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Evaluation of the effect of pentoxifylline on the prevention of paclitaxel-induced peripheral neuropathy in breast cancer patients: a randomized controlled study

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Abstract

Background Paclitaxel-induced peripheral neuropathy (PIPN) is one of the most common and debilitating toxicity. Up till now, no treatment or preventive medication is recommended by guidelines. Pentoxifylline has been found to prevent PIPN in animal models. This study aimed to evaluate the tolerability and efficacy of pentoxifylline in preventing PIPN. To our knowledge, this is the first clinical trial to evaluate the potential effect of pentoxifylline on the prevention of PIPN in breast cancer (BC) patients.

Results A simple-randomized placebo-controlled study was conducted on 60 BC patients receiving weekly paclitaxel and either pentoxifylline 400 mg twice daily (n = 30) or placebo (n = 30) for 12 weeks. Only 55 patients completed the study. The main objective was the evaluation of the effect of pentoxifylline on the incidence of PIPN which revealed no significant difference between the pentoxifylline group (85%) and the placebo group (100%). Secondary objectives included time to develop grade 2 or 3 (TTG 2/3) PIPN, the patient's quality of life (QOL), serum tumor necrosis factor-α (TNF-α) and malondialdehyde and the tolerability of pentoxifylline. The median TTG 2/3 PIPN was not reached in the pentoxifylline group compared to 77 days (95% confidence interval of 70.91 to 83.07) in the placebo group. However, the difference did not reach significance. The assessment of the impact of PIPN on QOL was performed at baseline and at weeks 4, 8 and 12 using Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-NTX) subscale. The magnitude of the worsening in the QOL was significantly lower in the pentoxifylline group than in the placebo group at weeks 4, 8, and 12 (p values = 0.028, 0.003, and 0.018, respectively). Analysis of the serum TNF-α and malondialdehyde revealed no significant differences between the groups. Pentoxifylline was safe, tolerable and did not affect paclitaxel toxicity.

Conclusion Oral pentoxifylline (400 mg twice daily) did not decrease the incidence of PIPN. However, it improved patients' QOL significantly.

Trial registration Clinical Trials.gov, NCT05189535. Registered 4 October 2021, https://classic.clinicaltrials.gov/ct2/show/NCT05189535.

Keywords FACT/GOG-NTX, Paclitaxel, Pentoxifylline, Peripheral neuropathy, Quality of life

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Background

Breast cancer (BC) is the most prevalent cancer worldwide, particularly in women. According to the American Cancer Society**,** one in every 8 women is diagnosed with BC at any time in their lives [1]. Female BC represents 11.6% of all cancer cases and is the fourth leading cause of cancer-related mortality worldwide [2]. It is estimated that in 2024, there will be 310,720 new cases of BC, with 42,250 deaths in women in the United States [3].

Chemotherapy protocols, including anthracycline followed by taxane, represent the cornerstone in the management of early and locally advanced stages of BC [4]. Paclitaxel, an antimitotic chemotherapy, is one of the most effective and widely used chemotherapies in BC in adjuvant and neoadjuvant settings [5]. Unfortunately, its use is limited by associated toxicity, mainly peripheral sensory neuropathy. The incidence of paclitaxel-induced peripheral neuropathy (PIPN) is approximately 97%. The risk of PIPN is associated with the cumulative dose, type of vehicle, and coadministration of neurotoxic medications [6–8]. Symptoms of PIPN range from mild pain and paresthesia to impaired fine skills, chronic pain, impaired motor function, and balance that may progress to paresis. It has a detrimental effect on quality of life (QOL) and clinical outcomes due to the disruption of daily function and treatment plans. Although the severity of symptoms and nerve function often improve gradually after stopping the insulting agent, recovery is incomplete, and residual symptoms may persist for years [8, 9].

The exact underlying pathophysiology of PIPN is not fully understood. However, this may be attributed to the accumulation of paclitaxel in the dorsal root ganglion, which induces mitochondrial dysfunction, the release of reactive oxygen species (ROS), and the subsequent induction of apoptosis and neuronal degeneration [10, 11]. Moreover, paclitaxel can activate immune reactions and stimulate macrophages to release potent proinflammatory cytokines and chemokines [12, 13]. Numerous medications have been evaluated as a preventive therapy for PIPN in BC patients such as N-acetyl cysteine, metformin, cilostazol and omega-3 [14–17]. However, none of them has been approved or recommended by guidelines, yet [9, 18]. Hence, there is a more need to explore agents that might help to ameliorate or prevent PIPN.

Pentoxifylline is a phosphodiesterase inhibitor (PDEi) used for the treatment of intermittent claudication and peripheral vascular disease [19]. Pentoxifylline has been reported to exert neuroprotective effects through its anti-inflammatory, immunomodulatory, and antioxidant effects [20, 21]. In a preclinical trial on oxaliplatin-induced peripheral neuropathy, pentoxifylline significantly improved neuropathic symptoms and nerve conduction velocity. Moreover, pentoxifylline reduced proinflammatory and oxidative stress biomarkers, including tumor necrosis factor α (TNF-α), and malondialdehyde (MDA), respectively in a dose-dependent manner [22]. In other animal studies, pentoxifylline significantly delayed the onset of PIPN and relieved neuropathic pain, mechanical allodynia, reduced inflammatory cytokines, and elevated anti-inflammatory mediators [23, 24]. In an experimental nerve injury study, pentoxifylline revealed a positive effect on axonal regeneration [25]. Moreover, in a randomized clinical trial (RCT), patients with diabetic neuropathy who received pentoxifylline 400 mg twice daily (BID) exhibited significant improvement in neuropathic symptoms through suppression of TNF-α, vasodilation and improvement in nerve blood supply [26]. Hence, this study aimed to evaluate the effect of pentoxifylline on the prevention and amelioration of PIPN in BC patients.

Methods

Study aim, design and setting

A prospective, randomized, placebo-controlled, single-blinded, 2-arm parallel study was conducted on 60 female Egyptian BC patients receiving adjuvant or neoadjuvant paclitaxel. This study aimed to evaluate the effect of pentoxifylline on preventing PIPN in BC patients. The study was carried out at an Egyptian university hospital, Cairo, Egypt.

Patients

All patients presenting to the Clinical Oncology Department were screened for eligibility criteria. Patients were included if they were adult female patients diagnosed with early or locally advanced breast cancer and planned to receive adjuvant or neoadjuvant weekly paclitaxel (80 mg/m^2) for 12 weeks [4, 5] with Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 and adequate bone marrow function (absolute neutrophilic count $\geq 1500/mm^3$ and platelet count $\geq 100{,}000/mm^3$), liver function (serum total bilirubin < 1.5 mg/dl) and renal function (estimated glomerular filtrating rate > 60 ml/min). The exclusion criteria included mental disease, preexisting peripheral neuropathy, comorbid disease known to increase the incidence of peripheral neuropathy (such as diabetes mellitus), recent surgery (≤ 1 month), myocardial infarction, hypersensitivity to pentoxifylline, or taking medications that induce or ameliorate neuropathy or increase the risk of bleeding.

Patients were randomly assigned at a 1:1 ratio by simple randomization using a free online random sample allocator (available at: https://www.graphpad.com/quickcalcs/randomize1/). The investigator assigned patients to either the pentoxifylline group (30 patients) who received 12 weeks of paclitaxel (80 mg/m^2) and oral pentoxifylline

400 mg BID during chemotherapy period or the placebo group (30 patients) who received the same regimen of paclitaxel in addition to the oral placebo BID during chemotherapy period. Patients started receiving either pentoxifylline or placebo on the first day of paclitaxel treatment.

Methodology

At baseline, all patients were subjected to physical and neurological examinations to assess the presence of pre-existing neuropathy. Demographic data and clinical characteristics were collected from patients' medical records and interviews. The study primary objective was the incidence and severity of PIPN. The secondary outcomes included the time to develop grade 2 or 3 (TTG2/3) PIPN, the incidence of dose delay (DD), dose reduction (DR) or drug discontinuation (DC), QOL, serum biomarkers and safety. Patients were educated about symptoms of sensory PIPN and were asked to report any symptoms. The investigator evaluated patients weekly, and the presence of neuropathic symptoms indicating PIPN was graded using the common terminology criteria for adverse events (CTCAE) version 4, in which higher grades indicate more severe neuropathy [27]. The paclitaxel dose was reduced to 65 mg/m^2 in subsequent cycles if the patient developed grade 3 (severe) neuropathy. Then, it was discontinued in patients with persistent grade 3 neuropathy despite DR (as per institutional protocol). Moreover, the TTG2/3 PIPN was recorded for each patient as a time in days from the first day of paclitaxel treatment until the development of ≥ grade 2 PIPN.

Patient QOL was evaluated at baseline, and weeks 4, 8, and 12 using the validated Arabic version of the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-NTX) subscale version 4, and the Arabic license was granted from FACIT.org. The questionnaire is composed of 11 items evaluating sensory, motor, and auditory impairments. Patients had to score each item on a 5-point scale (0 = not at all) to (4 = very much) depending on symptoms during the past 7 days. The final score is calculated according to FACIT.org scoring guideline. The total score ranges from 0 to 44 with higher scores indicating better QOL [28]. At week 12, a percent reduction in baseline QOL ≥ 10% was considered the minimal clinically important difference (MCID) [29].

Blood samples were drawn from patients at baseline and week 12 to measure the serum levels of TNF-α and MDA using commercial enzyme-linked immunosorbent assay (ELISA) and colorimetric kits, respectively. To assess the safety and tolerability of pentoxifylline, patients were informed that any observed adverse effects should be reported. Adverse effects were graded using CTCAE version 4.

Patient compliance was evaluated by the investigator every other week through pill counts. The full duration of follow-up per patient was 12 weeks.

Statistical methodology

The statistical analysis was carried out with IBM SPSS® Statistics version 26 (IBM Corp., Armonk, NY, USA). Categorical data are presented as percentages and frequencies and were compared using Chi-square test and Fisher's exact test. All numeric data were tested for normality using the Kolmogorov–Smirnov test and the Shapiro-Walk test. Normally distributed data are presented as the mean ± standard deviation (SD), while nonnormally distributed data are presented as the median and range. Comparisons between groups were performed using Student's t-test for parametric data and the Mann–Whitney test for nonparametric data. Comparisons within groups at 2 time points were performed using paired t-test for parametric data and Wilcoxon signed-rank tests for nonparametric data. Comparisons within the groups at the 4 time points were performed using Friedman's test followed by post hoc analysis if the comparisons were significant. The percent change was calculated as follows: [(time point data − baseline data)/baseline data)] *100. Analysis of TTG2/3 PIPN was performed using the Kaplan–Meier method, and p values were generated using the log-rank test. For multiple pairwise comparisons, adjusted p values were calculated. All p values were two-sided, and a p value < 0.05 was considered to indicate statistical significance.

Sample size determination

There was no previous study evaluating the effect of pentoxifylline on PIPN. Therefore, the sample size was calculated based on the effect of pentoxifylline on TNF-α. According to a previous study by Fernandes et al., the mean difference in TNF-α in the pentoxifylline group was 4.5 ± 4.4, whereas it was 1.16 ± 0.7 in the placebo group [30]. Setting the type-1 (α) error at 0.05 and the power (1-β) at 0.9, a minimal sample size of 21 patients per group was needed. To accommodate the dropout rate, 20% was added with a minimal sample size of 25 patients per group. The sample size was calculated by the G power program using the statistical test: Wilcoxon–Mann–Whitney test (two groups) [31].

Results

From November 2021 to June 2023, 229 patients were assessed for eligibility. Approximately 60 patients were recruited in the study, and the final analysis included 55 patients. Dropout was due to patient refusal to continue

(n = 1), loss to follow-up (n = 1), poor compliance (n = 1), and a diagnosis of systemic lupus (n = 1) and rheumatoid arthritis (n = 1). The study consort diagram is represented in Fig. 1.

Baseline evaluation

Baseline demographic data and clinical characteristics are presented in Table 1. The mean ± SD of all study participants' age, weight, height, and body surface area (BSA) were 50.42 ± 12.92, 78.96 ± 18.98, 157.71 ± 6.62 and 1.85 ± 0.23, respectively. Approximately 56% of patients were premenopausal, and 78.2% were literate. Approximately 75% of the patients had a performance status of 1. Eighty-five percent of the patients were hormone positive, and 40% were human epidermal growth factor receptor-2 (HER-2) positive. The most prevalent comorbid diseases were hypertension (16.1%), osteoporosis (14.3%), and hypothyroidism (10.9%). Most patients with right-sided BC accounted for 56.4% of the participants. Moreover, the major tumor histopathological type in the study was invasive ductal carcinoma (IDC) (90.7%), with approximately 39% of the participants having stage 3 disease. Approximately 35% of the patients underwent surgical intervention before chemotherapy, 20% of whom underwent modified radical mastectomy (MRM). Moreover, 96.4% of the patients received 10–12 doses of paclitaxel, with a median cumulative dose of 1686 mg. There was no significant difference between the two groups regarding demographic data and clinical characteristics.

Assessment of PIPN

Incidence and severity of PIPN

The overall incidence of any grade of PIPN was 92.7%, of which 58% of patients developed moderate to severe PIPN (grade 2/3). No patients in either group developed grade 4 PIPN. Approximately 15% of patients in the pentoxifylline group did not develop any grade of PIPN. There was a nonsignificant difference between the groups regarding the incidence and severity of PIPN, as shown in Table 2.

The overall incidence of DD in the two groups was 14.5%, with no significant difference between the groups (p value = 0.469). In the pentoxifylline group, five patients (18.5%) were dose-delayed due to the development of infection (n = 1), fever (n = 1), severe fatigue (n = 1), neutropenia (n = 1), and anemia (n = 1). In the placebo group, three patients (10.7%) were delayed due to the development of infection (n = 2) and neutropenia (n = 1).

The overall percentage of DR or DC was 9.1%. In the pentoxifylline group, only one patient was referred for DR at week 10 due to development of repeated

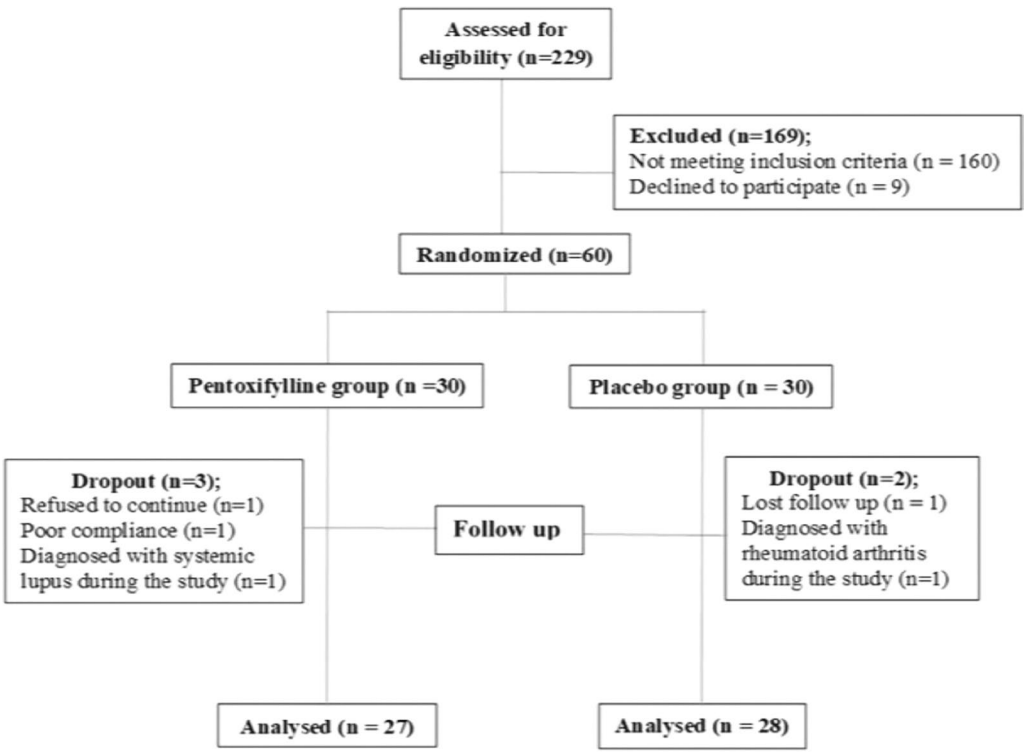

Fig. 1 The study consort diagram

Table 1 Baseline demographic data and clinical characteristics

Variable		Pentoxifylline group n = 27	Placebo group n = 28	*p* value
Age (year): mean ± SD		51.81 ± 12.95	49.07 ± 12.99	**0.436**[a]
Weight (Kg): mean ± SD		79.15 ± 16.13	78.79 ± 21.682	**0.944**[a]
Height (cm): mean ± SD		157.3 ± 6.83	158.11 ± 6.5	**0.654**[a]
Education status n (%)	Literate	24 (88.9)	19 (67.9)	**0.059**[b]
	Illiterate	3 (11.1)	9 (32.1)	
BSA (m^2): mean ± SD		1.85 ± 0.21	1.84 ± 0.26	**0.92**[a]
Menopausal status n (%)	Pre-menopausal	14 (51.9)	17 (60.7)	**0.508**[b]
	Post-menopausal	13 (48.1)	11 (39.3)	
ECOG n (%)	0	4 (14.8)	2 (7.1)	**0.438**[c]
	1	18 (66.7)	23 (82.1)	
	2	5 (18.5)	3 (10.7)	
Comorbidities n (%)	Hypertension	6 (22.2)	3 (10.7)	**0.295**[c]
	Hypothyroidism	2 (7.4)	4 (14.3)	**0.669**[c]
	Osteoporosis	5 (18.5)	3 (10.7)	**0.469**[c]
	Asthma	3 (11.1)	1 (3.6)	**0.352**[c]
Hormonal status n (%)	Positive	24 (88.9)	23 (82.1)	**0.705**[c]
	Negative	3 (11.1)	5 (17.9)	
HER-2 status n (%)	Positive	11 (40.7)	11 (39.3)	**0.912**[b]
	Negative	16 (59.3)	17 (60.7)	
Side of cancer n (%)	Right	13 (48.1)	18 (64.3)	**0.228**[b]
	Left	14 (51.9)	10 (35.7)	
Histopathological type: n (%)	IDC	24 (92.3)	25 (89.3)	**1.000**[c]
	ILC	0 (0)	1 (3.6)	
	Others	2 (7.7)	2 (7.1)	
Stage of cancer n (%)	I	8 (30.8)	10 (35.7)	**0.056**[b]
	II	4 (15.4)	11 (39.3)	
	III	14 (53.8)	7 (25)	
Type of surgery n (%)	WLE	5 (18.5)	3 (10.7)	**0.527**[c]
	MRM	4 (14.8)	7 (25)	
Protocol n (%)	Adjuvant	9 (33.3)	10 (35.7)	**0.853**[b]
	Neoadjuvant	18 (66.7)	18 (64.3)	
No. of doses n (%)	6–9 doses	1 (3.7)	1 (3.6)	**1.000**[c]
	10–12 doses	26 (96.3)	27 (96.4)	
Cumulative dose (mg) median (Range)		1699 (1140–1920)	1680 (1015–2016)	**0.315**[d]

BSA body surface area, *ECOG* Eastern Cooperative Oncology Group, *HER-2* human epidermal growth factor receptor-2, *IDC* invasive ductal carcinoma, *ILC* invasive lobular carcinoma, *MRM* modified radical mastectomy, *n* number of patients, *SD* standard deviation, *WLE* wide local excision

p value < 0.05 is considered significant

[a] Student's t-test, [b] Pearson Chi-Square test, [c] Fischer exact test, [d] Mann–Whitney test

paclitaxel-induced grade 2 neutropenia. In addition, one patient in the pentoxifylline group discontinued paclitaxel at week 10 due to persistent grade 3 PIPN. In the placebo group, two patients were referred with DR at weeks 7 and 10 due to the development of grade 3 PIPN. Additionally, one patient was referred for DR due to persistent paclitaxel-induced grade 2 diarrhea despite supportive treatment. However, the difference between the two groups was not significant regarding DR/DC (*p* value = 1.000).

Time to develop Grade 2 or 3 peripheral neuropathy

The median TTG2/3 neuropathy was not reached in the pentoxifylline group compared to 77 days with a 95% confidence interval (95% CI) of 70.91–83.07 in the placebo group. Paclitaxel delay due to toxicity was not

Table 2 Incidence and severity of PIPN

Variable		Pentoxifylline group n = 27	Placebo group n = 28	*p* value
Severity of neuropathy n (%)	G0 (not developed)	4 (14.8)	0 (0)	**0.144**[a]
	G1 (mild)	9 (33.3)	10 (35.7)	
	G2 (moderate)	13 (48.1)	14 (50)	
	G3 (severe)	1 (3.7)	4 (14.3)	

n number of patients, *PIPN* paclitaxel-induced peripheral neuropathy

p value < 0.05 is considered significant

[a] Fischer exact test

considered in patients with TTG2/3 neuropathy. A non-significant difference was found between the two groups regarding TTG2/3 neuropathy (p value = 0.397), as presented in Fig. 2.

Quality of life

The analysis of QOL was conducted on 53 patients. One patient in the pentoxifylline group and one patient in the placebo group were excluded due to DC and death, respectively. The median baseline QOL was significantly higher in the placebo group than in the pentoxifylline group (p value = 0.032). Additionally, within-group comparisons at different time points revealed a significant decrease in QOL in the two groups. The percent change was used for comparison to account for the baseline difference and to estimate the severity of the score reduction. The mean percent reduction ranged from − 3.36 to − 15.15% in the pentoxifylline group compared to − 11.7% to − 28.08% in the placebo group. The FACT/GOG-NTX score was significantly lower in the placebo group than in the pentoxifylline group (weeks 4, 8, and 12, p values = 0.028, 0.003 and 0.018, respectively). Moreover, the percentage of patients with a reduction in FACT/GOG-NTX score beyond the MCID was significantly higher in the placebo group (81.5%) than in the pentoxifylline group (53.8%), indicating better QOL in the pentoxifylline group, as summarized in Table 3.

Serum biomarkers

The final analysis of the serum biomarkers was conducted on 50 patients. Blood sample was not withdrawn from one patient in the pentoxifylline group who discontinued paclitaxel at week 10 before final sample withdrawal and four patients in the placebo group due to death (n = 1), and refusal of sample withdrawal (n = 3). At baseline, the MDA concentration was significantly greater in the

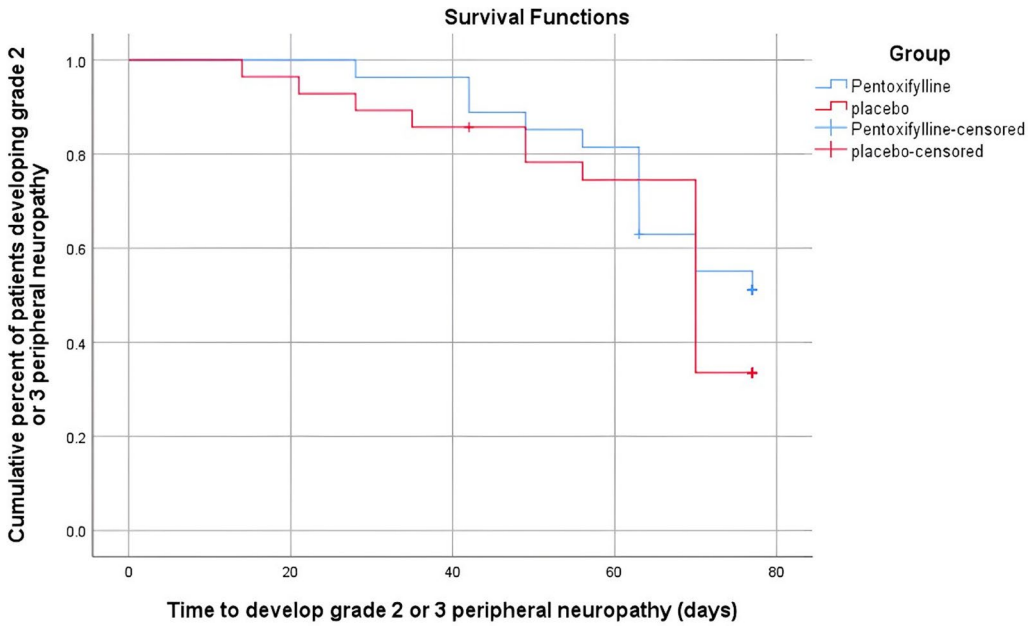

Fig. 2 Kaplan–Meier curve describing the time to develop grade 2 or 3 peripheral neuropathy

Table 3 Quality of life assessment using FACT/GOG-NTX subscale at different time points and percent change from baseline

Variable	Pentoxifylline group n = 26	Placebo group n = 27	*p* value
Baseline: median (range)	40.5 (27–44)	44 (33–44)	**0.032**[a*]
After 4 weeks: median (range)	40 (27–44)	38 (21–44)	**0.576**[a]
After 8 weeks: median (range)	36 (22–44)	31.9 (18–44)	**0.032**[a*]
After 12 weeks: median (range)	34.5 (16–44)	28 (14–42)	**0.073**[a]
Corrected *p* value	**0.000**[b 1*]	**0.000**[b 2*]	
% Change in QOL between baseline & week 4: mean ± SD	[−3.36] ± 12.65	[−11.7] ± 14.73	**0.028**[c*]
% Change in QOL between baseline & week 8: mean ± SD	[−12.64] ± 13.95	[−25.55] ± 16.43	**0.003**[c*]
% Change in QOL between baseline & week 12: mean ± SD	[−15.15] ± 19.97	[−28.08] ± 18.57	**0.018**[c*]
MCID[†] at week-12 n (%)	14 (53.8)	22 (81.5)	**0.031**[d*]

FACT/GOG-NTX Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity, *MCID* minimal clinically important difference, *n* number of patients, *QOL* quality of life, *SD* standard deviation

[†] MCID: indicates 10% or more reduction (worsening) in QOL

*p value < 0.05 indicates significance

[a] Mann–Whitney test, [b] Friedman's test, [c] Student's t test, [d] Pearson Chi-square test

[1] post hoc analysis showed a significant change in QOL between baseline & both of weeks 8 and 12, and between week 4 & week 12 in the pentoxifylline group

[2] post hoc analysis showed a significant change in QOL between baseline and weeks 8 &12 and between week 4 and both of weeks 8 & 12 in the placebo group

placebo group than in the pentoxifylline group, while the TNF-α concentration was not significantly different between the groups. After 12 weeks, TNF-α and MDA were significantly lower in both groups, as shown in Table 4. The percent change was used to compare the reduction in serum biomarkers between the two groups, and the comparison revealed a nonsignificant difference.

Evaluation of the safety and tolerability of pentoxifylline

The reported grade 3 toxicities in the pentoxifylline and placebo groups were neutropenia (7.4% vs 11.1%), anemia (7.4% in each group), headache (3.7% vs 3.8%), myalgia (7.4% vs 19.2%) and bone ache (11.1% vs 25%), respectively. Both groups were comparable regarding their safety profiles, in which reported toxicities were attributed to paclitaxel. Moreover, no patient developed grade 4 toxicity or DC due to pentoxifylline adverse effects. The toxicity profiles of both groups are presented in Supplement (1).

Discussion

Drug repurposing is a drug discovery strategy that evaluates the effectiveness of an already licensed drug for a new therapeutic indication. The drug repurposing process can bypass certain preclinical and clinical trials due to the existence of detailed information about drug pharmacokinetics, pharmacodynamics and safety profiles. Therefore, this strategy enables rapid approval of effective

Table 4 Baseline and post-treatment serum levels of biomarkers

Variable	Pentoxifylline group n = 26	Placebo group n = 24	*p* value
Baseline TNF-α Median (range)	370.22 (262.6–454.39)	376.8 (257–436.52)	**0.89**[a]
Post-treatment TNF-α: median (range)	238.8 (202.88–296.6)	232.54 (143.7–312.33)	**0.377**[a]
p value	**0.000**[*b]	**0.000**[*b]	
Baseline MDA Median (range)	4.26 (3.05–5.44)	4.88 (3.51–6.15)	**0.001**[a*]
Post-treatment MDA: median (range)	3.06 (1.98–4.2)	3.28 (1.72–4.12)	**0.915**[a]
p value	**0.000**[*b]	**0.000**[*b]	
% Change in TNF-α: median (range)	−36.27 ([−47.94]–[− 10.87])	−42.93 ([−65.07]–21.54)	**0.156**[a]
% Change in MDA: median (range)	−28.57 ([−50.62]–19.67)	−34.27 ([−63.78]–12.19)	**0.120**[a]

MDA malondialdehyde, *n* number of patients, *SD* standard deviation, *TNF-α* tumor necrosis factor α

*p value < 0.05 is considered significant

[a] Mann–Whitney test, [b] Wilcoxon Signed Rank test

medications in a safer and lower-cost manner. Moreover, drug repurposing is highly beneficial in cases of epidemic or difficult-to-treat diseases such as cancer, where saving time is crucial [32]. Pentoxifylline, which was initially approved for intermittent claudication, has shown potential neuroprotective effects in several conditions in previous studies [22, 23, 26].

To our knowledge, this is the first RCT to evaluate the effect of pentoxifylline on PIPN. The dose of pentoxifylline was selected based on pentoxifylline monographs and RCTs that demonstrated the efficacy and safety of oral pentoxifylline 400 mg BID for ameliorating diabetic polyneuropathy [26].

In a previous preclinical study, pentoxifylline significantly reduced the severity and delayed the onset of hyperalgesia in a PIPN rat model [23]. In the present study, the incidence of PIPN was not significantly different between the pentoxifylline group and the placebo group. The same was observed for TTG2/3 PIPN. However, the median TTG2/3 PIPN was not reached in the pentoxifylline group compared to 77 days in the placebo group, which means that pentoxifylline may delay the development of neuropathy. This nonsignificant difference between groups might be due to the majority of reported toxicities being mild to moderate with only 9.1% of the participants suffering from severe PIPN. In contrast, a previous RCT that evaluated the use of cilostazol, another PDEi similar to pentoxifylline, for the prevention of PIPN reported that cilostazol significantly decreased the incidence of grade 2/3 PIPN to 40% compared to 86.7% in the placebo group [16]. The difference in the results compared to the current work might be attributed to the use of different paclitaxel regimens and the lower cumulative dose of paclitaxel in the cilostazol study. However, cilostazol failed to reduce the overall incidence of any grade of PIPN in which all participants in both groups suffered from PIPN [16]. In the present study, 15% of patients in the pentoxifylline group did not develop PIPN suggesting that pentoxifylline might be successful in preventing PIPN. Hence, the use of a higher dose of pentoxifylline might be needed to determine the potential benefits of pentoxifylline on PIPN [24].

Chemotherapy-induced peripheral neuropathy (CIPN) is considered a disabling adverse effect that significantly impairs overall QOL in cancer survivors and increases the cost of treatment. By increasing survival, impaired QOL may persist for a long time with consequent loss of functioning and psychological stress. Therefore, the assessment of QOL has become a crucial outcome among cancer survivors, particularly in RCTs [33].

It is recommended that clinical and patient-reported outcome-based measures be combined in clinical trials to achieve a comprehensive assessment of CIPN severity and QOL [34, 35]. This is attributed to the fact that CTCAE, despite being the most widely used clinical tool to assess CIPN, has significant interobserver variability [36]. In addition, objective testing of CIPN using electromyography is expensive, painful and particularly assesses motor impairment, which is rare except in severe CIPN [37]. Additionally, electromyography is not applicable in most institutions in clinical practice and in nonfunded RCTs. Therefore, in the current study, patients were assessed with the FACT/GOG-NTX subscale in addition to the CTCAE to capture mild changes in different aspects, including sensory symptoms, auditory function, motor function, myalgia, fatigue, and pain. These aspects may be graded the same by the CTCAE. The FACT/GOG-NTX is a comprehensive, validated, and sensitive tool that was developed to assess the severity and impact of neurotoxicity on patients' QOL [28]. In addition, it is a self-reported questionnaire that is significantly correlated with the objective assessment of CIPN [38].

In the current study, patients in the placebo group had significantly better QOL at baseline than did those in the pentoxifylline group. Moreover, both groups showed a significant decrease in QOL, which was associated with the development of PIPN. Hence, the percent change was calculated to compensate for the baseline difference and to evaluate the magnitude of the effect in each group. The FACT/GOG-NTX score showed a less worsening in QOL in the pentoxifylline group than in the placebo group. In addition, the percentage of patients who developed MCID in terms of QOL was significantly lower in the pentoxifylline group than in the placebo group, which might reflect the ability of pentoxifylline to significantly prevent the detrimental effect of PIPN on QOL. However, these results were not in concordance with the CTCAE results. This might be attributed to the fact that the FACT/GOG-NTX assesses several aspects of peripheral neuropathy on a wider scale than the CTCAE, which classifies patients into only 4 subcategories. Moreover, CTCAE combines symptoms, disability, and QOL in a single grade [39]. Controversially, FACT/GOG-NTX can discriminate between patients with the same grade of PIPN with different clinical presentations [27, 28]. This might reflect the potential benefits of pentoxifylline in ameliorating the consequences of PIPN on QOL. Similarly, in the cilostazol study, QOL was significantly worse in the placebo group at the end of the study compared to the cilostazol group [16].

The neuroinflammatory pathway is one of the major pathophysiologic mechanisms leading to PIPN. Several inflammatory biomarkers, predominantly TNF-α, are significantly associated with the severity of PIPN [12, 40]. The inhibition of TNF-α was significantly associated

with the suppression of necroptosis and the alleviation of neuropathic symptoms [13]. Furthermore, mitochondrial damage and TNF-α production induce ROS release, leading to further mitochondrial damage, biomolecule destruction, and inflammatory pain. Additionally, ROS increase the production of MDA, which induces oxidative damage to the myelin sheath, contributing significantly to the pathogenesis of PIPN [41].

In this study, after 12 weeks of paclitaxel, the serum TNF-α and MDA levels were significantly reduced in both groups, but the differences between the groups were not significant. The reduction in the levels of TNF-α and MDA might be attributed to the fact that most patients included in the study received neoadjuvant paclitaxel, and the decrease in TNF-α and MDA reflects a reduction in tumor size and downstaging rather than an improvement in PIPN. This postulation was confirmed in several RCTs, where improvements in cancer-related outcomes in neoadjuvant patients were significantly correlated with reductions in inflammatory cytokines and ROS, particularly TNF-α and MDA, respectively [42, 43]. A preclinical trial revealed a dose-dependent reduction in TNF-α when pentoxifylline was co-administered with paclitaxel. However, this effect was not found in the low-dose group, which could explain the change in serum biomarkers in the current study as a result of using a low dose of pentoxifylline [24].

Previous RCTs revealed that pentoxifylline was generally safe and tolerable with mild adverse effects, including gastrointestinal upset, headache, dizziness, hot flushes, hypotension, and light-headedness [44, 45]. In this study, the most common toxicities in the pentoxifylline group were stomach upset, anemia, and neutropenia. However, these toxicities were comparable between the two groups without significant differences. Moreover, most of the reported toxicities revealed that pentoxifylline did not alter the paclitaxel toxicity profile and that pentoxifylline was safe and tolerable at a dose of 400 mg BID.

This study was limited by its small sample size and low dose of pentoxifylline. Therefore, further studies with larger sample sizes and higher doses of pentoxifylline are needed to evaluate the potential effect of pentoxifylline on PIPN.

Conclusion

Pentoxifylline 400 mg BID was safe and tolerable and significantly improved PIPN-related QOL parameters in BC patients receiving adjuvant or neoadjuvant weekly paclitaxel without significantly affecting the incidence of PIPN.

Abbreviations

BC	Breast cancer
BSA	Body surface area
95% CI	95% Confidence interval
CIPN	Chemotherapy induced peripheral neuropathy
CTCAE	Common terminology criteria for adverse events
DC	Drug discontinuation
DD	Dose delay
DR	Dose reduction
ECOG	Eastern Cooperative Oncology Group
ELISA	Enzyme-linked immunosorbent assay
FACT/GOG-NTX	Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity
HER-2	Human epidermal growth factor receptor 2
IDC	Invasive ductal carcinoma
ILC	Invasive lobular carcinoma
MCID	Minimal clinically important difference.
MDA	Malondialdehyde
MRM	Modified radical mastectomy
PIPN	Paclitaxel induced peripheral neuropathy
QOL	Quality of life
RCT	Randomized clinical trial
ROS	Reactive oxygen species
SD	Standard deviation
TNF-α	Tumour necrosis factor-α
TTG2/3	Time to develop grade 2 or 3
WLE	Wide local excision
PDEi	Phosphodiesterase inhibitor
BID	Twice daily

Supplementary Information

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Additional file 1.

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Author contributions

Sondos S. Saleh, and May A. Shawki were involved in the conception of the study. All authors (Sondos S. Saleh, Diaa Eldin Moussa, Nagwa A. Sabri, May A. Shawki) contributed to the design of the study. Sondos S. Saleh was responsible for research conduction. Sondos S. Saleh, and May A. Shawki contributed to the data analysis and manuscript drafting and writing. All authors contributed to the manuscript editing and critical revision. All of them agreed to the final version of the submitted manuscript and were accountable for all aspects of the current work.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval and consent to participate

The study protocol was revised and approved by the Research Ethics Committee of the Faculty of Pharmacy, Ain Shams University (Approval no. RHDIRB2020110301#44) and the Faculty of Medicine, Ain Shams University (Approval no. FMASU UNIV 3/22). The study was carried out according to the Declaration of Helsinki (2013). Written informed consent was obtained from the patients prior to participation in the study.

Consent for publication

Not applicable.

Competing interests
The authors declare that they have no competing interests.

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