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PREVENTION OF PACLITAXEL-INDUCED MOTOR NEUROPATHY OF FIBULAR AND TIBIAL NERVES WITH ALPHA-LIPOIC ACID AND IPIDACRIN HYDROCHLORIDE IN BREAST CANCER PATIENTS

Aim. To investigate neurofunctional parameters of motor nerves in breast cancer (BCa) patients with paclitaxel-induced peripheral neuropathy (PIPN) and to determine the feasibility of using alpha-lipoic acid (ALA) in combination with ipidacrine hydrochloride (IPD) for PIPN prevention. **Materials and Methods.** The study included 100 patients with BCa stages II—IV, who were treated with polychemotherapy (PCT) according to the AT (paclitaxel, doxorubicin) or ET (paclitaxel, epirubicin) scheme in the neoadjuvant, adjuvant, or palliative regimens. Patients were randomized into two groups (n = 50 in each): group I received PCT only; group II – PCT in combination with ALA + IPD. Electroneuromyographic (ENMG) studies of the motor fibular and tibial nerves were performed before the start of chemotherapy and after the 3rd and 6th cycles of PCT. **Results.** Comparison of ENMG parameters of the motor nerves of the lower extremities of BCa patients before the start of PCT with these parameters after 3 and 6 PCT cycles indicated a slightly pronounced but significant decrease in the M-response and partly the nerve conduction velocity, which progressed with an increase in the cumulative dose of paclitaxel. Despite this, the average values of ENMG parameters remained within normal limits even after 6 cycles of PCT. The detected changes indicated a tendency toward axonal damage and mild myelinopathy. Significantly higher M-response rates of motor nerves were found in patients of group II compared to group I only after 6 cycles of PCT with paclitaxel. **Conclusion.** The use of ALA and IPD improves the functional state of the axons in patients with BCa treated with paclitaxel.

Keywords: paclitaxel, chemotherapy, motor neuropathy, electroneuromyography, alpha-lipoic acid, ipidacrine hydrochloride.

Paclitaxel is a taxoid cytotoxic drug first isolated from the bark of the Pacific yew tree *Taxus brevifolia* in 1971 [1]. It acts *via* binding to the microtubules of malignant cell cytoskeleton, which leads to β-tubulin aggregation, disruption of mitotic spindles, cell cycle arrest in the G0/G1 and

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G2/M phases, and induction of apoptosis of dividing cells [2]. Taxanes also disrupt the cytoskeletal structure of healthy cells, leading to numerous side effects, including neurotoxicity through axonal damage and neuronal demyelination [3]. Paclitaxel-induced peripheral neuropathy (PIPN) is characterized by numbness, tingling, neuropathic pain, allodynia, or hyperalgesia, usually occurring in the distal extremities [4]. Motor neuropathy occurs less frequently and predominantly with high doses of paclitaxel, causing muscle weakness, which can occur in both proximal and distal parts of the body [5].

Symptoms of PIPN lead to disability, interfere with functional activity, and worsen the quality of life of patients. Severe neuropathy often necessitates dose reductions, even discontinuation of taxane use, which negatively affects the efficacy and long-term results of chemotherapy [6, 7].

Despite numerous studies, effective methods for the prevention and treatment of chemotherapy-induced peripheral neuropathy (CIPN) have not been found, and the studied agents have not shown significant results [8, 9]. In our previously published study with a similar design, we showed that an increase in the cumulative dose of paclitaxel causes the development and progression of axonal sensory neuropathy. The use of alpha-lipoic acid (ALA) and ipidacrine hydrochloride (IPD) allowed reducing a degree of axonal and myelin damage of the superficial peroneal and sural nerves in patients with breast cancer (BCa) [10]. The current study is aimed at further studying the effectiveness of CIPN prevention, in particular in reducing the neuropathy manifestations of the motor fibular and tibial nerves in BCa patients.

Materials and Methods

100 BCa patients treated at the CNE "Prykarpatskyi Clinical Oncology Center of the Ivano-Frankivsk Regional Council" in 2014—2022 were included in the study; it was approved by the Bioethics Commission of the Ivano-Frankivsk National Medical University. All patients and 30 practically healthy individuals (PHI) provided informed written consent to participate in the study. The patients were randomized into two groups (50 per group), who received polychemotherapy (PCT) in combination with an experimental neuropathy prevention scheme (group II) or PCT only (group I). There were no statistically significant differences between the groups in terms of the stage of the disease, age, concomitant diseases, and PCT regimens. The methodology, inclusion and exclusion criteria of the BCa patients, as well as the features of chemotherapy and neuropathy prevention have been described in detail in our previous publication, which described the effectiveness of ALA and IPD for the prevention of paclitaxel-induced sensory neuropathy based on electroneuromyography (ENMG) data on the superficial peroneal and sural nerves [10].

In the current study, ENMG of the fibular and tibial nerves was analyzed on a computerized two-channel electroneuromyograph Neuro-EMG-Micro (Neurosoft, RF) according to generally accepted methods before the beginning, after the 3rd and 6th cycles of PCT on both lower extremities, with subsequent averaging of the data. The following indicators were studied: the amplitude of the potentials of the maximum motor response to nerve stimulation at distal and proximal points (mV), the duration of the M-response to nerve stimulation at distal and proximal points (ms), the area of the M-response to nerve stimulation at distal and proximal points (mV × ms), terminal latency (TL) — the time from the moment of nerve stimulation at the distal point to the initial negative deviation of the M-response (ms), and the residual latency (RL). The nerve conduction velocity (NCV, m/s) was equal to the distance between two stimulation points (m) divided by the difference in terminal latencies of two M-responses (s).

For statistical processing of the data, the descriptive statistics was used.

Results and Discussion

All mean values of EMNG testing of the tibial and fibular nerves in patients with BCa before the PCT initiation did not significantly differ from such values of PHI. After 3 cycles of PCT, the ENMG indicators of the tibial nerves in the patients of group I showed a significant decrease in the M-response's amplitude, duration, and area at the distal and proximal stimulation points (by 27.3% and 26.5%; 28.4% and 28.9%; 19.1% and 19.4%, respectively) compared to the lower mean decrease in these in-

dicators in the patients of group II (by 26.7% and 23.3%; 28.1% and 26.3%; 16.3% and 17.5%, respectively) (Table 1).

The M-response's amplitude, duration, and area at the distal and proximal stimulation points of the fibular nerve in the patients of group I after three cycles of PCT were significantly lower (by 16.5% and 12.9%; 13.5% and 14.3%; 14.4% and 14.7%, respectively), while in group II, these values were lower by 12.8% and 10.7%; 11.4% and 10.4%; 8.4% and 10.1%, respectively (Table 2). Such electrophysiological changes indicate a decrease in the functional state of the tibial and fibular nerve axons after 3 cycles of PCT with paclitaxel, however, without significant differences between the groups.

After 6 cycles of PCT, the ENMG values of the tibial and fibular nerves tended to decrease. In particular, the amplitude of the M-response of the tibial nerves in the patients of group I was significantly lower by 11.4% and 13.4%, the duration by 13.8% and 6.9%, and the area by 18.1% and 13.0% at the distal and proximal points, respectively. In group II, only the amplitude of the M-response at the proximal point of the tibial nerve stimulation was significantly lower by 8.5% and the area at the distal point by 9.6%.

After 6 cycles of PCT compared to 3 cycles, in group I, the M-response's amplitude, duration, and the area for the fibular nerves were significantly lower: by 18.4% and 15.8%, 13.9% and 13.6%, and 15.5% and 15.2% at the distal and proximal points, respectively. In group II, after 6 cycles of PCT, the average values of the M-response's amplitude were significantly lower (by 10.2% and 9.6% at the distal and proximal points of stimulation of the fibular nerves) and the area — by 11.5% at the distal point. These data indicated a progressive deterioration in the functional state of the axons of both nerves with increasing the cumulative dose of paclitaxel, while the changes in the patients of group II were less pronounced.

Comparison of M-responses of the tibial and fibular nerves after 6 cycles of PCT between the groups showed significantly better indicators in group II: Higher M-response amplitudes of the tibial nerve at the distal site and of the fibular nerve at both distal and proximal sites, longer durations at both stimulation sites of the tibial and fibular nerves, as well as larger areas at the distal site of the tibial nerve and the proximal site of the fibular nerve. Such results indicated a significantly better functional state of the tibial and fibular nerve axons in patients of group II after 6 cycles of PCT with paclitaxel.

Also, with increasing cumulative dose of paclitaxel in the studied groups, we revealed a tendency to prolonged residual latency of the tibial nerves (Table 1), which indicated deterioration of impulse conduction in the terminals of nerve fibers, as well as terminal latency, which is responsible for the NCV in the distal parts of the nerve.

We also observed a slight increase in the tibial nerve NCV, which in the patients of group I after 6 cycles of PCT was significantly lower by 5.0% compared to the 3-cycle value, which indicated a significant decrease in the functional state of myelin.

Regarding the fibular nerves, after 3 cycles of PCT, a significant lengthening of the TL was observed in the patients of groups I and II (by 6.3% and 4.1% respectively), which indicated a decrease in the NCV in the distal sections. After 6 cycles of PCT, this trend persisted and was even more pronounced: the TL index significantly increased in the patients of groups I and II (by 5.6% and 4.5% respectively). In addition, after 3 cycles of PCT, a significant decrease in the NCV by 6.5% was recorded in the patients of group I, which indicated a deterioration in the functional state of the myelin of the fibular nerves.

The applied regimen for PIPN prevention in the patients of group II contributed to certain positive (but insignificant) trends in the RL, TL, and NCV values of the fibular and tibial nerves.

In recent years, oxidative stress has been considered a potentially important factor in the CIPN development [11—13]. It has been shown that neurons are more sensitive to oxidative stress due to a low activity of antioxidant enzymes [14]. Studies in the in vivo and in vitro systems have shown that treatment with ALA reduced the level of free radicals and oxidative stress, maintained antioxidant balance, and restored mitochondrial function with an improved conductivity and decreased damage to nerve structures, and lower neurological manifestations of peripheral neuropathy [15, 16]. Such data were confirmed by clinical randomized trials, which indicated a lower severity of CIPN in the patients treated with ALA compared to the placebo group [17, 18].

Table 1. **ENMG indicators of tibial nerve function in patients with BCa**

ENMG indicators	ENMG values (M ± m)						
	PHI n = 30	Group I before PCT n = 50	Group II before PCT n = 50	Group I after 3 PCT cycles n = 50	Group II after 3 PCT cycles n = 50	Group I after 6 PCT cycles n = 39	Group II after 6 PCT cycles n = 36
Amplitude of M-response to nerve stimulation at the distal point, mV	8.66 ± 0.18	8.33 ± 0.12	8.55 ± 0.15	6.06 ± 0.13 [a]	6.27 ± 0.18 [b]	5.37 ± 0.16 [a, c]	5.92 ± 0.22 [b, e]
Amplitude of M-response to nerve stimulation at the proximal point, mV	8.99 ± 0.17	8.84 ± 0.12	8.85 ± 0.15	6.50 ± 0.17 [a]	6.79 ± 0.16 [b]	5.63 ± 0.21 [a, c]	6.21 ± 0.21 [b, d]
Duration of M-response to nerve stimulation at the distal point, ms	7.76 ± 0.17	7.47 ± 0.14	7.59 ± 0.16	5.35 ± 0.13 [a]	5.46 ± 0.16 [b]	4.61 ± 0.13 [a, c]	5.22 ± 0.17 [b, e]
Duration of M-response to nerve stimulation at the proximal point, ms	7.85 ± 0.16	7.57 ± 0.12	7.68 ± 0.16	5.38 ± 0.11 [a]	5.66 ± 0.12 [b]	5.01 ± 0.14 [a, c]	5.37 ± 0.11 [b, e]
Area of M-response to nerve stimulation at the distal point, mV × ms	15.99 ± 0.40	15.78 ± 0.40	15.37 ± 0.29	12.77 ± 0.34 [a]	12.87 ± 0.25 [b]	10.46 ± 0.42 [a, c]	11.63 ± 0.35 [b, d, e]
Area of M-response to nerve stimulation at the proximal point, mV×ms	16.48 ± 0.39	16.26 ± 0.39	15.86 ± 0.39	13.11 ± 0.49 [a]	13.09 ± 0.41 [b]	11.41 ± 0.62 [a, c]	12.40 ± 0.51 [b]
Residual latency, ms	1.47 ± 0.06	1.48 ± 0.07	1.41 ± 0.05	1.59 ± 0.07	1.49 ± 0.05	1.54 ± 0.07	1.52 ± 0.06
Terminal latency, ms	3.25 ± 0.06	3.25 ± 0.07	3.19 ± 0.04	3.41 ± 0.06	3.28 ± 0.04	3.48 ± 0.06 [a]	3.36 ± 0.04 [b]
NCV of motor nerve fibers, m/s	50.67 ± 0.50	50.41 ± 0.54	49.36 ± 0.49	49.25 ± 0.53	48.92 ± 0.49	46.81 ± 0.70 [a, c]	48.60 ± 0.70

Notes: [a] difference is significant compared to group I before PCT, $p < 0.05$; [b] difference is significant compared to group II before PCT, $p < 0.05$; [c] difference is significant compared to group I after 3 cycles of PCT, $p < 0.05$; [d] difference is significant compared to group II after 3 cycles of PCT, $p < 0.05$; [e] difference is significant compared to group I after 6 cycles of PCT, $p < 0.05$.

Table 2. **ENMG indicators of fibular nerve function in patients with BCa**

ENMG indicators	ENMG values (M ± m)						
	PHI n = 30	Group I before PCT n = 50	Group II before PCT n = 50	Group I after 3 PCT cycles n = 50	Group II after 3 PCT cycles n = 50	Group I after 6 PCT cycles n = 39	Group II after 6 PCT cycles n = 36
Amplitude of M-response to nerve stimulation at the distal point, mV	6.65 ± 0.17	6.78 ± 0.14	6.85 ± 0.12	5.66 ± 0.16 [a]	5.97 ± 0.13 [b]	4.62 ± 0,21 [a, c]	5.36 ± 0,18 [b, d, e]
Amplitude of M-response to nerve stimulation at the proximal point, mV	6.85 ± 0.16	6.89 ± 0.13	7.00 ± 0.16	6.00 ± 0.14 [a]	6.25 ± 0.11 [b]	5.05 ± 0.18 [a, c]	5.65 ± 0.13 [b, d, e]
Duration of M-response to nerve stimulation at the distal point, ms	5.62 ± 0.20	5.65 ± 0.16	5.80 ± 0.19	4.89 ± 0.14 [a]	5.14 ± 0.16 [b]	4.21 ± 0.17 [a, c]	4.75 ± 0.14 [b, e]
Duration of M-response to nerve stimulation at the proximal point, ms	5.84 ± 0.19	5.93 ± 0.17	6.03 ± 0.17	5.08 ± 0.13 [a]	5.40 ± 0.17 [b]	4.39 ± 0.16 [a, c]	5.00 ± 0.15 [b, e]
Area of M-response to nerve stimulation at the distal point, mV×ms	15.53 ± 0.45	15.68 ± 0.39	15.90 ± 0.34	13.42 ± 0.47 [a]	14.57 ± 0.42 [b]	11.34 ± 0.56 [a, c]	12.90 ± 0.58 [b, d]
Area of M-response to nerve stimulation at the proximaal point, mV×ms	16.00 ± 0.62	16.15 ± 0.41	16.17 ± 0.45	13.78 ± 0.43 [a]	14.54 ± 0.46 [b]	11.68 ± 0.50 [a, c]	13.38 ± 0.59 [b, d]
Residual latency, ms	1.18 ± 0.06	1.23 ± 0.04	1.17 ± 0.04	1.31 ± 0.04	1.27 ± 0.05	1.42 ± 0.05 [a]	1.34 ± 0.05 [b]
Terminal latency, ms	2.80 ± 0.04	2.84 ± 0.04	2.82 ± 0.04	3.03 ± 0.04 [a]	2.94 ± 0.04 [b]	3.21 ± 0.04 [a, c]	3.08 ± 0.05 [b, d]
NCV of motor nerve fibers, s	52.88 ± 0.60	53.02 ± 0.55	51.69 ± 0.52	49.55 ± 0.57 [a]	51.21 ± 0.71	48.03 ± 0.64 [a]	49.65 ± 0.67 [b]

Notes: [a] difference is significant compared group I before PCT, $p < 0.05$; [b] difference is significant compared to group I before PCT, $p < 0.05$; [c] difference is significant compared to group I after 3 cycles of PCT, $p < 0.05$; [d] difference is significant compared to group II after 3 cycles of PCT, $p < 0.05$; [e] difference is significant compared to group I after 6 cycles of PCT, $p < 0.05$.

The disruption of intrasynaptic conduction during chemotherapy with neurotoxic agents has been demonstrated in numerous experimental studies. For this reason, phenylpyrimidine compounds, such as acetylcholinesterase inhibitors, which are used to treat Alzheimer's disease and dementia, namely donepezil, galantamine, and tacrine, are considered potential agents for use in CIPN [19]. Acetylcholinesterase inhibitors have been reported to have a good safety profile in humans, and preclinical studies have provided initial evidence of their efficacy in reducing neurological manifestations, including tactile allodynia and associated comorbid conditions, in in vivo models of oxaliplatin-induced peripheral neuropathy [20—22].

Earlier, we have demonstrated the efficacy of ALA and IPD in preventing PIPN in patients with BCa using the Total Neuropathy Score, which included the motor nerve electromyography (EMG) parameters. The results suggested that minor or no change in the total motor nerve action potential amplitude in combination with severe symptoms of motor dysfunction and muscle weakness indicates an idiosyncratic nature of these disorders [23].

Our results of ENMG of motor nerves in patients with BCa are consistent with the data of study [24] showing that in patients with BCa, ovarian, and non-small cell lung cancer treated with docetaxel or paclitaxel, symptoms or signs of sensory neuropathy developed in 100% of cases. The muscle weakness developed in 12% patients from the docetaxel group and in 100% patients from the paclitaxel group. Symptoms of motor neuropathy varied, i.e., they could appear or disappear at any stage of treatment, regardless of the development of sensory neuropathy. However, ENMG studies did not show clear changes in the motor nerves of the patients [24].

The lack of a blood-brain barrier in the dorsal root sensory ganglia may explain the selective toxicity of paclitaxel, which mainly affects sensory neurons, while the motor neurons of the anterior horns of the spinal cord remain more protected [25]. Such selectivity may reduce the risk of motor nerve damage, which, in turn, explains the minor changes in motor conduction observed in our study. All mean values of ENMG testing of the tibial and fibular nerves of the patients with BCa remained within the reference range, even after 6 cycles of PCT with paclitaxel. However, the changes detected by ENMG in the motor nerves against the background of paclitaxel use can be characterized as a tendency to axonal damage and mild myelinopathy. This may indicate the clinically significant damage to the motor nerves in patients receiving higher cumulative doses of chemotherapy.

To sum up, we can recommend the use of ALA and IPD for the prevention of PIPN in patients with BCa, since in the patients of group II after 6 cycles of PCT with paclitaxel, higher M-response values of the studied nerves were observed, which indicate a better condition of the axon.

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ПРОФІЛАКТИКА ВИКЛИКАНОЇ ПАКЛІТАКСЕЛОМ МОТОРНОЇ НЕЙРОПАТІЇ МАЛОГОМІЛКОВИХ ТА ВЕЛИКОГОМІЛКОВИХ НЕРВІВ ЗА ДОПОМОГОЮ АЛЬФА-ЛІПОЄВОЇ КИСЛОТИ ТА ІПІДАКРИНУ ГІДРОХЛОРИДУ У ХВОРИХ НА РАК МОЛОЧНОЇ ЗАЛОЗИ

Мета. Дослідити нейрофункціональні параметри моторних нервів хворих на рак молочної залози (РМЗ) із паклітаксел-індукованою периферичною нейропатією (ПІПН) та з'ясувати доцільність застосування альфаліпоєвої кислоти (АЛК) в комбінації з іпідакрином гідрохлориду (ІГХ) для її профілактики. **Матеріали та ме-**

тоди. У дослідження включено 100 хворих на РМЗ II-IV стадій, яким була показана поліхіміотерапія (ПХТ) за схемою АТ (паклітаксел, доксорубіцин) або ЕТ (паклітаксел, епірубіцин) у неоад'ювантному, ад'ювантному або паліативному режимі. Пацієнтів рандомізовано у дві групи (n = 50 у кожній): група I отримувала тільки ПХТ; група II — ПХТ в поєднанні з досліджуваними препаратами профілактики ПІПН (АЛК в комбінації з ІГХ). Проводили електронейроміографічне (ЕНМГ) дослідження моторних малогомілкових та великогомілкових нервів до початку хіміотерапії, а також після 3-го і 6-го циклів ПХТ**. Результати.** Порівняння показників ЕНМГ моторних нервів нижніх кінцівок хворих на РМЗ до початку ПХТ з показниками після 3-ох та 6-ти циклів вказало на незначно виражене, але достовірне зниження М-відповіді та часткове швидкості проведення збудження (ШПЗ), яке прогресувало зі збільшенням кумулятивної дози паклітакселу. Попри це, середні значення ЕНМГ показників залишались у межах норми навіть після 6 циклів ПХТ. Таким чином, виявлені зміни свідчать про тенденцію до аксонального ураження та маловираженої мієлінопатії. Встановлено достовірно вищі показники М-відповіді моторних нервів у пацієнтів II-ої групи в порівнянні з даними I-ої групи, однак тільки після 6-ти циклів ПХТ з паклітакселом, що вказувало на кращий функціональний стан аксону на фоні застосування препаратів АЛК та ІГХ. **Висновок.** Застосування АЛК та ІГХ покращує функціональний стан аксонів у пацієнтів з РМЗ, які отримували паклітаксел.

Ключові слова: паклітаксел, хіміотерапія, моторна нейропатія, електронейроміографія, альфа-ліпоєва кислота, інгібітори ацетилхолінестерази.