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ORIGINAL ARTICLE

A pilot study of minocycline for the prevention of paclitaxel-associated neuropathy: ACCRU study RU221408I

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Abstract
Purpose Paclitaxel is associated with both an acute pain syndrome (P-APS) and chronic chemotherapy-induced peripheral neuropathy (CIPN). Given that extensive animal data suggest that minocycline may prevent chemotherapy-induced neurotoxicity, the purpose of this pilot study was to investigate the efficacy of minocycline for the prevention of CIPN and the P-APS.
Methods Patients with breast cancer were enrolled prior to initiating neoadjuvant or adjuvant weekly paclitaxel for 12 weeks and were randomized to receive minocycline 200 mg on day 1 followed by 100 mg twice daily or a matching placebo. Patients completed (1) an acute pain syndrome questionnaire daily during chemotherapy to measure P-APS and (2) the EORTC QLQ-CIPN20 questionnaire at baseline, prior to each dose of paclitaxel, and monthly for 6 months post treatment, to measure CIPN.
Results Forty-seven patients were randomized. There were no remarkable differences noted between the minocycline and placebo groups for the overall sensory neuropathy score of the EORTC QLQ-CIPN20 or its individual components, which evaluate tingling, numbness and shooting/burning pain in hands and feet. However, patients taking minocycline had a significant reduction in the daily average pain score attributed to P-APS (p = 0.02). Not only were no increased toxicities reported with minocycline, but there was a significant reduction in fatigue (p = 0.02).
Conclusions Results of this pilot study do not support the use of minocycline to prevent CIPN, but suggest that it may reduce P-APS and decrease fatigue; further study of the impact of this agent on those endpoints may be warranted.

Keywords Minocycline · Chemotherapy-induced peripheral neuropathy · Paclitaxel neuropathy

Introduction

Paclitaxel is a chemotherapeutic agent widely employed against a variety of both early stage and advanced epithelial malignancies. One of the most frequent and troubling toxicities associated with its use is chemotherapy-induced peripheral neuropathy (CIPN), characterized by numbness, tingling, and shooting/burning pain, usually starting in the hands and feet. These symptoms may appear in the first several weeks of therapy and become more common and severe over time with continued exposure to the drug. While the symptoms of paclitaxel-induced CIPN tend to improve after paclitaxel is discontinued, in some patients, symptoms persist for years after completing chemotherapy. Paclitaxel is also associated with a syndrome of sub-acute aches and pain, often referred to as myalgias and arthalgias, which has been labeled as the paclitaxel-acute pain syndrome (P-APS). The pain often starts 1–2 days after the paclitaxel infusion, with the median duration of 4–5 days. The pain is usually located in the back, hips, shoulders, thighs, legs, and feet and, at

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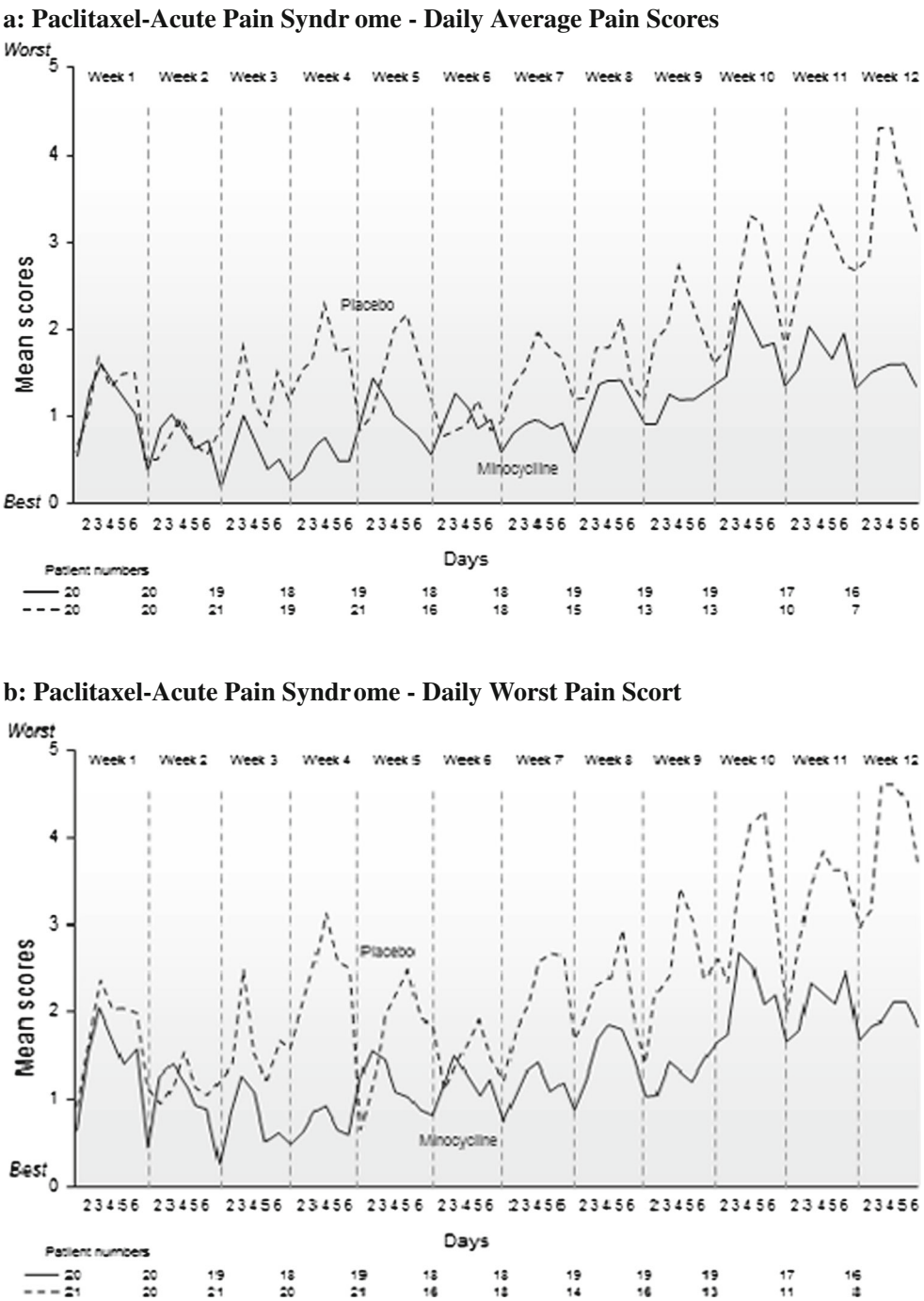


Fig. 1 Average pain (**a**) and worst pain (**b**) daily scores over 6 days following paclitaxel doses for each cycle. Higher scores represent more pain

times, radiates down the legs, arms, or back. Based on its clinical characteristics, as well as animal studies that demonstrated nerve injury within 24 h after receipt of a clinically appropriate dose of paclitaxel [1], it has been hypothesized that P-APS is a form of acute neurotoxicity and not due to effects of the drug on muscles or joints. To further support its neurotoxic mechanism, patients with severe P-APS tend to be at increased risk for developing chronic CIPN [2, 3].

Many agents have been studied for the prevention of CIPN, but, unfortunately, none have any proven benefit [4]. While there has been less investigation of agents for the prevention of P-APS, glutamine has been studied, with negative results [5]. More recently, a study was performed using pregabalin for the prevention of paclitaxel-associated neuropathy. This study included 46 patients who were randomly assigned to receive 75 mg of pregabalin or placebo twice daily while receiving weekly paclitaxel (80 mg/m^2) for 12 weeks. The investigators found no substantial reduction in the development of symptoms of P-APS or chronic

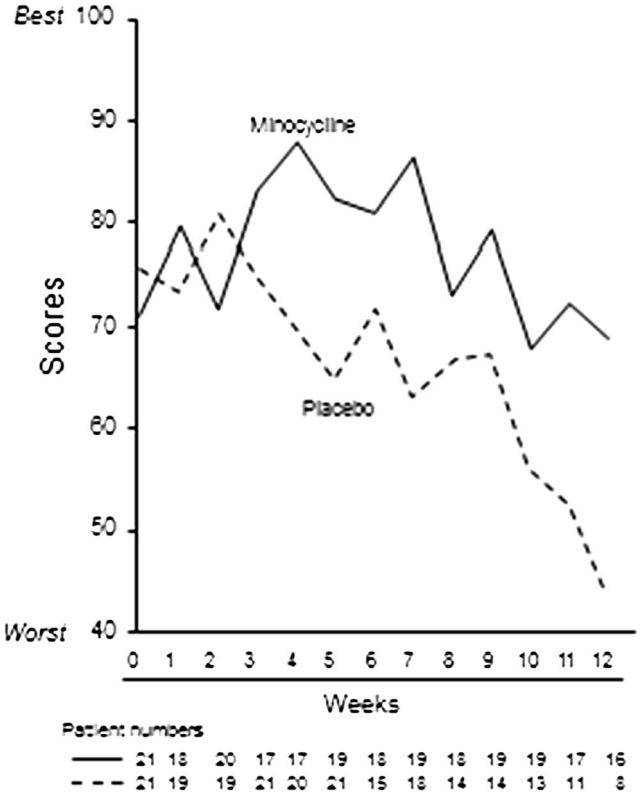


Fig. 2 Median patient-reported distress from aches and pain over the past week by cycle. Higher scores represent less trouble

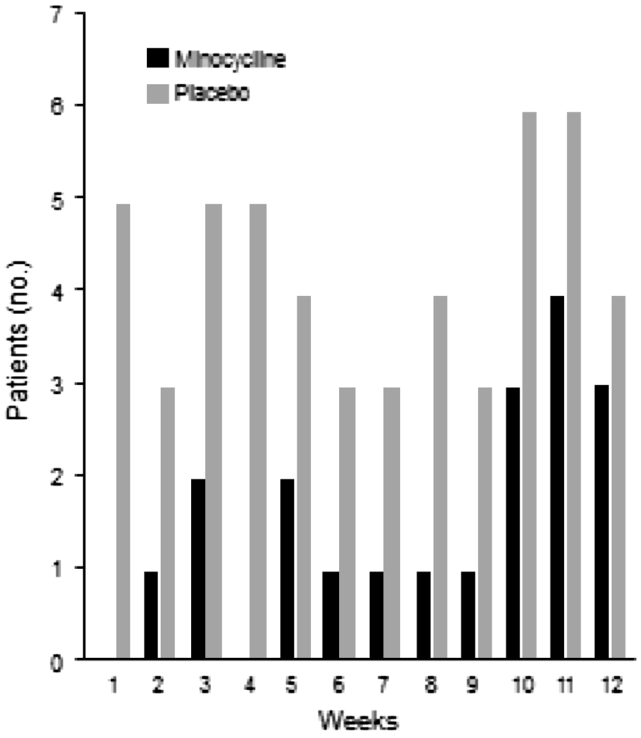


Fig. 3 Number of patients using opioid pain medications during each cycle, for the 12 weeks of treatment

neuropathy with this agent [6]. Therefore, further investigation is needed to try to identify agents that may have efficacy for the prevention of P-APS and CIPN.

Minocycline is a second-generation tetracycline derivative, traditionally used as an antibiotic and an anti-inflammatory drug. It effectively crosses the blood-brain barrier and has been shown to have neuroprotective properties in experimental animal models of neurological injury and neurodegenerative disease [7, 8]. Minocycline has also been found to have possible benefit in human studies of acute stroke and spinal cord injury [9, 10]. This drug has been investigated for the prevention of neuropathic pain in multiple experimental animal models, including models of nerve injury, peripheral nerve inflammation, and diabetic neuropathic pain [11–19]. The proposed mechanism by which minocycline may reduce neuropathic pain is by inhibition of spinal microglia activation, reducing the production of pro-inflammatory cytokines, thereby lessening nerve injury [20]. In addition, it is proposed that administration of minocycline may decrease cytokine production and inflammation in the dorsal root ganglion (DRG). It may be that the analgesic effects of minocycline are related to inhibition of Na+ channels in primary afferent neurons [21].

Five studies using experimental animal models have investigated minocycline for the prevention of paclitaxel-induced neurotoxicity, each demonstrating positive results [22–26]. In one rat study, animals that were pretreated with minocycline had significantly attenuated paclitaxel-evoked allodynia at days 4 and 12, with a trend toward improvement as early as day 2. In addition, it appeared that minocycline inhibited the increase in the number of ATF3 (activating transcription factor 3)-positive cells in the DRG on days 4 and 12 [24]. In another study, rats treated with paclitaxel and minocycline were noted to have reduced levels of paclitaxel-induced mechanical hyperalgesia, measured as the mechanical withdrawal threshold to the application of von Frey filaments to the hind paws, compared to animals treated with paclitaxel alone. In addition, minocycline prevented paclitaxel-induced thermal hyperalgesia, measured as the withdrawal latency to radiant heat. Reductions in mechanical hyperalgesia and thermal hyperalgesia were noted as early as 1 day after treatment. It was proposed that the immunomodulatory effects of minocycline were primarily responsible for these changes [23]. An additional animal study involved administration of minocycline 72 h prior to the first injection of paclitaxel. It was noted that paclitaxel-induced the activation of spinal astrocytes, recognized by an increase in GFAP (glial fibrillary acidic protein) expression in the spinal dorsal horn, as early as 4 h after the first injection of paclitaxel. Systemic prophylaxis with minocycline prevented activation of astrocytes and downregulation of glial glutamate transporters in the spinal dorsal horn induced by paclitaxel. [26] Furthermore, since paclitaxel has

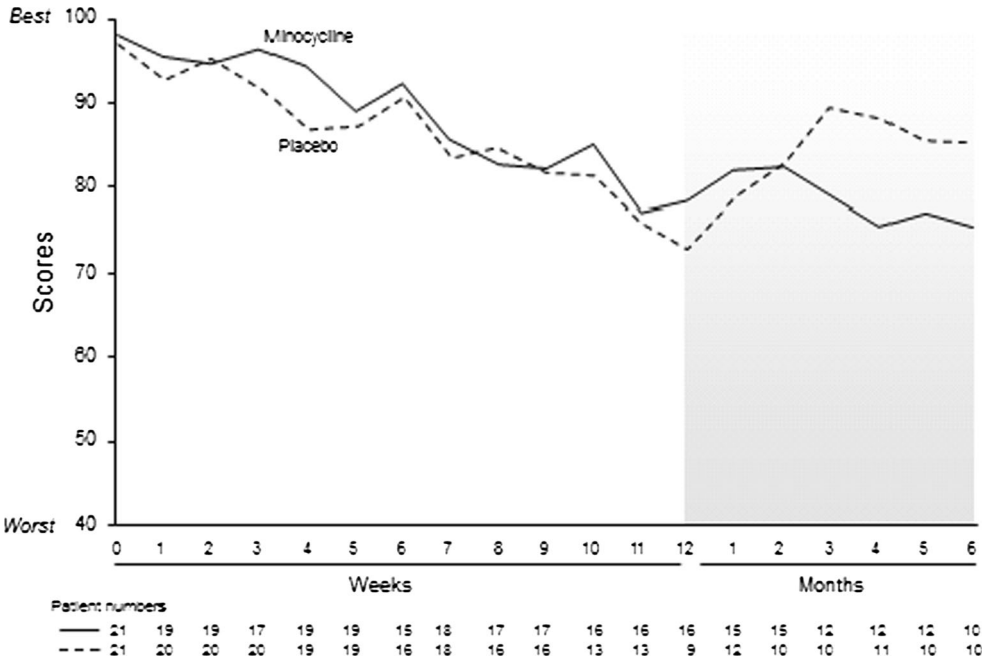


Fig. 4 CIPN scores during 12 weeks of treatment and over 6-month follow-up for the EORTC QLQ-CIPN20 sensory scores. Higher score represent fewer symptoms

clearly been shown to increase sensory neurons responses to TRPV1 (transient receptor potential vanilloid 1) by activation of toll-like receptor 4 (TLR4), minocycline-induced effects on pain signaling could result from suppression of TLR4 neuronal activation [27].

Based on these above noted data, the current study was developed to attempt to provide pilot data regarding the potential role of minocycline for the prevention of P-APS as well as paclitaxel-induced neuropathy, to support, hopefully, the conduct of a larger phase III placebo-controlled trial.

Methods

The current study was a multi-centric, randomized, double-blinded, pilot trial. Inclusion criteria included a diagnosis of breast cancer, age ≥18 years, ECOG performance 0 or 1, and life expectancy >6 months. All of the participants were scheduled to receive weekly paclitaxel at a dose of 80 mg/m^2 in the adjuvant or neoadjuvant setting for a planned course of 12 weeks without any other concurrent cytotoxic chemotherapy; concurrent trastuzumab and/or other antibody and/or small molecule treatments, except for PARP (poly adenosine diphosphate ribose polymerase) inhibitors, was allowed. Participants needed to have the ability to complete questionnaires by themselves or with assistance and the ability to provide informed written consent. Exclusion criteria included pregnant or nursing women, previous diagnosis of diabetic or other peripheral neuropathy, fibromyalgia, prior exposure to neurotoxic chemotherapy or a history of allergic or other adverse reactions to tetracycline or minocycline.

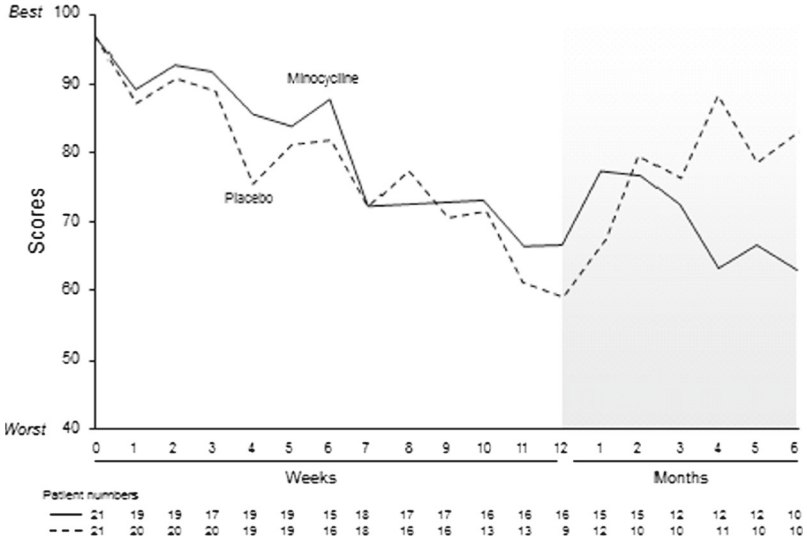
Patients were randomized to either the placebo or minocycline arm. Patients on the active therapy arm received 200 mg of minocycline (two 100 mg capsules) on day one followed by 100 mg twice daily until the 12 weeks of chemotherapy were completed, while the control group received matching placebos. Treatment was stopped 1 week after the last planned paclitaxel dose. Patients were instructed to use 500 mg of acetaminophen every 6 h and/or 5 mg of oxycodone every 1–2 h as needed for breakthrough pain associated with the P-APS.

At the time of registration, patients had a history and physical examination and completed a pre-treatment 9-item questionnaire that addressed 1) the presence of symptoms related to baseline pain and 2) potential minocycline toxicities.

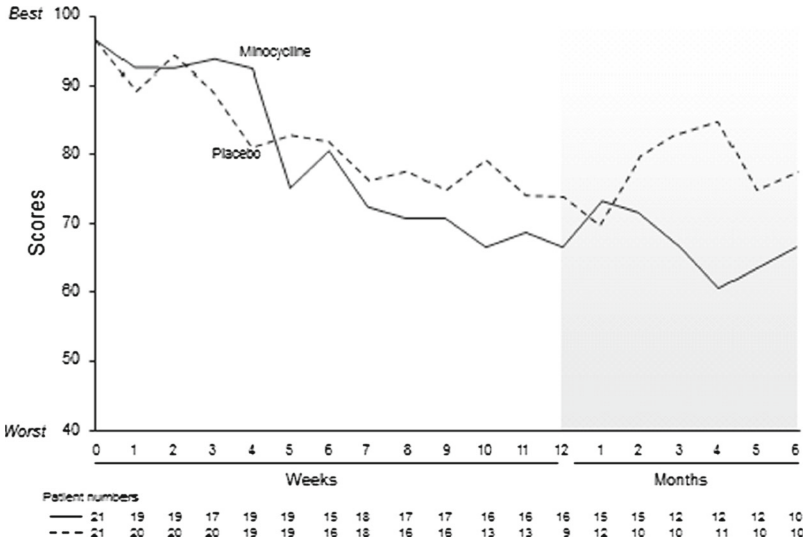
P-APS symptoms were measured by asking patients to keep a daily symptom log, comprising of 10 items regarding pain symptoms and the use of pain medications on days 2–7 following each paclitaxel dose. These items asked about aches and pain attributed to the paclitaxel treatments. A 15-question summary questionnaire regarding symptom quality, location, alleviating/aggravating factors, and medication use was administered on the eighth day following each paclitaxel dose (typically the day when the patient

Fig. 5 EORTC QLQ-CIPN20 selected individual item scores during treatment and over 6-month follow-up for tingling fingers/hands (**a**), tingling toes/feet (**b**), numbness fingers/hands (**c**), numbness of toes/feet (**d**), shooting burning pain of fingers/hands (**e**), and shooting burning pain of toe/feet (**f**). Higher scores represent fewer symptoms ▶

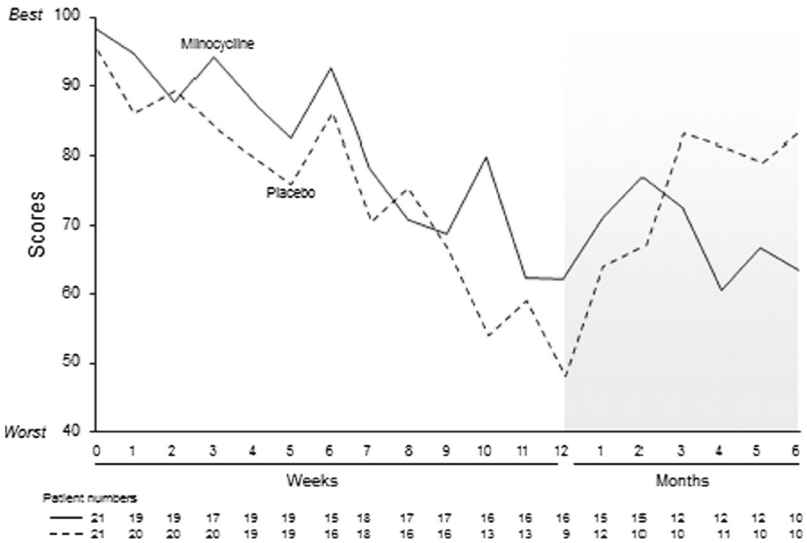
a. EORTC QLQ-CIPN20 Sensory Score -Tingling in Fingers/Hands



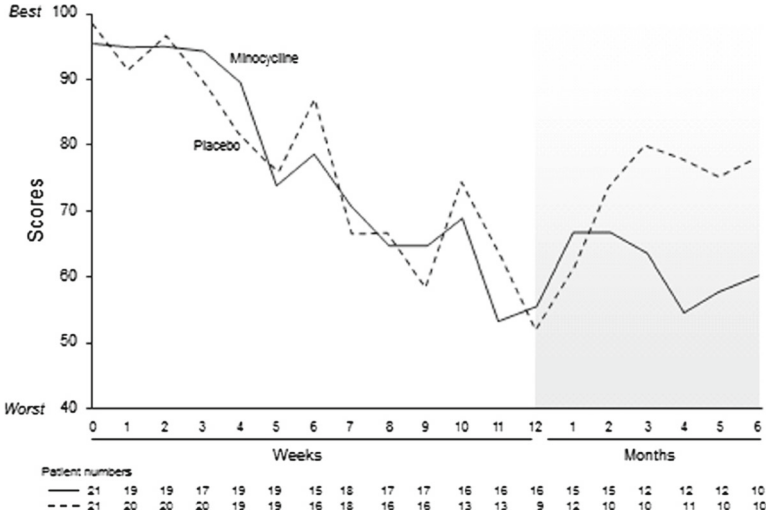
b. EORTC QLQ-CIPN20 Sensory Score -Tingling in Toes/Feet



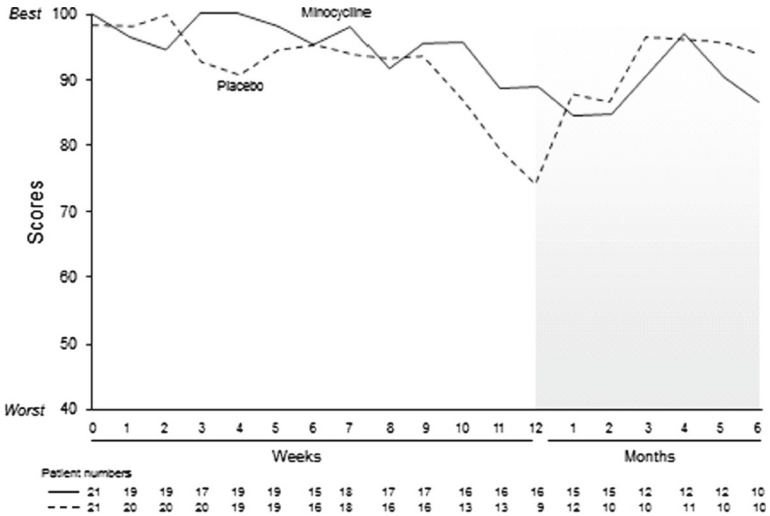
c. EORTC QLQ-CIPN20 Sensory Score - Numbness in Fingers/Hands



d. EORTC QLQ-CIPN20 Sensory Score - Numbness in Toes/Feet



e. EORTC QLQ-CIPN20 Sensory Score - Shooting/Burning Pain in Fingers/Hands



f. EORTC QLQ-CIPN20 Sensory Score - Shooting/Burning Pain in Toes/Feet

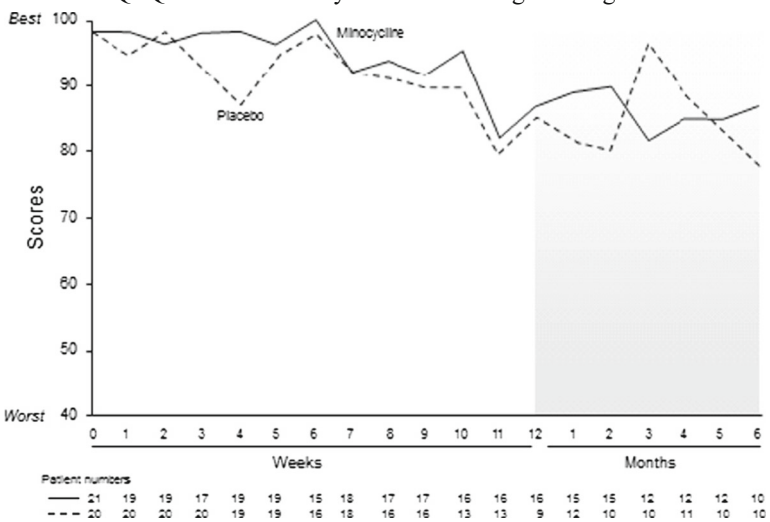


Fig. 5 (continued)

returned for her next dose of treatment). These instruments were those used to define this syndrome in previous publications [2, 3, 28]. CIPN was measured using the European Organization for Research and Treatment of Cancer Quality-of-Life (EORTC QLQ-CIPN20) questionnaire, which was completed at baseline, prior to each dose of paclitaxel and then monthly, following completion of paclitaxel treatment, for 6 months. The EORTC QLQ-CIPN20 is a 20-item self-report questionnaire that contains nine items assessing sensory function, eight items assessing motor function, and three items assessing autonomic function. Items are scored from 1 to 4 with 1 representing "not at all" and 4 representing "very much." The EORTC QLQ-CIPN20 has been tested in cancer patients receiving a variety of chemotherapy agents and has been shown to be reliable, valid, and responsive to change. Cronbach's alpha coefficients for the three subscales are 0.82, 0.73, and 0.76, respectively [29, 30]. Adverse events were monitored with the patient questionnaires, noted above, as well as with the physician-reported National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

The primary goals of this trial were to obtain pilot data regarding the possible effect of minocycline on the prevention of paclitaxel-induced CIPN and P-APS. An additional goal was to look at the potential toxicities of minocycline in this setting. To accomplish the goals of this trial, a variety of endpoints were utilized in an exploratory fashion. Pain scores and other continuous variables were converted to a 0–100 scale, where 100 = best possible quality of life. Area under the curve (AUC) for the entire course of treatment was calculated for worst, least, and average pain, as well as for the EORTC QLQ-CIPN20. Demographics, clinical data, and adverse events were summarized using descriptive statistics. Pain scores (maximum, average, and least), EORTC QLQ-CIPN20 scores, and AUCs between the two groups were compared using a Wilcoxon rank-sum test. Opioid and non-prescription drug use, adverse events, and other categorical variables were compared using chi-square or Fisher exact tests. Patients with missing data were excluded from analysis of associated endpoints.

Results

This study accrued 47 patients between 11/21/2014 and 7/21/2015, from 13 individual sites. Two patients canceled and were not evaluable for primary endpoint analyses. Baseline demographics were balanced among the remaining 45 patients (22 on the minocycline arm and 23 on the placebo arm). All patients were females with mean age of 54.9 (standard deviation of 10.9). Of these 45 patients, 2 patients did not complete their booklets at their baseline and 1 patient did not complete a booklet for the duration of the study.

Paclitaxel acute pain syndrome

There was a significant difference in the daily average AUC pain score attributed to P-APS, favoring minocycline (median 96.0 vs 84.3; $p = 0.02$), and also a trend toward improvement in the daily worst pain AUC score over the 12 cycles (median 94.9 vs 83.0, $p = 0.06$), although no difference was apparent during the first cycle (week) of treatment (Fig. 1). In addition, patients in the minocycline group reported that their P-APS aches and pains were less distressing compared to the placebo group (median 84.6 vs 68.9 $p = 0.02$; Fig. 2), and there was a trend toward less use of opioid pain medications for control of P-APS during cycle one (0 vs 23%, $p = 0.05$) and in other cycles (27.3 vs 52.2%, $p = 0.09$) (Fig. 3). One patient did not answer any of these pain questions at baseline, and one patient did not answer their average pain question at baseline. These patients were excluded from this analysis.

Chemotherapy-induced peripheral neurotoxicity

Despite the decrease in P-APS associated with minocycline use, there was no substantial difference in the overall EORTC QLQ-CIPN20 sensory subscale between minocycline and placebo (Fig. 4), nor any difference in reported tingling, numbness, or shooting/burning pain during treatment or for 6 months following treatment (Fig. 5). Three patients, for whom we either did not have baseline neuropathy scores ($n = 1$) or post-baseline scores ($n = 2$), are excluded from this analysis.

Minocycline toxicity evaluation

Dizziness, fatigue, headache, skin discoloration, and tooth discoloration toxicities were evaluated, with no findings to suggest that minocycline increased any of these symptoms. In fact, patients who received minocycline reported significantly less fatigue (median AUC 76.7 vs 59.0, $p = 0.02$; Fig. 6).

Discussion

Data from the current study suggest, but do not prove, that minocycline decreases P-APS symptoms, as patients who received minocycline had lower daily average pain scores, reported less distress from aches and pains after paclitaxel, and tended to take less opioid medications. Symptoms of P-APS have been reported in up to 71% of patients being treated with paclitaxel at doses of 70 to 90 mg/m^2 weekly and 88% of

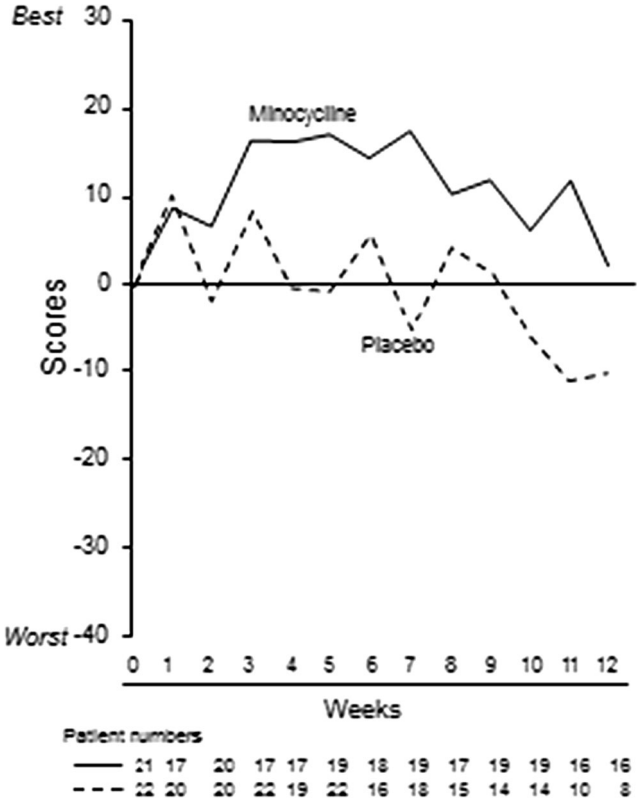


Fig. 6 Fatigue AUC scores during 12 weeks of treatment. Higher scores represent less fatigue

those receiving doses of at least 175 mg/m^2 every 2 to 4 weeks [2, 3]. The discomfort associated with this syndrome can be distressing for patients and treatment with opioid medications has been reported for 12–20% of patients receiving weekly paclitaxel and up to 41% who received every 3 week paclitaxel [2, 3]. No agent has previously been shown to decrease this acute pain syndrome, although analgesics appear to alleviate it.

Given that this trial supports the possibility that minocycline might decrease this problem, it is reasonable to consider possible mechanisms for this effect. It may be related to the ability of minocycline to inhibit activation of microglia, reducing production of pro-inflammatory cytokines [20]. It may also be related to its ability to prevent the loss of intra-epidermal nerve fibers (IENFs) and interruption of macrophage responses [22, 24]. Finally, the protection against P-APS may be related to prevention of astrocyte activation and downregulation of glial glutamate transporters [26]. It is interesting to note that while there was no suggestion of a difference in P-APS symptoms in cycle 1, differences in symptoms become apparent with later cycles. Due to logistical reasons, minocycline in the current study was not given prior to the first day of chemotherapy. In contrast, in many of the animal studies, minocycline was given 24–72 h prior to the first dose paclitaxel [22, 24, 26]. The current data suggest that minocycline might be more effective against week 1 P-APS if started 1–3 days prior to the first dose of paclitaxel.

In contrast to the positive findings of the acute pain syndrome, the results of this trial do not support the conduct of a larger trial to test whether minocycline can reduce paclitaxel-induced peripheral neuropathy. As previous studies have demonstrated a potential relationship between the severity of P-APS symptoms and subsequent development of CIPN [2, 3], it is reasonable to consider why minocycline appears to prevent P-APS but not CIPN. The animal studies described above primarily investigated the ability of minocycline to reduce short-term nerve damage induced by paclitaxel. Perhaps those findings, like P-APS, are more related to acute nerve inflammation and injury, which can be attenuated by minocycline, while CIPN may be more a function of paclitaxel-induced microtubule dysfunction causing temporary, and sometimes permanent, damage to sensory neurons and their myelin sheaths, especially of the long axons extending to and from the patient's distal extremities.

The findings of the current trial are consistent with a previous study of minocycline for the prevention of bortezomib-induced neurotoxicity, the preliminary results from which have been reported [31]. A phase II randomized placebo-controlled trial of minocycline vs. placebo, administered during induction therapy with bortezomib for multiple myeloma, was conducted at MD Anderson to assess its impact on the development of peripheral neuropathy. With about 40 evaluable patients, there was no evidence that minocycline reduced physician-judged neuropathy or improved fingertip touch perception. While numbness from baseline to week 10 was about half as prominent in patients receiving minocycline, this was not a statistically significant difference. Two other MD Anderson trials have been developed to assess the ability of minocycline to reduce neuropathy, including another trial in multiple myeloma, similar to the previous one but focusing on patients receiving maintenance therapy, which has completed accrual, and a trial in patients with colorectal cancer to determine whether minocycline can decrease neuropathy in patients receiving oxaliplatin.

An interesting finding from our study was the positive effect of minocycline on treatment-related fatigue. While the observed improvement in fatigue over the 12 weeks of treatment was a surprise to the study team, this is consistent with data from a study reported at ASCO 2016 which investigated minocycline for the prevention of symptoms in patients with non-small-cell lung cancer undergoing concurrent chemoradiation therapy [32]. In that trial, patients were randomized to receive minocycline (100 mg twice daily) or a placebo over the course of chemoradiation therapy. With 40 evaluable patients (19 minocycline, 21 placebo), AUCs for fatigue over 12 weeks were significantly lower in the minocycline group (odds ratio 0.65, $p = 0.03$). A fatigue-moderating effect of minocycline has also been observed in animal models. One

study used a mouse model to discriminate between two components of cancer-related fatigue: loss of muscle mass and altered mood/motivation. Minocycline administration reduced depressive-like behavior and improved grip strength without altering muscle mass. It also reduced tumor-induced expression of IL-1 β (interleukin-1 beta), a marker of neuroinflammation [33]. Another study used a mouse model to explore the role of minocycline and licofelone for chronic fatigue stress. In this study, mice were put on a running wheel apparatus for 6-min test sessions daily for 21 days, which normally produces a fatigue-like condition. Pre-treatment with either licofelone or minocycline significantly attenuated fatigue-like behavior and oxidative damage, and restored mitochondrial enzyme complex activities; licofelone and minocycline used together seemed to potentiate their individual fatigue-protective effects [34].

It could be considered a weakness of our study that we enrolled only patients receiving weekly paclitaxel at 80 mg/m^2, as opposed to those receiving doses of 175 mg/m^2 or higher every 2–3 weeks, since patients receiving higher dose of paclitaxel are more likely to experience severe symptoms of P-APS [2, 3] and therefore might show greater benefit from a treatment that reduces this symptom. We also studied only patients being treated for breast cancer and enrolled only women. This design was chosen because the lower dose weekly schedule is the one most commonly employed in treating early stage breast cancer; a subsequent study could be designed specifically to assess the efficacy of minocycline at preventing or reducing P-APS and fatigue in patients receiving higher doses of paclitaxel and in other malignancies for which paclitaxel is commonly employed. Another potential weakness may be that the minocycline was not started in advance of the first dose of paclitaxel.

While the results of this study do not support conducting a large, phase III trial of minocycline for the prevention of CIPN, they do support further investigation of the effect of minocycline on P-APS and the potential utility of minocycline for decreasing chemotherapy-related fatigue.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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