (41.2)	
Male	21 (65.6)	20 (58.8)	
ECOG performance status, n (%)			0.77
Grade 0	25 (78.1)	26 (76.5)	
Grade 1	6 (18.8)	8 (23.5)	
Grade 2	1 (3.1)	0 (0.0)	
Cancer stage, n (%)			0.42
II	2 (6.3)	1 (2.9)	
III	22 (68.8)	19 (55.9)	
IV	8 (25.0)	14 (41.2)	
Charlson comorbidity index, n (%)			0.87
0	25 (78.1)	26 (76.5)	
1+	7 (21.9)	8 (23.5)	
Treatment site, n (%)			0.63
MDA	15 (46.9)	18 (52.9)	
LBJ	17 (53.1)	16 (47.1)	

SD = standard deviation; ECOG = Eastern Cooperative Oncology Group; MDA = MD Anderson Cancer Center; LBJ = Lyndon B. Johnson Hospital.

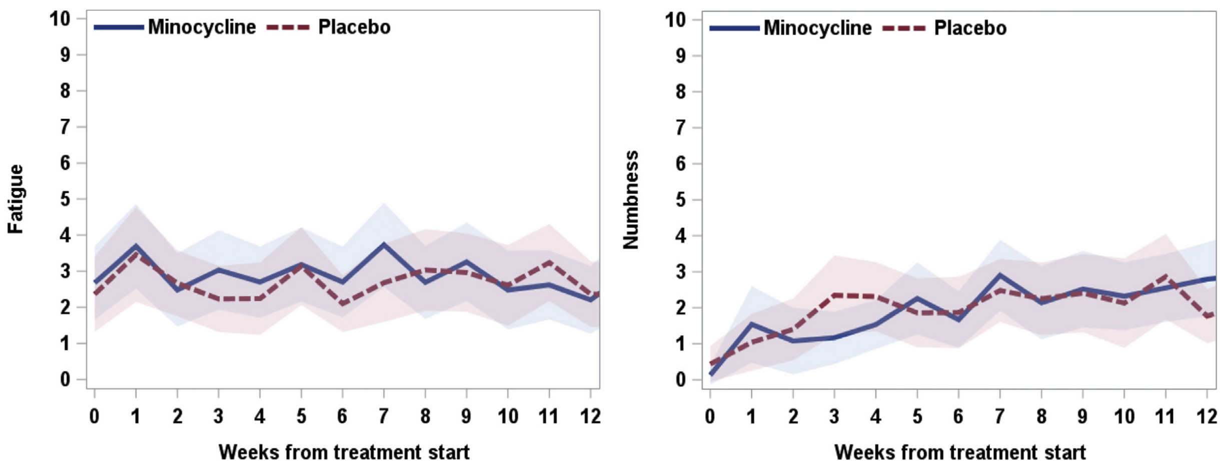

Fig. 1. Longitudinal symptom severity on fatigue and the chemotherapy-induced peripheral neuropathy symptom numbness/tingling over the course of the trial, by treatment arm (mean, 95% confidence interval).

four-month numbness AUC of 205.76 (equivalent to a mean daily AUC of 1.7), with a standard deviation (SD) of 168.3. Therefore, with 42 evaluable patients per arm, we expected to be able to detect a difference of 103.5 (standardized difference of 0.61) on the symptom AUC between the two arms with 80% power and a two-tailed 5% significance test.

Descriptive analyses were used to demonstrate patients' demographic and clinical characteristics and symptom burden. Clinical characteristics were compared between treatment arms using independent *t*-tests for continuous variables and chi-squared tests for categorical variables. CIPN-20, levels of inflammatory markers were tabulated between arms, with means, SDs, effect sizes and *P*-values. For the longitudinal component, linear mixed-effect models provided the effect of symptom reduction for fatigue and numbness/tingling by treatment arm and the changes over time. Group-based trajectory models were used to identify high- vs. low-symptom development patterns over time, with each group of patients presented a consistent trend on symptom severity during the trial.[24,25] Logistic regression analysis provided the predictive value of severity of each baseline symptom for persistent high severity. We mapped MDASI-numbness/tingling with three EORTC-CIPN20 subscales via general mixed-effects models, with adjustment of time and treatment. SAS 9.4 (Gary, NC) was used for all analysis.

Results

Patient Characteristics

Demographic and clinical characteristics by study arm are shown in Table 1. Of the 66 patients, 62% had stage III and 33% had stage IV disease.

The 33 patients from MD Anderson were primarily white non-Hispanic (64%), whereas the 33 patients from LBJ were primarily Hispanic/Latino (85%). There were no differences by age, sex, or CRC stage in patients between the two institutions, but years of education, employment rate, and income were all significantly lower in patients from LBJ (all $P < 0.001$).

Compliance and Toxicity

Compliance With Symptom Assessment. The overall MDASI-GI compliance rate, calculated as the ratio of the actual number of MDASI-GI questionnaires completed by patients divided by the number of possible assessments, was 84.7% from baseline to four months for patients in both treatment arms. All patients contributed patient-reported outcomes (PRO) data at baseline and at two or more additional points.

Compliance With Intervention. From April 2013 to May 2018, 120 of 971 screened patients were identified as eligible and provided study-specific informed consent. Of the 120 enrolled patients, 28 from the minocycline arm and 26 from the placebo arm dropped out of the study after randomization. Reasons that patients did not complete the study included canceled chemotherapy at start or later (transition from chemotherapy to hospice), switching to definitive therapy with surgery or radiation after 2-3 cycles treatment, AE-related discontinuation of chemotherapy (infection, nausea, fatigue, severe CIPN), not reachable/lost to follow-up, and noncompliance with study medication protocols. Only one patient refused to complete the PRO questionnaires. One patient assigned to the minocycline arm was removed from the study because our investigational pharmacy erroneously distributed placebo to this patient instead of minocycline. The 66 evaluable patients achieved a good compliance rate. Overall study medication compliance based on pill count was 72.4% (SD = 28.1%). No significant differences between two arms were found for any of these

Table 2
The AUCs Comparison for Numbness/Tingling and Fatigue Between Arms

	Treatment											
	Minocycline ($n = 32$)					Placebo ($n = 34$)						
	Mean	Std	Median	Min	Max	Mean	Std	Median	Min	Max	*P*-value	Cohen's d
AUC_MDASI-Fatigue	47.92	36.42	42.50	0.00	120.50	40.31	30.92	39.25	0.00	101.00	0.3624	0.23
AUC_MDASI-Numbness/Tingling	35.41	27.35	30.00	1.00	116.50	31.50	27.80	26.25	0.00	113.00	0.5673	0.14

reasons. There was no significant difference in compliance by arm ($P = 0.83$).

Toxicity of the Trial

No Grade 3 or higher AEs that were potentially related to study medication were reported. All chemotherapy-related issues (seven Grade 3 AEs) were addressed within a few days. Two Grade 1 AEs reported in the minocycline arm and two in the placebo arm ($P = 0.95$) were judged to be potentially related to the study medication. Five Grade 2 AEs in the minocycline arm and seven in the placebo arm were related to chemotherapy, not the trial agent.

Primary Endpoint for Minocycline Intervention

We observed no significant differences between minocycline and placebo in their impact on PROs, nor were there significant differences in toxic effects by treatment site. Fig. 1 presents the severity of the two worst symptoms reported by our cohort (neuropathy [MDASI-GI-reported numbness/tingling] and fatigue) by treatment arm. Between arms, the AUCs for numbness/tingling (35.4 ± 27.4 vs. 31.5 ± 27.8, Cohen's d = *0.14,* $P = 0.57$) and fatigue (47.9 ± 36.4 vs. 40.3 ± 39.3, Cohen's d = *0.23,* $P = 0.36$) did not differ, see Table 2.

Consistent with the MDASI-numbness/tingling item, the three subscales of European Organization for Research and Treatment of Cancer CIPN20 questionnaire (sensory, motor, and autonomic) did not differ between arms over time, see Table 3. By a longitudinal analysis, patient-reported numbness/tingling on MDASI was highly relevant to CIPN-Sensory subscale score over time, regardless treatments (est = .0557, $P < 0.0001$), although numbness/tingling also significantly related to scores of CIPN-Motor and CIPN-Autonomic subscales ($P < 0.0001$ and $P = 0.0103$).

Exploratory Analyses

Inflammatory Marker Testing. For patients who contributed both PRO data and blood samples, from which levels of inflammatory markers were determined, we

Table 3
Comparison of Subscales of CIPN20 by Timepoints Between Arms

	CIPN20													
	Treatment													
	Minocycline						Placebo							
	N	Mean	Std	Median	P25	P75	N	Mean	Std	Median	P25	P75	*P*-value	Cohen's d
Sensory														
Month 0	25	1.03	0.08	1.00	1.00	1.00	22	1.00	0.02	1.00	1.00	1.00	0.114	0.51
Month 1	31	1.26	0.33	1.17	1.00	1.33	27	1.24	0.39	1.17	1.00	1.33	0.628	0.06
Month 2	27	1.32	0.35	1.17	1.00	1.50	25	1.33	0.35	1.25	1.08	1.50	0.846	0.03
Month 3	26	1.32	0.30	1.29	1.08	1.42	26	1.29	0.35	1.17	1.00	1.42	0.497	0.03
Month 4	21	1.34	0.35	1.17	1.17	1.42	24	1.34	0.40	1.17	1.08	1.50	0.809	0.00
Motor														
Month 0	25	1.04	0.07	1.00	1.00	1.06	22	1.01	0.04	1.00	1.00	1.00	0.050	0.53
Month 1	31	1.09	0.15	1.00	1.00	1.13	27	1.15	0.26	1.00	1.00	1.21	0.580	0.28
Month 2	27	1.25	0.34	1.08	1.00	1.33	25	1.22	0.60	1.00	1.00	1.19	0.232	0.06
Month 3	26	1.15	0.25	1.00	1.00	1.19	26	1.13	0.22	1.00	1.00	1.25	0.754	0.08
Month 4	21	1.19	0.31	1.00	1.00	1.25	24	1.18	0.33	1.03	1.00	1.13	0.951	0.03
Autonomic														
Month 0	25	1.31	0.43	1.00	1.00	1.50	22	1.27	0.46	1.00	1.00	1.50	0.534	0.09
Month 1	31	1.37	0.40	1.33	1.00	1.67	27	1.40	0.45	1.33	1.00	2.00	0.921	0.07
Month 2	27	1.43	0.50	1.33	1.00	2.00	25	1.45	0.74	1.00	1.00	1.50	0.569	0.03
Month 3	26	1.49	0.54	1.50	1.00	1.67	26	1.42	0.55	1.00	1.00	2.00	0.508	0.13
Month 4	21	1.40	0.49	1.00	1.00	2.00	24	1.47	0.59	1.33	1.00	1.83	0.715	0.13

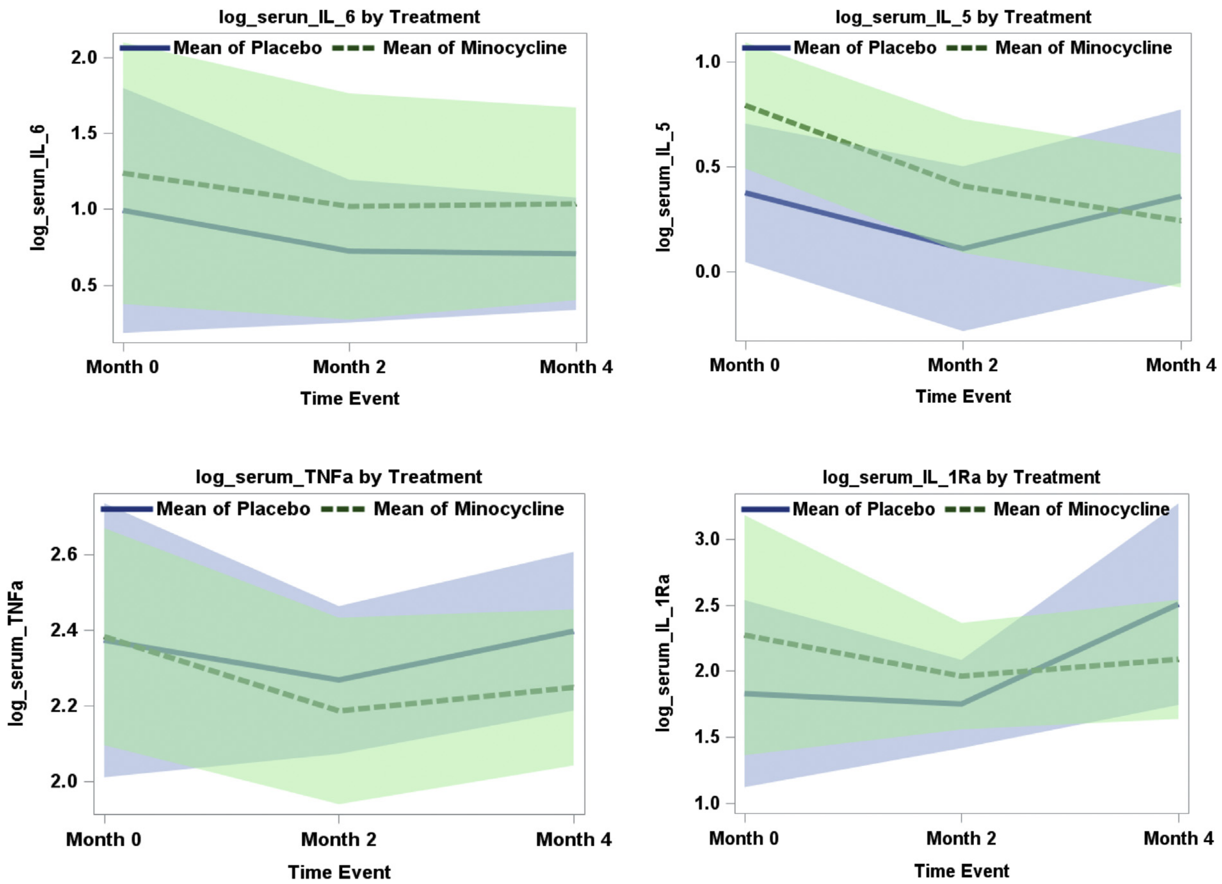

Fig. 2. Serum of inflammatory markers by treatment groups (mean, 95% confidence interval).

did not observe a significant difference for any marker between arms at baseline (minocycline group $N = 14$; placebo = 15), at the end of month 2 (minocycline = 18; placebo = 18), or at the end of the study (end of month 4, minocycline = 20, placebo = 17), see Fig. 2. All serum samples were detectable, including IL-1R, IL-5, Il-6, IL-6R, TNF-α, sTNF-R1, sTNF-R2.

Prevalence of the High-Severity Symptom Burden. Patients had no existing neuropathy at enrollment. Fatigue, pain, and disturbed sleep were the most severe MDA-SI-GI—reported symptoms for all patients during the first cycle of therapy. Regardless of trial groups, no significant differences in severity of these four symptoms were detected between the two institutions (public vs. tertiary) over time.

Fig. 3 presents the high- and low-severity group trajectories for all patients with numbness/tingling, fatigue, pain, and disturbed sleep over time during therapy, identified by trajectory analysis. During the four-month study period, 56.4% of all patients were in the high-severity fatigue group, with mean severity greater than or equal to 4; 44.7% of patients were in the high-severity numbness group, and severity of numbness increased significantly over time (est = 0.94, $P < 0.001$); 44.0% were in the high-severity disturbed-sleep group; and 46.2% were in the high-severity pain group. The average scores for MDASI-GI pain by group were in the mild range, 3.12 (SD = 2.64) in the high-severity pain group and 0.32 (SD = 1.29) for the low-severity pain group; the difference was significant ($P < 0.001$). There were 41% of all patients presents both high-severity CIPN and fatigue, and 33% of all patients presents both high-severity CIPN and pain, who likely suffered from neuropathic pain.

Higher baseline fatigue predicted high-severity fatigue during treatment (odds ratio 1.22, 95% confidence interval 1.00—1.49, $P = 0.04$); and higher baseline pain was predictive of high-severity pain (odds ratio 1.35, 95% confidence interval 1.09—1.67, $P = 0.002$).

Discussion

Although minocycline was well tolerated, in this Phase II randomized, placebo-controlled trial, we did not observe effectiveness to reduce patient-reported

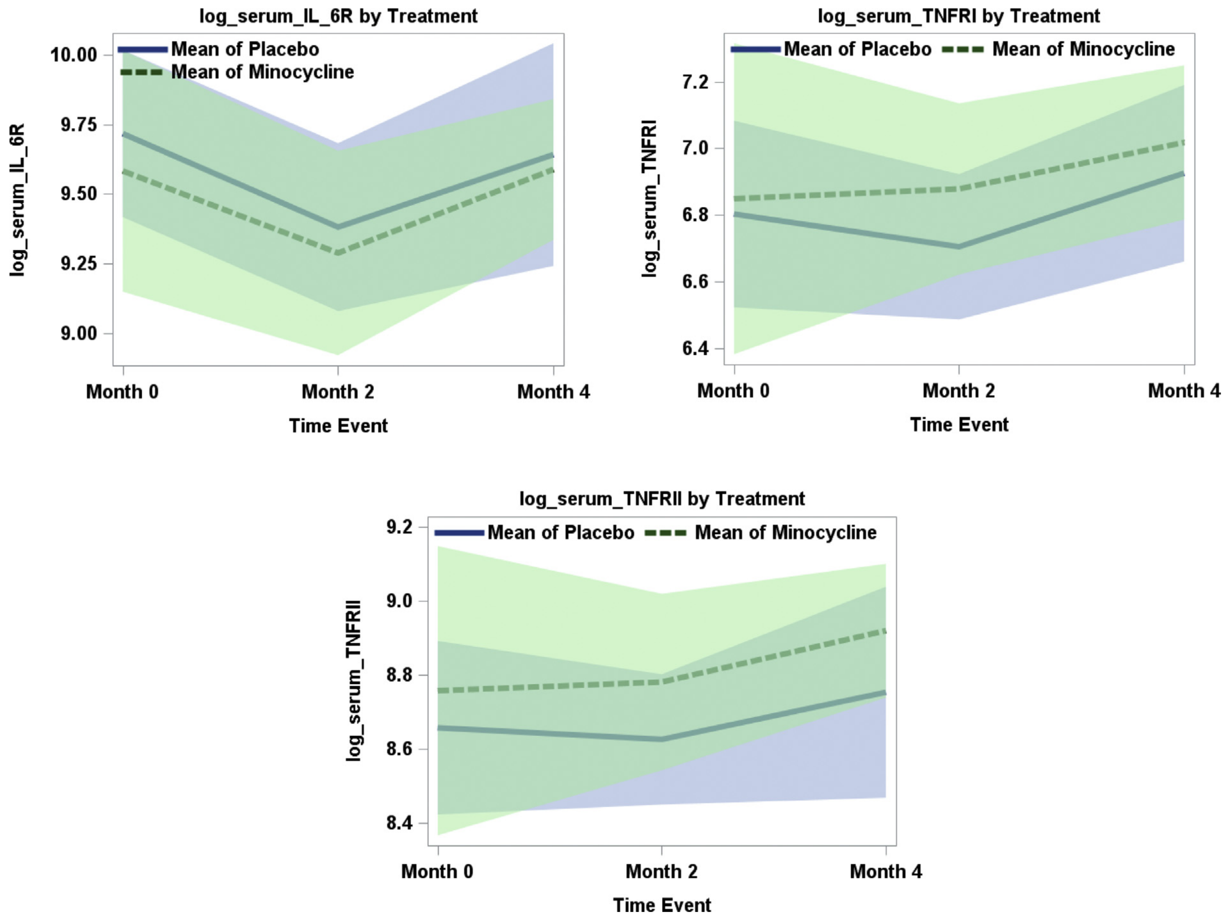

Fig. 2. (*continued*).

numbness/tingling or fatigue by minocycline, compared with placebo. In addition, paralleling the negative clinical results, none of our findings suggested that minocycline modulated the level of inflammatory markers. Therefore, further clinical study of minocycline for treatment-related symptom management in patients with CRC undergoing standard oxaliplatin-based chemotherapy is not encouraged. Although the expectation for an effective reduction of major symptom burden, CIPN and fatigue, by one medication might be not the reality, given these outcomes and the current fact that oxaliplatin is a cornerstone in the treatment of CRC, clinical studies to investigate effective ways to better manage these bothersome symptoms are still urgently needed.

Between our two study sites, we found that the level of patient care was roughly equivalent (oncology management at LBJ is provided by MD Anderson oncologists), disease conditions of the study sample were similar, and similar therapy was provided. Although the patients treated at LBJ were more likely to be members of underserved groups, the reasons that patients dropped out of the trial, the rates of early withdrawal from standard care due to toxicity, and the major symptom burden were similar for the two sites. Thus, this study revealed no mediating disparity effect of socioeconomic status on the severity of CIPN and fatigue in patients with CRC during standard oxaliplatin-based chemotherapy.

To identify patients who would likely to report significant symptom burden during standard chemotherapy over four months among patients with CRC, by trajectory analysis with the weekly MDASI symptom assessment, we observed that 44.7% of patients reported significantly more severe CIPN (numbness/tingling determined by MDASI), and 56.4% of patients reported persistently more severe fatigue, compared with other patients under this trial.

The outcome results from the trial's primary PRO measure, the single MDASI-GI item "numbness/tingling" (a core symptom of CIPN) on a 0 to 10 scale, were consistent with results from three subscales of the European Organization for Research and Treatment of Cancer CIPN20 questionnaire items (sensory, motor, and autonomic) in this cohort of patients who had no preexisting neuropathy. We observed that single-item numbness/tingling on the MDASI could well represent the longitudinal change on sensory scale of CIPN20, meanwhile this single item also

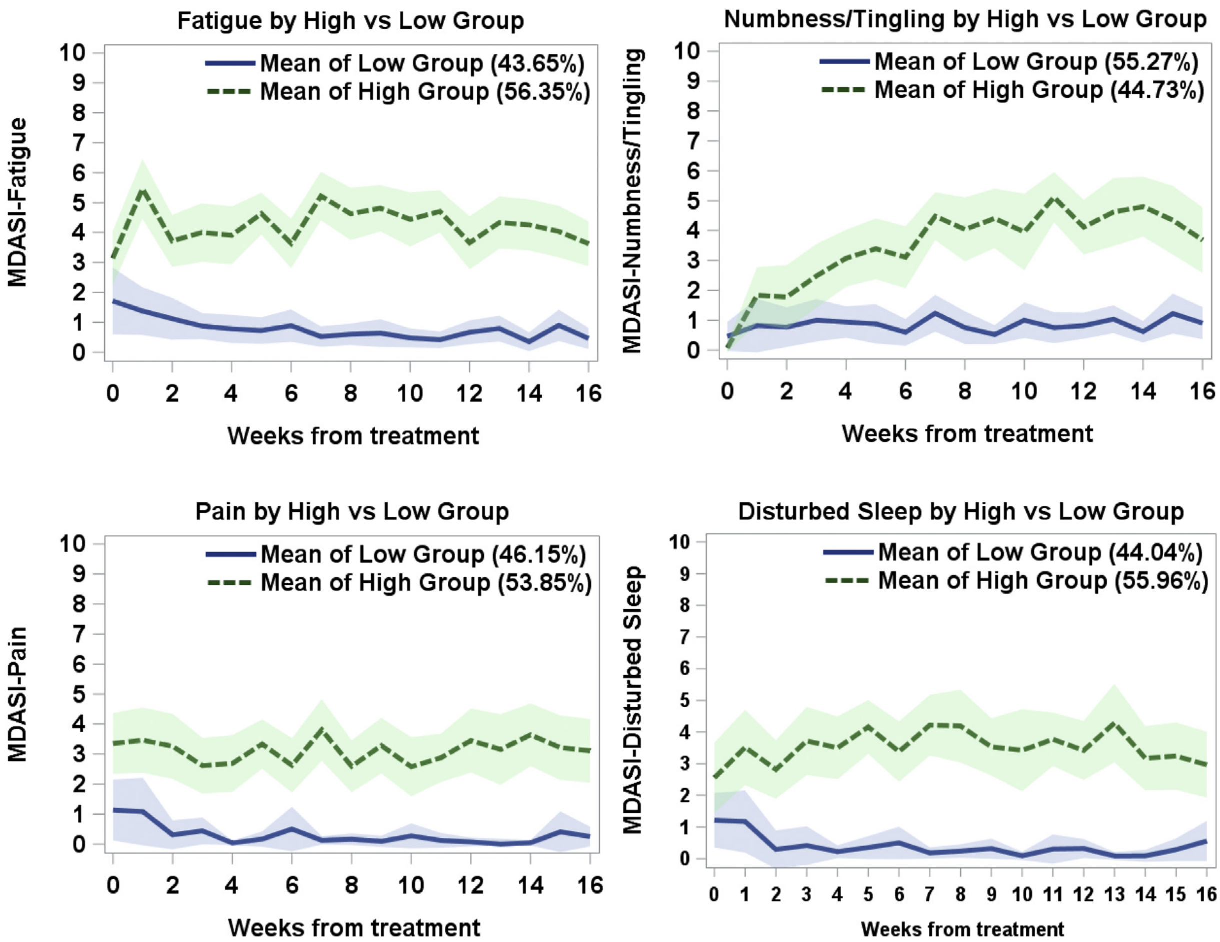

Fig. 3. Trajectories of major symptom burden over treatment period ($n = 66$).

significantly relevant to the severity of motor and autonomic subscale of CIPN. For the sake of simplicity and less burden for patients, it supports the value for further study of the utility of the single item in a clinical trial that uses multiple assessment points.

In addition, for the purpose of better patient care with attention to the most bothersome symptom burden in patients with CRC, severe pretherapy fatigue and pain, perhaps driven by a combination of the disease and previous therapy, may be indicative of risk for the development of high symptom burden during chemotherapy. These might even be considered as simple screening items for use in routine care before chemotherapy is used.

The study was limited by non—dose-dependent trial design for intervention or prevention of CIPN and fatigue. The lack of an impact on inflammatory markers indicates that the dose may have been suboptimal. The dosage (200 mg/day) was chosen on the basis of minocycline's known safety in other clinical applications, which have used this daily dose. However, the lack of any positive signal does not encourage dosing studies at higher levels. The second limitation is lack of information of drug bioavailability and effects of an ingested compound in the study. This might provide more useful interpretation of the reason of this negative trial.

Conclusion

Minocycline for the management of treatment-related symptoms is feasible and has a low-toxicity profile at 100 mg twice a day. However, the use of minocycline at this dose yielded no positive evidence of its capacity to reduce either fatigue or neuropathy on MDASI symptom ratings associated with oxaliplatin-based therapy. Furthermore, we did not observe the impact of treatment site on symptom development nor the mediating effect on efficacy of minocycline intervention. The absence of evidence of reduced inflammation by minocycline on any tested marker suggests that the trial provides little new information on the role that inflammation might play in the development of neuropathy or fatigue in patients with CRC undergoing standard oxaliplatin-based chemotherapy, and the results do not support further trials of minocycline for treatment-related symptom reduction in these patients. However, this study does demonstrate the feasibility of a pathway from basic animal behavioral studies to early-phase clinical trials as we learn more about the mechanisms responsible for treatment-related symptoms.

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References

1. Grothey A. Reintroduction of oxaliplatin: a viable approach to the long-term management of metastatic colorectal cancer. Oncology 2010;79:389–399.

2. Wang XS, Shi Q, Williams LA, et al. Prospective study of patient-reported symptom burden in patients with non-small cell lung cancer undergoing proton or photon chemoradiation therapy. J Pain Symptom Manage 2016;51:832–838.

3. Thong MS, Mols F, Wang XS, et al. Quantifying fatigue in (long-term) colorectal cancer survivors: a study from the population-based patient reported outcomes following initial treatment and long term evaluation of survivorship registry. Eur J Cancer 2013;49:1957–1966.

4. Hannestad J, DellaGioia N, Ortiz N, Pittman B, Bhagwagar Z. Citalopram reduces endotoxin-induced fatigue. Brain Behav Immun 2011;25:256–259.

5. Miller AH. Cytokines and sickness behavior: implications for cancer care and control. Brain Behav Immun 2003;17:S132–S134.

6. Wang XS, Shi Q, Williams LA, et al. Inflammatory cytokines are associated with the development of symptom burden in patients with NSCLC undergoing concurrent chemoradiation therapy. Brain Behav Immun 2010;24:968–974.

7. Wood LJ, Nail LM, Gilster A, Winters KA, Elsea CR. Cancer chemotherapy-related symptoms: evidence to suggest a role for proinflammatory cytokines. Oncol Nurs Forum 2006;33:535–542.

8. Mishra MK, Basu A. Minocycline neuroprotects, reduces microglial activation, inhibits caspase 3 induction, and viral replication following Japanese encephalitis. J Neurochem 2008;105:1582–1595.

9. Boyette-Davis J, Xin W, Zhang H, Dougherty PM. Intraepidermal nerve fiber loss corresponds to the development of Taxol-induced hyperalgesia and can be prevented by treatment with minocycline. Pain 2011;152:308–313.

10. Cata JP, Weng HR, Dougherty PM. The effects of thalidomide and minocycline on taxol-induced hyperalgesia in rats. Brain Res 2008;1229:100–110.

11. Padi SS, Kulkarni SK. Minocycline prevents the development of neuropathic pain, but not acute pain: possible anti-inflammatory and antioxidant mechanisms. Eur J Pharmacol 2008;601:79–87.

12. Raghavendra V, Tanga F, DeLeo JA. Inhibition of microglial activation attenuates the development but not existing hypersensitivity in a rat model of neuropathy. J Pharmacol Exp Ther 2003;306:624–630.

13. Noble W, Garwood CJ, Hanger DP. Minocycline as a potential therapeutic agent in neurodegenerative disorders characterised by protein misfolding. Prion 2009;3:78–83.

14. Pachman DR, Dockter T, Zekan PJ, et al. A pilot study of minocycline for the prevention of paclitaxel-associated neuropathy: ACCRU study RU221408I. Support Care Cancer 2017;25:3407–3416.

15. Gunn GB, Mendoza TR, Garden AS, et al. Minocycline for symptom reduction during radiation therapy for head and neck cancer: a randomized clinical trial. Support Care Cancer 2019;27:1–9.

16. Cleeland CS, Mendoza TR, Wang XS, et al. Levels of symptom burden during chemotherapy for advanced lung cancer: differences between public hospitals and a tertiary cancer center. J Clin Oncol 2011;29:2859–2865.

17. Tilley BC, Alarcón GS, Heyse SP, et al. Minocycline in rheumatoid arthritis. A 48-week, double-blind, placebo-controlled trial. MIRA Trial Group. Ann Intern Med 1995;122:81–89.

18. Wang XS, Williams LA, Eng C, et al. Validation and application of a module of the M. D. Anderson Symptom Inventory for measuring multiple symptoms in patients with gastrointestinal cancer (the MDASI-GI). Cancer 2010;116:2053–2063.

19. Postma TJ, Aaronson NK, Heimans JJ, et al. The development of an EORTC quality of life questionnaire to assess chemotherapy-induced peripheral neuropathy: the QLQ-CIPN20. Eur J Cancer 2005;41:1135–1139.

20. van Zuiden M, Heijnen CJ, van de Schoot R, et al. Cytokine production by leukocytes of military personnel with depressive symptoms after deployment to a combat-zone: a prospective, longitudinal study. PLoS One 2011;6:e29142.

21. Dantzer R, Meagher MW, Cleeland CS. Translational approaches to treatment-induced symptoms in cancer patients. Nat Rev Clin Oncol 2012;9:414—426.

22. Bonelli RM, Hodl AK, Hofmann P, Kapfhammer HP. Neuroprotection in Huntington's disease: a 2-year study on minocycline. Int Clin Psychopharmacol 2004;19:337—342.

23. Cappelleri JC, Bushmakin AG, Zlateva G, Sadosky A. Pain responder analysis: use of area under the curve to enhance interpretation of clinical trial results. Pain Pract 2009;9:348—353.

24. Haviland A, Jones B, Nagin D. Group-based trajectory modeling extended to account for nonrandom participant attrition. Sociological Methods Res 2011;40: 367—390.

25. Shi Q, Mendoza TR, Gunn GB, Wang XS, Rosenthal DI, Cleeland CS. Using group-based trajectory modeling to examine heterogeneity of symptom burden in patients with head and neck cancer undergoing aggressive non-surgical therapy. Qual Life Res 2013;22: 2331—2339.