

# A Randomized, Double-Blind, Placebo-Controlled Trial of Omeprazole as A Promising Drug for Protection Against Chemo Induced Neuropathy.

Aya M. Sadek<sup>1\*</sup>, Sahar K. Hegazy<sup>1</sup>, Zyad M. Hamada<sup>3</sup>, Khaled M. Abouelkhair<sup>2</sup>

<sup>1</sup>Clinical Pharmacy Department, Faculty of Pharmacy, Tanta University, El-Gharbia Government, El-Guiesh Street, Tanta 31527, Egypt

<sup>2</sup>Clinical Oncology and Nuclear Medicine Department, Faculty of Medicine, Mansoura University, El-Gomhoria Street, Dakahlia 35516, Egypt

<sup>3</sup>Intern-Faculty of Medicine, Mansoura University, El-Gomhoria Street, Dakahlia 35516, Egypt

## ABSTRACT

**Background:** Patients with gastrointestinal cancers receiving oxaliplatin-fluorouracil chemotherapy protocols are exposed to sensory neuropathy. This study aimed to investigate whether omeprazole can protect from neuropathy in those patients. **Methods:** This prospective, randomized, double-blinded, placebo-controlled trial included 46 cases with gastrointestinal cancers randomly classified into two equal groups: the control group involving patients received 12 cycles of [Fluorouracil + Leucovorin + Oxaliplatin (FOLFOX4)] with placebo capsules, and the omeprazole (Omeprazole) group involving patients received 12 cycles of FOLFOX4 plus omeprazole 40 mg orally TID for five days to start two days before each chemotherapy cycle for 6 months. Malonaldehyde, organic cation transporter 2 (OCT2), and neurotensin (NT) were measured at baseline and after three months of treatment initiation. The clinical assessment of neurotoxicity was performed at baseline, 2 weeks after the first cycle, after three months, and at the end of treatment.

**Results:** A significant decrease in the frequency of patients with grade II neuropathy in the omeprazole group compared to the control group after three months of intervention ( $p < 0.001$ ). There was a significant decline in NT and OCT2 levels in the omeprazole group ( $p = 0.004$  and  $p = 0.005$ ). The OME group had a lower percentage of individuals with chronic neuropathy (73.91%) in comparison with the control (95.65%), but with no statistically significant difference, however, it has been observed that the appearance of chronic neuropathy tends to be late in the OME group at the 8th cycles.

**Conclusion:** Omeprazole may serve as a promising candidate for drug repositioning to protect against oxaliplatin-induced neuropathy, owing to its safety and efficacy in decreasing oxaliplatin neurotoxicity.

**Keywords:** Oxaliplatin, Peripheral Neuropathy, Omeprazole, Organic Cation Transporter 2, Neurotensin.

**How to cite this article:** Sadek AM, Hegazy SK, Hamada ZM, Abouelkhair KM., A Randomized, Double-Blind, Placebo-Controlled Trial of Omeprazole as A Promising Drug for Protection Against Chemo Induced Neuropathy. *Int J Drug Deliv Technol.* 2026;16(1s): 862-873; DOI: 10.25258/ijddt.16. 862-873

**Source of support:** Nil.

**Conflict of interest:** None

## INTRODUCTION

Oxaliplatin (L-OHP), a platinum-based agent, is the most eminent chemotherapeutic agent that is used for the treatment of many types of gastrointestinal cancer, such as colorectal cancer (CRC), pancreatic cancer, and gastric cancer<sup>[1]</sup>. With the wide use of L-OHP, there are many side effects that appear. Oxaliplatin-induced peripheral neuropathy (OIPN) is the most adverse side effect. It is the most dose-limiting toxicity of L-OHP<sup>[2]</sup>.

Acute neurotoxicity often occurs during or shortly after infusion. The symptoms manifest as cold-induced distal paresthesia and/or dysesthesia, such as tingling, neuropathic pain, and numbness, which is usually mild and disappears in 48 to 72 hrs in most patients. Chronic cumulative peripheral neuropathy can also develop from prolonged use of L-OHP, causing deep sensory loss, ataxia, and functional impairment<sup>[3]</sup>.

In clinical practice, several drugs are used for chemo-induced peripheral neuropathy (CIPN). Nevertheless, most of these available drugs were shown to have poor efficacy<sup>[4]</sup>.

Several studies aimed at repositioning an existing approved drug for the management of CIPN. This approach saves time and cost due to the previous knowledge of the pharmacokinetics and safety of these drugs. In this regard, several studies were conducted to repurpose proton pump inhibitors (PPIs), including omeprazole (OME), against CIPN. OME, a proton pump inhibitor (PPI), is used for the treatment of gastric or duodenal ulcers. Reports show that OME has an antioxidant effect, so it may help in protection against OIPN, which is induced by excessive oxidative stress<sup>[5]</sup>.

In 2022, the suppression effect of OME against peripheral neuropathy was investigated by Mine et al.<sup>[6]</sup> who reported that the repeated administration of OME suppresses OIPN

\*Author for Correspondence: PG\_165466@pharm.tanta.edu.eg.

without affecting the antitumor effect of L-OHP in rodent model and clinical data due to its antioxidant effect.

Moreover, OCT2, which is a key transporter of platinum drug uptake and cytotoxicity, contributes to platinum accumulation in the kidneys, inner ear, and peripheral nervous system (PNS), leading to nephrotoxicity, ototoxicity, and peripheral neuropathy. Also, it has been reported that OCT2 is expressed in 20% of dorsal root ganglion (DRG) neurons [5]. Additionally, it was found that cellular uptake of L-OHP was increased by 16- to 35-fold in cells overexpressing mouse OCT2 or human OCT2, and this process was associated with increased L-OHP induced cytotoxicity [7].

OME has been reported to decrease the expression of OCT2 in the kidney. So, OME may similarly decrease OCT2-mediated uptake into DRG and protect against development of neuropathy and subsequent neuronal cell body damage [8].

In 2023, according to the retrospective investigation by Kobayashi et al., [9] patients taking PPIs had significantly lower frequencies of CIPN (grade  $\geq 2$ ) and L-OHP termination than patients not taking PPIs. Additionally, the beginning time of grade  $\geq 2$  CIPN was considerably longer in PPI-using patients, but this did not impact the therapeutic efficacy of L-OHP.

Furthermore, a recent in vitro study in 2025 by Mori et al. [10], showed that the repeated administration of PPIs prevented OIPN as a class effect. Additionally, a real-world database analysis was conducted in 2025 and suggested that OME may have a suppressive effect on OIPN by inhibiting platinum influx into the DRG and exerting a potential neuroprotective effect [11].

Another retrospective cohort study used data from 1015 patients who started treatment with L-OHP and showed that the number of patients who discontinued L-OHP due to OIPN was significantly lower in the PPI group ( $p = 0.0264$ ) [12].

As far as the authors are aware, no prior randomized clinical trials have examined the protective role of OME against OIPN in gastrointestinal cancer patients. OME may therefore have a protective effect against OIPN, according to our assumption. This innovative clinical trial was carried out to examine the protective impact of OME against OIPN in patients receiving targeted therapy and conventional chemotherapy to test our hypothesis.

## PATIENTS AND METHODS

### PATIENTS

A total of 71 patients admitted to the Clinical Oncology and Nuclear Medicine department at Mansoura University Hospital in Egypt between January 2023 and September 2024 with colorectal cancer, gastric cancer, or pancreatic cancer underwent eligibility screening. After screening, the ultimate investigation involved 46 participants with gastrointestinal cancer who fulfilled the selection criteria and were randomly allocated into two groups. All 46 patients underwent analysis both at baseline, two weeks after the 1<sup>st</sup> cycle, after 3 months, and at the end of treatment. In the control group, 2 cases dropped out at the 6<sup>th</sup> and 8<sup>th</sup> sessions, and in the OME group, 1 case dropped

out at the 6<sup>th</sup> session due to cancer progressing, so the chemotherapy protocol had been changed.

**The inclusion criteria** involved patients recently diagnosed with CRC, pancreatic or gastric cancer with age between 18 and 65 years according to Response Evaluation Criteria in Solid Tumor 1.1 (RECIST 1.1) [13]. Those patients were included if they didn't receive chemotherapy before and were scheduled to receive modified FOLFOX-4 for 12 cycles. All patients had a performance status of 0-2 according to the Eastern Cooperative Oncology Group (ECOG) score [14].

**The exclusion criteria** involved Pregnant/breastfeeding women, smokers, patients with status related to oxidative stress, patients with diabetes, osteoporosis, fractures, any autoimmune disease, and patients with abnormal kidney function ( $S.cr > 1.5$  mg/dl or  $Cr.cl < 45$  ml/min) and liver diseases (bilirubin  $> 1.5$  mg/dl / ALT, AST  $> 2-4$  ULN). In addition, patients with pre-existing peripheral neuropathy due to other causes (e.g., brain tumor, seizures, or any other neuropathic disorder); patients taking neuroprotective medications (phenytoin, tricyclic antidepressants, etc.) and drugs including Marivan, methotrexate, ketoconazole, and others that can interfere with omeprazole's metabolism were out of the study. CRC patients receiving protocols containing capecitabine and previously introduced to neurotoxic chemotherapy for at least 6 months beforehand the study was also not included.

### Study design

This was a prospective, randomized, double-blinded, placebo-controlled parallel study. Patients were recruited from the Clinical Oncology and Nuclear Medicine department at Mansoura University Hospital in Egypt between January 2023 and September 2024. The study was registered on clinicaltrials.gov (ID: NCT05680870) on 11 Jan 2023. The study was conducted on 46 patients with gastrointestinal cancers who received 12 cycles of FOLFOX4 for 6 months. The dosing regimen and dose intensity of L-OHP were displayed in **Table 1**.

**Table 1: Dose intensity of oxaliplatin and dosing regimen of FOLFOX4**

Dose intensity of oxaliplatin (cumulative dose) after 12 cycles	Dosing regimen
Control group 1909 ± 203.33 Omeprazole group 1860.0 ± 197.60	Oxaliplatin 85mg/m <sup>2</sup> by IV within 120 min (day1). Leucovorin: 200 mg/m <sup>2</sup> by IV within 120 min on (day 1, 2). Fluorouracil: 400 mg/m <sup>2</sup> IV Polus, then 600 mg/m <sup>2</sup> continuous IV over 22 h on (day 1, 2);

Data are presented as mean ± SD, folfox4: fluorouracil + leucovorin + oxaliplatin

### Randomization and blindness:

The allocation sequence was generated using a computer-generated random number list with an allocation ratio of 1:1, as shown in **Figure 1**. Allocation concealment was

ensured using sequentially numbered, opaque, sealed envelopes prepared by an independent researcher. Out of 71 patients assessed for eligibility, 56 were randomized, with a total of 10 patients dropping out during the follow-up period due to loss of follow up, changing protocol, or chemotoxicity. The allocation concealment of the 46 patients who were randomized by a neutral researcher using sequentially numbered opaque sealed envelope methods using computer software with assignment codes for each available allocation to receive either OME (Omeprazole; SEDICO pharmaceutical company, Egypt) 40 mg orally TID for 5 days each cycle to start two days before the cycle plus 12 cycles of FOLFOX4 for 6 months (OME group; n=23) or placebo capsules in the same regimen of OME plus 12 cycles of FOLFOX4 for 6 months (control group; n=23). The investigator was provided with a randomization code for each available allocation. This randomized trial was double-blinded, in which both participants and researchers didn't know which participant was in which group, and participants didn't know if they were getting the real drug or a placebo. Also, the outcome assessor and statistician were blinded. The blindness was maintained by ensuring that both OME and placebo capsules had the same physical properties. All patients were instructed to take treatment half an hour before meals to optimize its bioavailability. OME, a proton pump inhibitor, was used in the trade name Omeprazole 40mg capsule. The chemical structure is 5-methoxy-2-(4-methoxy-3,5-dimethyl-2-pyridinyl) methylsulfinyl)-1H-benzimidazole. The choice of Omeprazole was based on its availability in the market, its affordable cost, and its capsule formulation, which enhances absorption in the case of high divided doses. Placebo capsules were prepared to match the physical properties of OME capsules with the absence of the active ingredient.

OME has not been examined previously to protect from oxaliplatin-induced neuropathy in clinical settings. Thus, we couldn't rely on the formerly stated standard effective neuroprotective dose, but the rat model study in 2022 by Mine et al. [6] showed that increasing the dose of OME increases the neuroprotection of rats. Moreover, previous studies found that patients with Zollinger Ellison syndrome can tolerate OME up to 180 mg/day [15]. So, we hypothesized that the dose of OME could be 40 mg TID for 5 days with each cycle of FOLFOX4 for 6 months.



CONSORT 2010 Flow Diagram

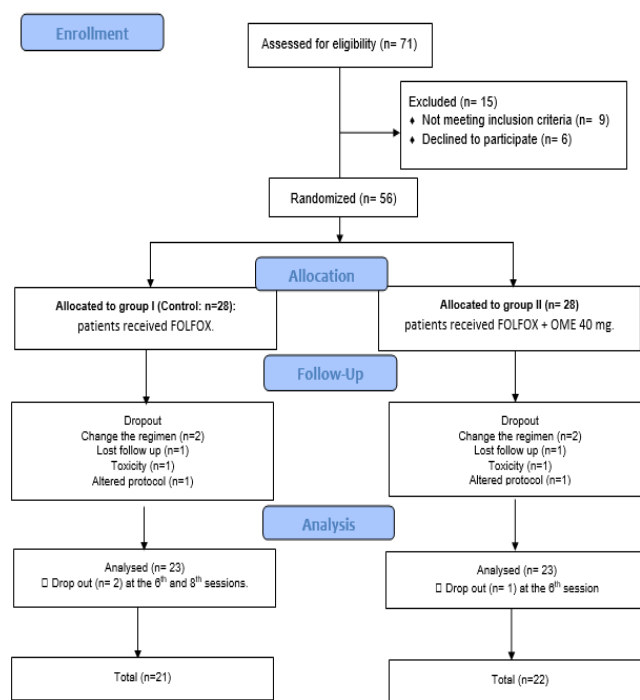


Figure 1: CONSORT Flow chart showing the studied patients

**METHODS:**

Patients were submitted to a physical and clinical examination, collection of demographic data and medical history, calculation of body mass index (BMI) and body surface area (BSA) using the Mosteller formula [16], and cumulative dose of L-OHP. The type of surgery was also recorded.

At baseline and 3 months after treatment initiation, 5 ml venous blood were withdrawn onto vacutainer serum separator tubes, immediately centrifuged and the sera were separated and frozen at -20°C till use.

**Estimation of MDA, NT and OCT2:**

Serum levels of MDA, NT and OCT2 were estimated by ELISA kits which were provided by SunRed biotechnology co., Ltd., Shanghai, China (Catalogue No: DLR-MDA-Ge, DLR-NT-Hu, 201-12-4441, respectively).

**Clinical evaluation of oxaliplatin induced neuropathy:**

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, Version 5, 2017) was used to grade peripheral neuropathy. The Neurotoxicity-12 item questionnaire score (Ntx-12) was obtained from the Validated Functional Assessment of Cancer Therapy/Gynecologic Oncology Group (FACT/GOG-Ntx-12). The BPI-SF's worst item was used to measure the severity of neuropathic pain at baseline, two weeks after the first cycle, three months after treatment, and at the termination of the 12th cycle.

**Determination of participants' adherence and drug tolerability:**

The drug was given every two weeks, and the participants' compliance was evaluated by counting the tablets and looking at how often they refilled their prescriptions. During chemotherapy cycles, participants were additionally contacted by phone and in-person meetings to check on their compliance and report any negative drug responses using an adverse drug reaction reporting form. Additionally, the side effects were gathered from the patient sheet and laboratory data. Any negative side effects associated with the study drug were inquired about by the patients. If a patient took < 90% of the prescribed prescription during any month of the study, they were deemed non-adherent and removed from the study.

**Outcomes:**

**The primary outcome** was the proportion of patients with acute neuropathy more than grade II and patients with chronic neuropathy through evaluation of study biomarkers (Malonaldehyde (MDA), NT, OCT2) and clinical parameters (NCI-CATCAI, NTX-12, and BPI scale).

**The secondary outcome** was the proportion of patients who arrived the last cycles without chronic neuropathy, specifically after 6 cycles through evaluation of Kaplan Meier. Prediction of chronic neuropathy occurrence through cox regression.

**Sample size calculation:**

The sample size calculation was performed using G. power 3.1.9.2 (Universität Kiel, Germany). Based on the following considerations: two tailed, 0.05  $\alpha$  error, 90% power of the study, based on the reported OR (95%CI) for omeprazole was 0.280 (0.070-1.133), according to a previous study [9]. Therefore, 46 patients were allocated.

**Ethical approval:**

The 1964 Helsinki Declaration's ethical guidelines and subsequent revisions were followed when conducting the study. In December 2022, the project received approval from the Faculty of Medicine Research Ethics Committee at Mansoura University in Egypt as well as the Research Ethical Committee (REC-FPTU) at Tanta University in Egypt. The study's risks and advantages were explained to each participant. Participants and the ethical committee were promptly informed of any unexpected risks that surfaced during the study. The enrolled patients' information was kept private. Written informed permission was provided by each patient who was enrolled.

**Statistical analysis:**

Data were analyzed using SPSS, Version 25.0. The student's t-test was employed to detect the statistical significance of the difference of the parametric variable expressed by mean  $\pm$  SD. and Mann Whitney Test (U test), Willcoxon Test (Z test) and repeated measures ANOVA test, Chi-Square test, Fisher's exact test, spearman's correlation and the log-rank test were used. Cox regression analysis was done for the prediction of risk factors when the dependent variable is categorical with time of event. A hazard ratio (HR) is a measure of association between an exposure and an outcome. The Shapiro-Wilk test was done to detect the normality of data distribution. A p-value is considered

significant or highly significant if it is <0.05 or <0.001, respectively, at a confidence interval (CI) 95%.

**RESULTS**

**Patients' characteristics:**

At baseline, there was non-significant variation between the two study groups concerning demographic, clinical data, BMI, BSA, and dose intensity of oxaliplatin in the treatment regimen and of omeprazole, as demonstrated in **Tables 2-3**.

**Table 2: Demographic, clinical and anthropometric baseline data of patients in the studied groups**

		Control group (N = 23)	Omeprazole group (N = 23)	95%CI	p
Gender	Male	9(39.1%)	14(60.9%)	0.3507 to 1.179	0.140 <sup>a</sup>
	Female	14(60.9%)	9(39.1%)		
Age (years)		51.96 $\pm$ 9.70	47.09 $\pm$ 12.13	- 11.387 to 1.667	0.176 <sup>b</sup>
Comorbidities	No	18(78.3%)	20(87%)	0.4019 to 1.710	0.747 <sup>a</sup>
	HTN	3(13%)	2(8.7%)		
	Others	2(8.7%)	1(4.3%)		
Weight (kg)		80.78 $\pm$ 17.20	85.30 $\pm$ 15.87	-5.314 to 14.354	0.146 <sup>b</sup>
Height (cm)		168.2 $\pm$ 5.37	171.0 $\pm$ 6.70	- 0.8082 to 6.408	0.155 <sup>b</sup>
BMI (kg/m <sup>2</sup> )		28.58 $\pm$ 6.03	28.97 $\pm$ 4.62	-2.802 to 3.582	0.807 <sup>b</sup>
BSA		1.93 $\pm$ 0.21	2.0 $\pm$ 0.21	- 0.0548 to 0.1948	0.086 <sup>b</sup>
Performance status	ECOG score 0-1	23 (100%)	23 (100%)	---	---

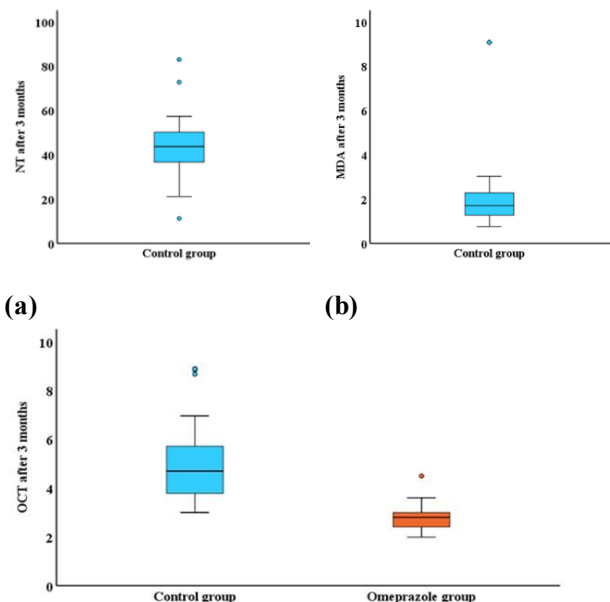
Data are presented as Mean  $\pm$  SD, numbers and percentages., a data was analyzed by Chi-Square test, b data were analyzed by Student t-test, p < 0.05 was considered statistically significant. control group: patients with colon, gastric, pancreatic, rectal or colorectal cancer treated with FOLFOX4. omeprazole group: patients with colorectal, gastric, pancreatic, or colon cancer treated with FOLFOX4 and omeprazole 40 mg three times a day for five days per cycle. BMI: body mass index, BSA: body surface area, ECOG: Eastern Cooperative Oncology Group

**Table 3: Chemotherapy and dose intensity of oxaliplatin and omeprazole for the studied groups at baseline**

		Control (N = 23)	Omeprazole (N = 23)	p
Chemotherapy	All preoperative	1(4.3%)	2(8.7%)	0.838 <sup>a</sup>
	Pre- and post-operative	7(30.4%)	6(26.1%)	
	All postoperative	9(39.1%)	11(47.8%)	
	Not operative, chemotherapy only	6(26.1%)	4(17.4%)	
Cumulative dose for oxaliplatin	1909 ± 203.33 (1574.4 - 2256)	1860.0 ± 197.60 (1507 - 2313.6)	0.983 <sup>b</sup>	
Omeprazole cumulative dose	40 mg* 5 days * 12 cycles	2400 mg	-	

numerical data are presented median, minimum and maximum; categorical data are presented by numbers and percentages. a data was analyzed by Chi-Square test, b data was analyzed by Mann Whitney test, p < 0.05 was considered statistically significant. control group: patients with colon, gastric, pancreatic, rectal or colorectal cancer treated with FOLFOX4. omeprazole group: patients with colorectal, gastric, pancreatic, or colon cancer treated with FOLFOX4 and omeprazole 40 mg three times a day for five days per cycle.

At baseline, there was non-significant variation between the studied groups regarding NT, MDA, and OCT2 levels (p > 0.05). After three months, the OME group exhibited lower levels of NT, OCT2, and MDA than the control group (p < 0.001). Regarding the comparison between before and after treatment in each group, the control group showed a significant increase in OCT2, NT, and MDA (p < 0.001), while the OME group exhibited a significant decrease in NT and OCT2 levels (p<sub>2</sub>=0.004, p<sub>2</sub>=0.005, respectively) but a non-significant reduction of MDA concentration (p<sub>2</sub>=0.212). In terms of percentage change, the control group showed an increase in NT, OCT2, and MDA levels, while the OME group showed a decrease in NT, OCT2, and MDA levels, with significant differences between both groups (p < 0.001). The effect of OME on study biomarkers is displayed in Figure 2.



**Figure 2: (a) change in serum level of NT after 3 months of treatment initiation; (b) change in serum level of MDA after 3 months of treatment initiation; (c) change in serum level of OCT2 after 3 months of treatment initiation**

Control group: patients with colon, gastric, pancreatic, rectal, or colorectal cancer treated with FOLFOX4. Omeprazole group: patients with colon, gastric, pancreatic, rectal, or colorectal cancer treated with FOLFOX4 plus omeprazole 40 mg 3 times for five days per cycle.

**Clinical assessment at baseline, three months and after six months regarding neuropathy:**

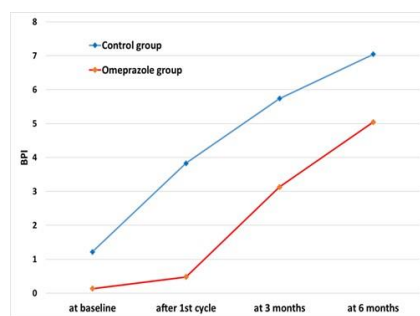
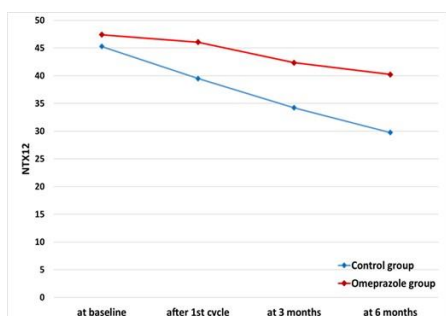
At baseline, no significant difference was found between the two studied groups regarding the clinical evaluation of neuropathy, while after three months of treatment, there was a significant difference. Concerning NCI-CTCAE classification, there were 15 patients vs 1 patient with grade II neuropathy in the control and omeprazole groups, respectively, and after six months of treatment there were 8 patients vs no patients with grade III & IV neuropathy in the control and OME groups, respectively, as shown in Table 4.

**Table 4: Comparison of the clinical evaluation between the studied groups at baseline, 3 months after treatment initiation and at the end of treatment according to NCI-CATCAE**

	Control Group (n=23)			P value
	Baseline	3 months	6 months	
Neuropathy	5(21.73%)	23(100%)	21(100%)	<0.001*
GI Sensory	3(13%)	4(17.40%)	0(0%)	
GII Sensory	2(8.7%)	15(65.20%)	12(57.14%)	
GIII/IV Sensory	0(0%)	4(17.40%)	8(38.1%)	

<b>GI motor</b>	0(0%)	0(0%)	1(4.76%)	
	<b>OME Group (n=23)</b>			
	<b>Baseline</b>	<b>3 months</b>	<b>6 months</b>	
<b>Neuropathy</b>	3(13.04%)	20(86.96%)	22(100%)	<b>&lt;0.001*</b>
<b>GI Sensory</b>	2(8.70%)	19(82.60%)	21(95.45%)	
<b>GII Sensory</b>	1(4.30%)	1(4.30%)	1(4.55%)	
<b>GIII/IV Sensory</b>	0(0%)	0(0%)	0(0%)	
<b>GI motor</b>	0(0%)	0(0%)	0(0%)	

categorical data are presented by numbers and percentages. a data was analyzed by Chi-Square test, \*\* p < 0.01 was considered highly significant, control group: patients with colon, gastric, pancreatic, rectal or colorectal cancer treated with folfox4. omeprazole group: patients with colorectal, gastric, pancreatic, or colon cancer treated with folfox4 and omeprazole 40 mg three times a day for five days per cycle. The OME group showed significantly higher NTX12 levels than the control group at different time points, which means less neuropathy as shown in **Figure 3a** and significantly lower BPI levels in omeprazole group than control group at different time points which means less pain **Figure 3b**.



**Figure 3:(a) Ntx-12 total score for the two studied groups throughout the course of treatment (b) change of pain score (BPI) between the two studied groups throughout the course of treatment**

**Clinical evaluation of chronic neuropathy between the two study groups:**

The OME group had a lower percentage of individuals with chronic neuropathy (73.91%) in comparison with the control (95.65%), but with no statistically significant difference, however, it has been observed that the appearance of chronic neuropathy tends to be late in the OME group at the 8th cycles, indicating that chronic neuropathy occurred in later sessions in the OME group compared to the control group, as shown in **Table 5**.

**Table 5: Clinical evaluation of chronic neuropathy between the studied groups**

	<b>Control N = 23</b>	<b>Omeprazole N = 23</b>	<b>95%CI</b>	<b>p</b>
<b>Chronic neuropathy</b>	--	--	0.05072 to 1.902	--
<b>Absent</b>	1 (4.35%)	5 (21.7%)		<b>0.095<sup>a</sup></b>
<b>Dropout</b>	n=2, at 6 <sup>th</sup> , 8 <sup>th</sup> sessions	n=1, at 6 <sup>th</sup> session	--	
<b>Present</b>	22 (95.65%)	17 (73.91%)	0.6297 to 24.761	

<b>Mean ± SD.</b>	10.44 ± 1.10	5.87 ± 1.58	-5.440 to 3.700	<b>&lt;0.001**</b> <sup>b</sup>
<b>3<sup>rd</sup></b>	2(9.09%)	0(0%)	0.3697 to 0.7049	0.489 <sup>a</sup>
<b>4<sup>th</sup></b>	3(13.64%)	0(0%)	0.3550 to 0.6963	0.233 <sup>a</sup>
<b>5<sup>th</sup></b>	4(18.18%)	0(0%)	0.3400 to 0.6863	0.108 <sup>a</sup>
<b>6<sup>th</sup></b>	5(22.73%)	0(0%)	0.3246 to 0.6754	<b>0.049*<sup>a</sup></b>
<b>7<sup>th</sup></b>	4(18.18%)	0(0%)	0.3400 to 0.6863	0.108 <sup>a</sup>
<b>8<sup>th</sup></b>	4(18.18%)	1(5.88%)	0.3511 to 0.7025	0.346 <sup>a</sup>
<b>9<sup>th</sup></b>	0(0%)	2(11.76%)	0.4205 to 0.7523	0.489 <sup>a</sup>
<b>10<sup>th</sup></b>	0(0%)	5(29.41%)	0.4647 to 0.8026	<b>0.049*<sup>a</sup></b>
<b>11<sup>th</sup></b>	0(0%)	6(35.29%)	0.4817 to 0.8203	<b>0.022*<sup>a</sup></b>

12 <sup>th</sup>	0(0%)	3(17.65%)	0.4343 to 0.7684	0.233 <sup>a</sup>
------------------	-------	-----------	------------------------	--------------------

Numerical data are presented as mean ± SD, categorical data are presented by numbers and percentages. a data was analyzed by Fisher exact test, b data was analyzed by Student t-test. c data was analyzed by Chi-Square test, p<0.05 was considered statistically significant; \* p < 0.05 \*\* p < 0.01. control group: patients with colon, gastric, pancreatic, rectal or colorectal cancer treated with folfox4. omeprazole group: patients with colorectal, gastric, pancreatic, or colon cancer treated with folfox4 and omeprazole 40 mg three times a day for five days per cycle.

**Correlation analysis of biological markers and the study parameters:**

Correlation analysis was performed between change in NT, MDA, and OCT2 levels with different parameters among

the studied groups, including age, sex, BMI, BSA, comorbidities, baseline clinical evaluation, baseline levels of MDA, OCT, and NT, presence of chronic neuropathy, and acute neuropathy after 3 months of treatment. A significant positive correlation between NT change and acute neuropathy grades at the end (p=0.046, rs=0.420) and a significant negative correlation with NT level at baseline (p=0.009, rs=-0.531) in the control group were noticed. There were significant negative correlations between MDA change and MDA level at baseline in the control group (p=0.013, rs=-0.511), as well as a significant positive correlation between MDA change and age in the omeprazole group (p=0.004, rs=0.573). Moreover, there was a significant positive correlation between OCT2 change and BMI in the omeprazole group (p=0.021, rs=0.477). Otherwise, no significant differences were detected (p>0.05) as shown in **Table 6**.

**Table 6: Correlations between change in NT, MDA and OCT2 levels and study parameters among the studied groups**

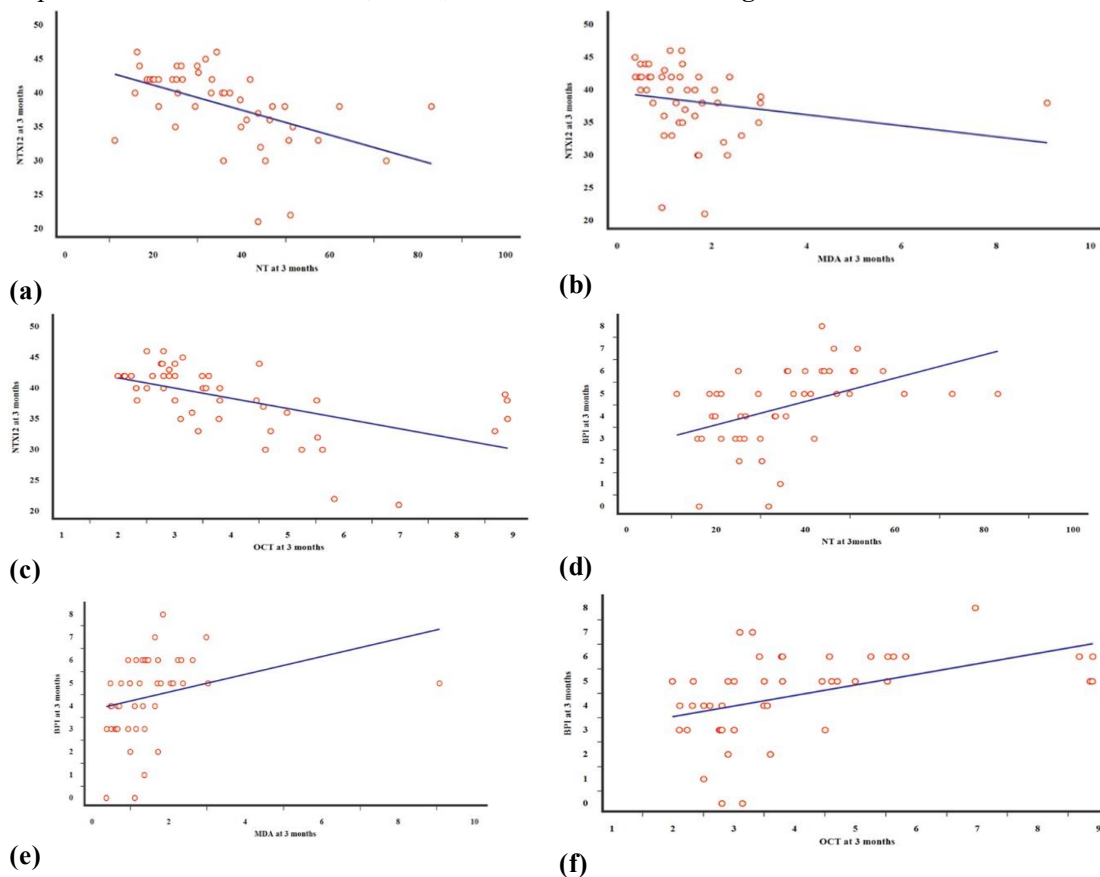
	Change in NT				Change in MDA				Change in OCT			
	Control group		Omeprazole group		Control group		Omeprazole group		Control group		Omeprazole group	
	rs	p	rs	p	rs	p	rs	p	rs	p	rs	p
<b>Age</b>	0.317	0.140	-0.125	0.569	0.078	0.724	0.573	<b>0.004*</b>	-0.283	0.191	0.018	0.936
<b>Sex (females vs males)</b>	-0.201	0.357	-0.134	0.541	0.201	0.357	-0.121	0.583	-0.121	0.583	0.107	0.626
<b>BMI</b>	0.174	0.426	0.130	0.553	0.363	0.089	0.270	0.213	-0.362	0.089	0.477	0.021*
<b>BSA</b>	0.327	0.128	0.185	0.398	0.113	0.609	0.296	0.170	-0.281	0.194	0.411	0.051
<b>Comorbidities (present vs absent)</b>	-0.238	0.273	-0.117	0.596	0.318	0.139	-0.195	0.374	-0.048	0.829	0.039	0.860
<b>NT baseline</b>	-0.531	<b>0.009*</b>	-0.412	0.051	0.001	0.996	0.129	0.556	-0.273	0.208	-0.072	0.744
<b>MDA baseline</b>	0.084	0.703	0.121	0.583	-0.511	<b>0.013*</b>	-0.277	0.201	0.197	0.368	0.153	0.485
<b>OCT baseline</b>	0.179	0.414	-0.202	0.356	0.270	0.213	-0.115	0.603	-0.067	0.761	-0.313	0.146
<b>Clinical evaluation at baseline</b>	0.171	0.434	0.068	0.757	-0.109	0.620	-0.117	0.594	0.410	0.052	-0.053	0.810
<b>Chronic neuropathy (present vs absent)</b>	-	-	0.207	0.344	-	-	-0.079	0.719	-	-	0.191	0.383
<b>Acute neuropathy after 3 months</b>	0.178	0.417	-0.304	0.158	-0.033	0.880	-0.040	0.855	-0.044	0.840	-0.348	0.104

<b>Acute neuropathy at the end</b>	0.420	0.046*	0.326	0.129	0.007	0.973	0.372	0.080	-0.040	0.855	0.256	0.239
------------------------------------	-------	--------	-------	-------	-------	-------	-------	-------	--------	-------	-------	-------

rs: Spearman's correlation coefficient; \*, p<0.05 is considered significant.; \*\* p<0.01.

**Correlation of clinical parameters with biological markers at 3 months:**

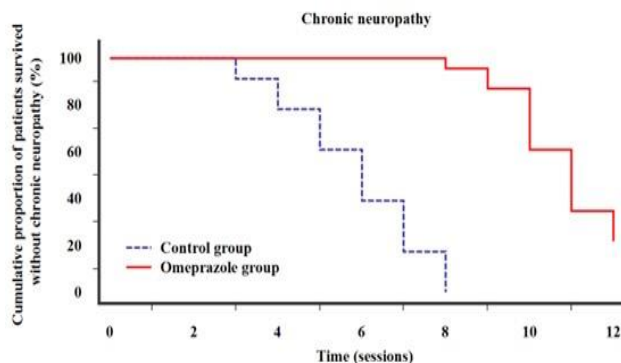
At 3 months, NTX12 showed significant negative correlations with NT, MDA, and OCT2. Conversely, BPI showed significant positive correlations with NT, MDA, and OCT2 as shown in **Figure 4**.



**Figure 4:**(a) Correlation of NTX12 levels with NT at 3 months (b) Correlation of NTX12 levels with MDA at 3 months (c) Correlation of NTX12 levels with OCT2 at 3 months. (d) Correlation of BPI levels with NT at 3 months (e) Correlation of BPI levels with MDA at 3 months. (f) Correlation of BPI levels with OCT2 at 3 months

**Prediction of outcome:**

A Kaplan-Meier analysis for chronic neuropathy in both groups, revealing a stark contrast in the cumulative proportion of patients without chronic neuropathy. The OME group showed the median time to detect chronic neuropathy was later in OME when compared to the control group (11th vs. 6th session). In addition, the OME group showed a higher rate without chronic neuropathy than the control group as shown in **Figure 5**.



**Figure 5:** Kaplan Meier for the time occurrence of chronic neuropathy among the two studied groups through 12 cycles of chemotherapy over 6 months. Showing proportion of patients who arrived the last chemotherapy cycles without chronic neuropathy specifically after 6 cycles

The Cox regression analysis for predictors of chronic neuropathy occurrence demonstrated that the type of treatment was a highly significant predictor of chronic neuropathy ( $p < 0.001$ ), with HR = 0.019, 95% CI = 0.003–0.134, indicating a substantial protective effect associated with OME treatment in protecting from chronic neuropathy. Other factors such as age, sex, comorbidities, and baseline measurements did not show significant predictive value for chronic neuropathy occurrence, as shown in **Table 7**

**Table 7: Cox regression analysis for the predictors of chronic neuropathy occurrence**

	p	HR	95% C. I
Sex	0.286	1.398	0.755–2.589
Age	0.062	1.027	0.999–1.056
Comorbidities	0.774	1.127	0.498–2.551
BMI	0.759	1.010	0.948–1.076
BSA	0.430	0.555	0.129–2.397
NT at baseline	0.090	1.022	0.997–1.047
MDA at baseline	0.141	0.620	0.328–1.173
OCT2 at baseline	0.415	1.163	0.809–1.670
Omeprazole vs control treatment	<0.001**	0.019	0.003–0.134

hr.: Hazard Ratio; ci, confidence interval. \*\*  $p < 0.01$  is considered highly significant

## DISCUSSION

This study is intended to investigate the role of OME in OIPN in gastrointestinal cancer patients. In preclinical research on a rat model, L-OHP-induced mechanical hypersensitivity was significantly suppressed by OME administration. Axonal damage and myelin sheath dysfunction were significantly suppressed [6].

Furthermore, a former retrospective study of two real-world clinical databases in 2023 reported that concurrent PPI use upgrades L-OHP-induced CIPN in patients with colorectal cancer without disturbing the therapeutic efficiency of L-OHP [9].

Some studies showed that neurotoxicity is a result of oxidative stress-induced demyelination, mitochondrial dysfunction, microtubular damage, and apoptosis [17]. Since OME exhibits antioxidant and anti-inflammatory effects, a novel study showed that OME blocks stress-triggered elevation of hydroxyl radical and is linked to lipid peroxidation and protein oxidation [18]. So, OME has a major role in protecting from oxidative stress.

Since omeprazole also has antioxidant properties, it may reduce oxidative stress and inhibit myelopathy and axonopathy by a similar pathway. Its antioxidant effects are common to many PPIs, and a correlation may exist between

its differential antioxidant capacity and its neuropathy-inhibiting effects [19].

Mine et al., [6] in their study indicated that the reporting odds ratio (ROR) of peripheral neuropathy in oxaliplatin-treated patients was significantly decreased in patients concomitantly administered with omeprazole. There was also a significant decrease in ROR for any PPI. The reason for the significant suppression by PPIs as a whole may be due to the heavy influence of omeprazole and pantoprazole, which are reported in large numbers. Furthermore, it is a known clinical fact that omeprazole is a safe drug with few adverse events. Therefore, it is possible that PPIs may be clinically applied as a prophylactic agent for OIPN in the future. It is expected that clinical evidence on the usefulness of PPIs including omeprazole for OIPN will be developed. During the current study there was a significant decrease in MDA level (a biomarker for oxidative stress) in the OME group compared to the control group, but a non-significant reduction in serum level of MDA in the OME group after three months of treatment compared to the baseline in the same group.

Our findings look in alignment with some reports demonstrating that MDA is a non-specific biomarker [20]. So, some cases may exhibit high levels during assessment due to other reasons like the presence of inflammation. OME also has some anti-inflammatory actions. It has been reported that OME attenuates human neutrophil adherence to endothelial cells in vitro by inhibiting the expression of intercellular adhesion molecule-1, vascular adhesion molecule-1, and IL-8 [21].

Moreover, NT is a neuropeptide widely distributed in the CNS and acts as a neurotransmitter/modulator. It is known to play a role in immunologic processes, inflammatory and neurodegenerative illnesses [22]. Notably, it is commonly known that NT signaling pathways play a role in neuropathic pain by stimulating mast cells and releasing neuro-sensitizing mediators [23-25]. Considering the current study's findings, the OME group's serum level of NT significantly decreased three months after therapy when compared to the controls and baseline data.

Furthermore, previous reports demonstrated that OCT2 is the key factor of platinum drug uptake and cytotoxicity and contributes to platinum accumulation in the kidneys, inner ear, and PNS, leading to nephrotoxicity, ototoxicity, and peripheral neuropathy. It has been reported that OCT2 is expressed in 20% of DRG neurons [5].

Also, reports have demonstrated that OCT2 mediates the intracellular accumulation of L-OHP in mice, rats, and humans [26]. While OME was described to reduce the renal expression of OCT2 [6], our current study assumed the hypothesis that OME may similarly suppress OCT2-mediated uptake into DRG and the development of neuropathy.

Notably, the detection of OCT2 within human DRG has remained challenging, owing to the absence of readily available, appropriate commercial antibodies [27]. So, in our study, OCT2 was detected in serum. It was challenging that serum OCT2 level simulates neuronal OCT2 level. Exploratory, it was found that after three months of therapy,

the OME group's OCT2 serum level significantly decreased in comparison to the control group.

In the current study, clinical assessment revealed that the peripheral neuropathy was lower in the OME group compared to the control group. Additionally, results obtained from NCI-CTCAE neuropathy grading and Ntx-12 reveal the effective role of OME in decreasing neuropathy level. Noticeably, there was a protection against grade II and grade III neuropathy in the OME group. In addition, the appearance of chronic neuropathy tends to be late in the OME group, becoming noticeable after 6 to 8 cycles.

During this study, Kaplan-Meier analyzed chronic neuropathy in both groups, revealing a stark contrast in the cumulative proportion without chronic neuropathy. The OME group showed the median time to detect chronic neuropathy was later in the OME group when compared to the control group (11th vs. 6th session). In addition, the OME group showed a higher percentage without chronic neuropathy compared to the control group, with a significant difference ( $p < 0.001$ ). Of note, elderly patients may need a short course of FOLFOX4 (6 cycles) only [28]. So, our study results are considered a promising candidate that helps in protection against neuropathy in elderly patients with short-course FOLFOX4, as they are considered the most affected population with neurotoxicity. Hence, the co-administration of OME with short courses of chemotherapy protocols (6 cycles) containing OHP may be useful in elderly patients to continue the chemotherapy regimen without stoppage due to neurotoxicity. According to numeric pain scale (BPI-SF), arise in the pain scale indicates an increase in OIPN. Neuropathic pain appeared late at the 8th cycle in the OME group compared to the control group which appeared early. Our findings seem compatible with the results of an in vivo/in vitro prospective study in 2016 that investigated how OME affected neuropathic pain of chronic constriction neuropathy [29]. The study showed that OME in high doses (50 mg/kg/day) for 14 days reduced the values of tumor necrosis factor, interleukin-1 $\beta$ , and interleukin-6 in comparison with their control groups. It also reduced the oxidative stress through the regulation of superoxide dismutase and catalase activities and reducing MDA level, so controlling neuropathic pain.

In our study, the dose of OME is dependent on being in high doses tolerable to patients according to recent prospective studies on a rat model that showed the effectiveness of OME against neuropathy in high doses [6, 29]. Additionally, previous studies found that patients with Zollinger Ellison syndrome can tolerate OME up to 180 mg/day [15]. According to the current study's exclusion criteria and the studied tolerable high dose of OME, we hypothesized that 40 mg of OME TID for 5 days every cycle for 6 months of chemotherapy treatment would be suitable, and actually it was safe for our participants with no side effects.

Correlation analysis of the current study was done at the treatment end between measured biological markers (NT, MDA, OCT2) and clinical parameters (NTX-12, BPI, NCI-CATCAE) and showed that low biological marker levels are

associated with high NTX-12 scores, so a lower degree of neuropathy. There is also a positive correlation between biological markers with BPI and NCI-CATCAE, which means that low biological marker values are associated with low scores of BPI and NCI-CATCAE, so there is a lesser degree of neuropathy. These results indicate the possibility of using these biological markers as a marker for neuropathy.

Furthermore, the MDA variation was significantly positively correlated with age in the OME group. This result seems compatible with the findings of a clinical investigation that indicated the presence of increased oxidative stress in elderly patients, so there is an increase in MDA level [30]. There was also a significant positive correlation between OCT2 change and BMI in the OME group. This result is compatible with a study on a rat model that showed that in mice fed a high-fat diet (HFD), the amount of OCT2 in the kidney increased 1.92 and 2.46 times at 4 and 12 weeks [31]. According to the current study, which suggested that OME may suppress OCT2 uptake into DRG, the suppression effect of OME on OCT2 in the kidney was confirmed. So, serum OCT2 may increase in high-BMI patients, as its increment in the kidney of HFD-fed mice.

OME was well tolerated, and there were no side effects with patients. Of note, OME was used for a short term only 6 months and intermittently (5 days per cycle). So, no need to investigate vitB<sub>12</sub> levels, magnesium, hematological indices nor liver functions, as these parameters are affected only with OME when taken for long term with high doses [32]. Also, patients with high risk of these side effects were excluded such as those with autoimmune disease, or osteoporosis.

## CONCLUSION:

Our findings suggest that OME may have an effective protective role against acute and chronic OIPN in patients with colon or other cancers receiving FOLFOX4. Because of its effectiveness and safety, OME might be a desirable option for medication repositioning against OIPN.

As far as we are aware, this is the first prospective randomized double-blinded clinical trial to investigate how OME affects cancer patients in the Middle East who have peripheral neuropathy brought on by L-OHP. Additionally, the current work has other points of strength, including the randomized nature of the study design, double blindness and the Kaplan-Meier analysis for chronic neuropathy. However, there were some limitations, including the relatively small size and inability to carry out radiological tests and nerve study tests like nerve conduction velocity (NCV), and high-dose OME should be used with these exclusions mentioned before for the safety criteria.

Therefore, we recommend conducting more, longer-term, and larger-scale studies that include the implications of varying OME dosages that should be modified considering the BMI and BSA to create a thorough assessment about the role of OME against neuropathy to avoid any side effects. Moreover, to increase patient adherence and decrease frequency, future pharmaceutical firms should concentrate

on creating OME dosage forms in greater doses and maintaining good bioavailability. Using objective scales for assessment of neuropathy.

**Declarations:**

**Acknowledgments:**

We are so grateful to the physicians, especially Professor Khaled M. Abouelkhair for his efforts, assistance and sincere recommendations and profitable supervision and thankful for nurses at clinical oncology and nuclear medicine department (Mansoura University Hospital). We are thankful to the Faculty of Pharmacy, Tanta University for the great technical support and so grateful for Dr. Sahar Hegazy for her efforts, support and profitable supervision.

**Funding:** Our research didn't receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

**Declaration of competing interest:** All authors declare that they have no known personal relationships or conflicting financial interests that could affect the work reported in this manuscript.

**Declaration of generative AI in scientific writing:** We declare that we did not use generative AI in scientific writing.

**Data availability:** Data and analytical methods will be available, upon reasonable request.

**Consent to participate:** All enrolled patients gave their written informed consents before participating in the study.

**Consent to publish:** Not applicable and no personal data for any participant is included.

**Authors' contributions:**

S.K.H. was responsible for formal analysis and investigation. K.M.A. was responsible for supervision and project administration. A.M.S. was responsible for writing original draft, visualization and statistical analysis. K. M. A. and A.M.S. were responsible for samples collections and data curation. S.K.H. and Z.M.H. were responsible for methodology and investigation. All authors reviewed the manuscript.

**REFERENCE**

1. Chocry M, Leloup L, Parat F, Messé M, Pagano A, Kovacic H. Gemcitabine: An Alternative Treatment for Oxaliplatin-Resistant Colorectal Cancer. *Cancers*. 2022;14:58-94.
2. Yang Y, Zhao B, Gao X, Sun J, Ye J, Li J, et al. Targeting strategies for oxaliplatin-induced peripheral neuropathy: clinical syndrome, molecular basis, and drug development. *J Exp Clin Cancer Res*. 2021;40:33-61.
3. Staff NP, Cavaletti G, Islam B, Lustberg M, Psimaras D, Tamburin S. Platinum-induced peripheral neurotoxicity: From pathogenesis to treatment. *J Peripher Nerv Syst*. 2019;24:26-39.
4. Yamamoto S, Egashira N. Drug Repositioning for the Prevention and Treatment of Chemotherapy-Induced Peripheral Neuropathy: A Mechanism- and Screening-Based Strategy. *Front Pharmacol*. 2020;11:60-80.
5. Wei G, Gu Z, Gu J, Yu J, Huang X, Qin F, et al. Platinum

accumulation in oxaliplatin-induced peripheral neuropathy. *J Peripher Nerv Syst*. 2021;26:35-42.

6. Mine K, Kawashiri T, Inoue M, Kobayashi D, Mori K, Hiromoto S, et al. Omeprazole Suppresses Oxaliplatin-Induced Peripheral Neuropathy in a Rodent Model and Clinical Database. *Int J Mol Sci*. 2022;23:34-75.

7. Yamada T, Iwasawa T, Tsuchiya R, Ito T, Kato K. Ergothioneine Attenuates Oxaliplatin-Induced Peripheral Neuropathy Without Compromising Antitumor Efficacy. *Int J Mol Sci*. 2025;26:10-63.

8. Gao H, Zhang S, Hu T, Qu X, Zhai J, Zhang Y, et al. Omeprazole protects against cisplatin-induced nephrotoxicity by alleviating oxidative stress, inflammation, and transporter-mediated cisplatin accumulation in rats and HK-2 cells. *Chem Biol Interact*. 2019;297:130-40.

9. Kobayashi A, Ikemura K, Wakai E, Kondo M, Okuda M. Proton Pump Inhibitors Ameliorate Oxaliplatin-induced Peripheral Neuropathy: Retrospective Analysis of Two Real-world Clinical Databases. *Anticancer Res*. 2023;43:5613-20.

10. Mori Y, Mine K, Kawashiri T, Koura Y, Ueda M, Kaneko R, et al. Class effects of proton pump inhibitors in preventing oxaliplatin-induced peripheral neurotoxicity. *J Pharmacol Sci*. 2025;159:279-82.

11. Tsukushi Y, Koriyama K, Kobuchi S, Matsumoto K, Ito Y, Sakaeda T. Model-informed drug repurposing of proton pump inhibitors for the prevention of oxaliplatin induced peripheral neuropathy: A real-world data analysis and pharmacometrics approach. *Cancer Chemother Pharmacol*. 2025;95:79-98.

12. Mine K, Kawashiri T, Mori K, Mori Y, Ishida H, Kudamatsu H, et al. Proton pump inhibitor concomitant use to prevent oxaliplatin-induced peripheral neuropathy: Clinical retrospective cohort study. *Pharmacotherapy*. 2025;45:435-47.

13. Edeline J, Boucher E, Rolland Y, Vauléon E, Pracht M, Perrin C, et al. Comparison of tumor response by Response Evaluation Criteria in Solid Tumors (RECIST) and modified RECIST in patients treated with sorafenib for hepatocellular carcinoma. *Cancer*. 2012;118:147-56.

14. Azam F, Latif MF, Farooq A, Tirmazy SH, AlShahrani S, Bashir S, et al. Performance Status Assessment by Using ECOG (Eastern Cooperative Oncology Group) Score for Cancer Patients by Oncology Healthcare Professionals. *Case Rep Oncol*. 2019;12:728-36.

15. Rezaizadeh H, Olson E. Gastroesophageal Disorders. In: Wu GY, editor. *Pocket Handbook of GI Pharmacotherapeutics*. Cham: Springer International Publishing; 2016. p. 3-16.

16. El Edelbi R, Lindemalm S, Eksborg S. Estimation of body surface area in various childhood ages--validation of

- the Mosteller formula. *Acta Paediatr.* 2012;101:540-4.
17. Was H, Borkowska A, Bagues A, Tu L, Liu JYH, Lu Z, et al. Mechanisms of Chemotherapy-Induced Neurotoxicity. *Front Pharmacol.* 2022;13:75-97.
18. Biswas K, Bandyopadhyay U, Chattopadhyay I, Varadaraj A, Ali E, Banerjee RK. A novel antioxidant and antiapoptotic role of omeprazole to block gastric ulcer through scavenging of hydroxyl radical. *J Biol Chem.* 2003;278:10993-1001.
19. Abed MN, Alassaf FA, Jasim MHM, Alfahad M, Qazzaz ME. Comparison of Antioxidant Effects of the Proton Pump-Inhibiting Drugs Omeprazole, Esomeprazole, Lansoprazole, Pantoprazole, and Rabeprazole. *Pharmacology.* 2020;105:645-51.
20. Khoubnasabjafari M, Ansarin K, Jouyban A. Reliability of malondialdehyde as a biomarker of oxidative stress in psychological disorders. *Bioimpacts.* 2015;5:123-7.
21. Dean L, Kane M. Omeprazole Therapy and CYP2C19 Genotype. In: Pratt VM, Scott SA, Pirmohamed M, Esquivel B, Kattman BL, Malheiro AJ, editors. *Medical Genetics Summaries.* Bethesda (MD): National Center for Biotechnology Information (US); 2012. p. 34-76.
22. Christou N, Blondy S, David V, Verdier M, Lalloué F, Jauberteau MO, et al. Neurotensin pathway in digestive cancers and clinical applications: an overview. *Cell Death Dis.* 2020;11:10-27.
23. Vachon P, Massé R, Gibbs BF. Substance P and neurotensin are up-regulated in the lumbar spinal cord of animals with neuropathic pain. *Can J Vet Res.* 2004;68:86-92.
24. Kyriatzis G, Khrestchatisky M, Ferhat L, Chatzaki EA. Neurotensin and Neurotensin Receptors in Stress-related Disorders: Pathophysiology & Novel Drug Targets. *Curr Neuropharmacol.* 2024;22:916-34.
25. Werida RH, Elshafiey RA, Ghoneim A, Elzawawy S, Mostafa TM. Role of alpha-lipoic acid in counteracting paclitaxel- and doxorubicin-induced toxicities: a randomized controlled trial in breast cancer patients. *Support Care Cancer.* 2022;30:7281-92.
26. Huang KM, Leblanc AF, Uddin ME, Kim JY, Chen M, Eisenmann ED, et al. Neuronal uptake transporters contribute to oxaliplatin neurotoxicity in mice. *J Clin Invest.* 2020;130:4601-6.
27. Sprowl JA, Ciarimboli G, Lancaster CS, Giovinazzo H, Gibson AA, Du G, et al. Oxaliplatin-induced neurotoxicity is dependent on the organic cation transporter OCT2. *Proc Natl Acad Sci U S A.* 2013;110:11199-204.
28. Iveson TJ, Kerr RS, Saunders MP, Cassidy J, Hollander NH, Taberero J, et al. 3 versus 6 months of adjuvant oxaliplatin-fluoropyrimidine combination therapy for colorectal cancer (SCOT): an international, randomised, phase 3, non-inferiority trial. *Lancet Oncol.* 2018;19:562-78.
29. Chanchal SK, Mahajan UB, Siddharth S, Reddy N, Goyal SN, Patil PH, et al. In vivo and in vitro protective effects of omeprazole against neuropathic pain. *Sci Rep.* 2016;6:30-76.
30. Mutlu-Türkoğlu U, İlhan E, Öztezcan S, Kuru A, Aykaç-Toker G, Uysal M. Age-related increases in plasma malondialdehyde and protein carbonyl levels and lymphocyte DNA damage in elderly subjects. *Clin Biochem.* 2003;36:397-400.
31. Lu X, Dong Y, Jian Z, Li Q, Gong L, Tang L, et al. Systematic Investigation of the Effects of Long-Term Administration of a High-Fat Diet on Drug Transporters in the Mouse Liver, Kidney and Intestine. *Curr Drug Metab.* 2019;20:742-55.
32. Al Ali HS, Jabbar AS, Neamah NF, Ibrahim NK. Long-Term Use of Omeprazole: Effect on Haematological and Biochemical Parameters. *Acta Med Indones.* 2022;54:585-94...