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CLINICAL SIGNS OF CHEMOTHERAPY-INDUCED NEUROPATHY IN CANCER PATIENTS AND PHARMACOTHERAPY CORRECTION OPTIONS

Abstract

The objective of the study was to analyze the clinical signs of chemotherapy-induced neuropathy (CIPN) in cancer patients and explore pharmacotherapy correction options using vitamin B supplements. **Materials and methods.** During the first stage that lasted from May to September 2017 after the screening period, 219 patients (mean age of (50.4 ± 6.9) years) were selected for the study; 105 (46.7%) of them were female patients undergoing chemotherapy treatment cycles at Samara Regional Oncological Clinic. The methods of standard neurological examination and patient questioning established clinical signs of polyneuropathy: its localization, the main manifestations, including sensory and/or pain disorders. The patients were further randomized into two groups: group 1 received vitamin B supplements, and group 2 received no vitamin B supplements. The patients were observed for 60 days. **Results.** The incidence of polyneuropathy in oncology patients receiving chemotherapy turns out to be very high. The phenotype of clinical signs and their severity and localization is probably related to the type of the drug agent used. Our study demonstrated the effectiveness of the use of step-by-step therapy with group B supplements in order to reduce the clinical manifestations of polyneuropathy.

Key words: *polyneuropathy, chemotherapy, oncology*

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VAS — visual analog scale, QOL — Quality of Life, BMI — Body Mass Index, ICD-10 — International Classification of Diseases, 10th Edition, MP — medicinal preparation, FOLFOX — folinic acid / 5-fluorouracil/oxaliplatin, SD — standard deviation

Recently, the issue of the complications that cancer patients face who are either undergoing or have completed chemotherapy cycles has become extremely pressing for specialists of outpatient clinics. The number of cancer patients being treated with chemotherapeutic drugs is rising due to their high therapeutic effectiveness and survival rate. However, this type of treatment increases the risks of acute and delayed side effects, including damage to the peripheral nervous system in the form of polyneuropathies.

To date, this problem has not been the focus of attention of oncologists. Rather, it has been more widely studied by specialists in internal medicine (neurologists, therapists, general practitioners) who perform follow-up patient monitoring on an outpatient basis. The polyneuropathy induced by chemotherapeutic drugs leads to a deterioration in the quality of life (QOL) of cancer patients, causing them severe limitations of motor and sensory functions in the upper and lower extremities [1–4]. It is currently known that polyneuropathy develops in

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almost 90 % of patients of this category, and subsequently more than 30 % of patients exhibit some symptoms of damage to peripheral nerve fibers after completion of the treatment [5].

The development of polyneuropathy with clinical manifestations is described as one of the side effects in the product label of the following most commonly used chemotherapeutic drugs: platinum-based (cisplatin, carboplatin and oxaliplatin), bortezomib, taxanes, vinca alkaloids (vincristine), thalidomide, and lenalidomide [6–11]. This prompts the need to discuss a number of issues related to the development of new MP without possible pronounced side effects and the introduction of preventive strategies aimed at reducing the risk of polyneuropathy. The decrease in clinical manifestations of polyneuropathy not only improves the QOL of cancer patients, but it also increases their survival rate [12]. The follow-up of such patients requires knowledge of algorithms for early diagnosis of the peripheral nervous system damage and opportunities to administer medication therapy to minimize its manifestations.

The objective of our study is to investigate the clinical manifestations of polyneuropathy in cancer patients who are undergoing chemotherapy and the ability to treat them with vitamin B supplements.

Materials and methods

The study was registered as a monitoring program, "Polyneuropathy: risks of early and late complications of chemotherapy in cancer patients (**POSEIDON**)", was conducted in two stages. (The acronym POSEIDON is based on the original Russian wording for the procedure.)

During the first stage that lasted from May to September 2017 after the screening period, 219 patients (mean age of (50.4 ± 6.9) years) were selected for the study through the method of sequential inclusion, of which 105 (46.7 %) were female patients undergoing chemotherapy at the State Budgetary Healthcare Institution Samara Regional Clinical Oncology Dispensary (SBHI SRCOD). Patients were divided into the following groups by the localization of the tumor: 52 patients (the 1st group) with colon cancer (C18.9), 94 patients (the 2nd group) with breast cancer (C50.0), 52 patients (the 3rd group) with lung cancer (C34.0), and 21 patients (the 4th group) with prostate cancer (C61.0). The inclusion criteria were the following: 1. A verified cancer that was not older than 12 months; 2. Chemotherapy treatment. The exclusion criteria were the following: 1. The history of polyneuropathy before the chemotherapy cycle initiation; 2. The patients' written refusal to participate in the study. The methods of standard neurological examination and patient questioning established clinical signs of polyneuropathy: its localization, the main manifestations, including sensory and/or pain disorders.

During the second stage, a subanalysis of patients with three or more clinical manifestations of polyneuropathy was performed. The patients were further randomized into two groups using the sealed envelopes method in accordance with the following pharmacotherapy procedures: in the 1st group (main, n = 30) patients received vitamin B supplements, and in the 2nd group (comparison, n = 30) this medicinal therapy was not administered. The duration of the second stage was 60 days, and during this period three visits (V) were performed, of which V_1–V_2 during the period of therapy with vitamin B supplements (for the main group of patients), and V_3 — during the control period. According to the protocol, the time of visits was determined as follows: V_1 — initially, when included in the study and the therapy started, V_2 — after 31 days, and V_3 — after 60 days. For patients in the 1st group, intramuscular injection of a combined MP containing vitamins B_1, B_6, B_{12} was chosen as a therapy regimen for 10 days, and then they were orally administered for 3 weeks. It should be noted that patients were not prescribed analgesics, anticonvulsants or antidepressants to reduce manifestations of polyneuropathy. This step in the study was undertaken in order to exclude the influence of other MP on the symptoms of polyneuropathy. At all visits, the severity of the studied clinical manifestations of polyneuropathy was assessed using a visual analog scale (VAS) in centimeters. Within the V_1, before prescribing group B vitamins, the patients were thoroughly familiarized with the design of the study in a step-by-step fashion, and they were informed about all possible side effects. Patients signed an informed consent to the

use and processing of their personal data and to the participating in the study. In addition, all patients were informed that at any moment they could abandon the study for any reason.

Statistical analysis of the obtained data was performed using the IBM SPSS Statistics 21 software package (License No. 20130626-3). In order to compare independent groups, a one-way analysis of variance (one-way ANOVA) was used. In cases of deviation from the zero-hypothesis of equality of means, post hoc analyses (group comparisons in pairs) were performed in accordance with Tukey's test. The description of normally distributed quantitative features is given, including indication of the mean value of the feature and the standard deviation ($M \pm SD$). Descriptive statistics were used using the parametric criterion (Student's t-test) to perform the analysis. The median, upper (25th) and lower (75th) quartiles — Me (Q25–Q75) were indicated to describe the characteristics with a different distribution than the normal one. Differences between the studied parameters were considered statistically significant at $p < 0.05$.

The study was performed in accordance with the standards of Good Clinical Practice and principles of the Declaration of Helsinki. The Research Protocol has been approved by the Ethical Committee of the Samara State Medical University.

Results

During the first stage, we performed an analysis of the entire group of patients in accordance with their main clinical and demographic characteristics, which are detailed in Table 1.

The mean duration of the underlying disease was (5.5 ± 3.2) months, during which time (3.8 ± 1.7) cycles of chemotherapy were performed. Polyneuropathy was revealed in 77.2 % of cases, with a mean duration of (2.9 ± 1.8) months. Most patients had distal polyneuropathy with localization in the area of the hands (55.0 %) and feet (42.0 %). Sensory disorders were represented by a variable range of complaints: 89.9 % of cases reported numbness, 52.0 % reported a feeling of tingling, and 40.8 % reported creeping sensation. Neurological examination showed an isolated decrease

Table 1. *Clinical and demographic characteristics of patients at study enrollment*

Characteristics	Whole group, n=225
Age, years	50,5 (42,5–65,0)
BMI, kg/m²	22,5 (20,8–25,6)
Principal Diagnosis (ICD-10)	
Malignant neoplasm of colon (C18.9), n/%	52/23,1
Malignant neoplasm of breast (C50.0), n/%	94/41,8
Malignant neoplasm of lung (C34.0), n/%	52/23,1
Malignant neoplasm of prostate (C61.0), n/%	21/9,3
Duration of underlying disease, months, m±SD	5,5±3,2
Number of chemotherapy cycles, n, m±SD	3,8±1,7
Polyneuropathy, n (%):	169/77,2
Duration, months, m±SD	2,9±1,8
Localization	
Lower limbs, n/%:	
Distal	71/42,0
Proximal	59/34,9
Distal and proximal	25/14,8
Upper limbs, n/%:	
Distal	93/55,0
Proximal	58/34,3
Distal and proximal	25/14,8
Lower and upper limbs, n/%:	30/17,8
Type of sensory impairment, n/%	
Burning pain	36/21,3
Pressing pain	0/0
Shooting pain	23/13,6
Dull pain	52/30,8
Aching pain	3/1,8
Tingling	88/52,0
Burning sensation	60/35,5
Freezing sensation	66/39,0
Sensation similar to electric shock	28/16,6
Creeping sensation	69/40,8
Numbness	152/89,9

Note. Acronyms used in tables 1-3: BMI — body mass index, FOLFOX — folinic acid/5 fluorouracil/oxaliplatin, ICD-10 — International Classification of Diseases, 10th revision, SD — standard deviation.

Table 2. *Polyneuropathy characteristics in groups of patients by tumor localization and chemotherapy agents used*

Characteristics	Group 1 (ICD10 code: C18.9), n=52	Group 2 (ICD10 code: C50.0), n=94	Group 3 (ICD10 code: C34.0), n=52	Group 4 (ICD10 code C61.0), n=21
Age in years	59,7 (57,0-62,5)	47,0 (36,5-51,0)	47,5(42,5-53,0)	61,5(58,0-64,5)
Male, n/%	48/92,3	-	44/84,6	21/100,0
BMI, kg/m^2	22,3 (20,6-23,1)	21,9 (19,5-22,4)	21,8 (20,3-23,4)	21,9 (20,8-23,2)
Duration of underlying disease, m±SD	5,5	5,6	5,8	6,5
Number of chemotherapy cycles, m±SD	3,7	3,3	3,6	2,9
Treatment, n/%				
FOLFOX protocol	52/100	-	-	-
Doxorubicin	-	61/64,9	-	-
Taxotere	-	12/12,8	-	-
Docetaxel	-	2/2,1	-	16/76,2
Paclitaxel	-	19/20,2	12/23,0	-
Cisplatin	-	-	16/30,8	-
Carboplatin	-	-	5/9,6	-
Gemcitabine	-	-	19/36,5	5/23,8
Polyneuropathy, n (%):	51/98,0	59/62,8	40/76,9	19/90,5
Duration, months, m±SD	2,3	2,0	2,2	2,5
Localization				
Lower limbs, n/%:				
Distal	28/53,8	6/10,0	19/47,5	18/94,7
Proximal	22/42,3	8/13,3	8/20,0	10/52,6
Distal and proximal	14/26,9	1/1,7	6/15,0	6/31,5
Upper limbs, n/%:				
Distal	47/90,4	33/55,0	12/30,0	1/5,3
Proximal	9/17,3	36/60,0	13/32,5	1/5,3
Distal and proximal	8/15,4	10/16,7	6/15,0	1/5,3
Clinical signs of peripheral neuropathy, n/%				
Burning pain	23/44,2	13/21,7	-	-
Pressing pain	-	-	-	-
Shooting pain	22/42,3	1/1,7	-	-
Dull pain	24/46,1	15/25,0	-	13/68,4
Aching pain	-	3/5,0	-	-
Tingling	27/51,9	30/50,5	24/60,0	7/36,8
Burning sensation	23/44,2	-	26/65,0	11/57,8
Freezing sensation	33/63,5	15/25,0	10/25,0	8/42,1
Sensation similar to electric shock	13/25,0	2/3,3	6/15,0	7/36,8
Creeping sensation	23/44,2	36/60,0	10/25,0	-
Numbness	52/100,0	47/78,3	37/92,5	16/84,2

in superficial sensitivity in the lower extremities in 99 patients (45.2 %), and 155 patients (70.8 %) reported this symptom in combination with manifestations in the hands.

At this stage, we examined the manifestations of polyneuropathy presented in the Table 2 in detail depending on the localization of the tumor while aiming to clarify the relationship with chemotherapy regimens, which is important to understanding the features of the patient's phenotype.

Patients in all groups did not have statistically significant differences in BMI, duration of the disease, number of cycles of chemotherapy, and duration of polyneuropathy in comparison by ANOVA. As far as drug therapy is concerned, we found that all patients diagnosed with C18.9 received chemotherapy treatment in accordance with the FOLFOX protocol. Most patients (64.9 %) diagnosed with C50.0 received doxorubicin. Patients diagnosed with C34.0 received the following basic chemotherapeutic drugs: paclitaxel (23.0 %), cisplatin (30.8 %), and gemcitabine (36.5 %), and 76.2 % of those in the group of patients who were diagnosed with C61.0 received docetaxel. In all groups there was a high frequency of occurrence of polyneuropathy, but in patients diagnosed with C50.0 it was significantly lower than in patients diagnosed with C18.9 ($p = 0.029$), C34.0 ($p = 0.041$), and C61.0 ($p = 0.035$).

We noted that each of the studied diseases was characterized by specific features of damage to the peripheral nervous system. Thus, patients diagnosed with C18.9 commonly exhibit signs of polyneuropathy mainly in the distal segments (90.4 %) of the upper extremities. In patients with breast cancer, the phenotype of polyneuropathy is characterized mainly by damage to the upper extremities, both distally and proximally. In patients with lung cancer, the injury of the upper and lower extremities (mainly distally) was recorded without significant differences ($p < 0.05$). A special phenotype is demonstrated by the clinical pattern of patients with prostate cancer, where in 94.7 % of cases distal damage of the lower extremities was present. Therefore, after carrying out this stage of the study, we can conclude that it is most likely that the combination of cancer and the applied chemotherapy regimen determines the patient's phenotype. The clinical pattern of this phenotype is dominated by a particular localization of the peripheral nervous system.

During the second stage of the study, the influence of the pharmacotherapy regimens on the regression of the neurological deficit was studied. The obtained data are presented in the Table 3.

Patients from the 1st and 2nd groups had comparable main clinical and demographic indicators: gender ($p = 0.75$), age ($p = 0.69$), mean duration

Table 3. *Changes in signs of peripheral neuropathy at V1-V3*

Clinical signs of peripheral neuropathy	Study group, n=30/30/25			Control group, n=30/30/26			ANOVA p
	V_1	V_2	V_3	V_1	V_2	V_3	p_1- p_2
1. Tingling sensation, VAS, cm, m±SD	3,8±1,5	3,1±1,1 p_{V1}-p_{V2}=0,047	3,1±1,2 p_{V2}.p_{V3}=0,898 p_{V1}.p_{V3}=0,047	3,6±1,2	4,2±1,5 p_{V1}-p_{V2}=0,046	4,7±1,2 p_{V2}-p_{V3}=0,055 p_{V1}-p_{V3}=0,031	0,562
2. Creeping sensation, VAS, cm, m±SD	4,0±1,1	3,2±0,8 p_{V1}-p_{V2}=0,043	3,1±1,0 p_{V2}-p_{V3}=0,799 p_{V1}-p_{V3}=0,043	3,8±1,0	4,5±1,2 p_{V1}-p_{V2}=0,41	5,1±1,0 p_{V2}-p_{V3}=0,065 p_{V1}-p_{V3}=0,037	0,398
3. Numbness, VAS, cm, m±SD	4,4±1,2	3,6±1,3 p_{V1}-p_{V2}=0,038	3,5±1,4 p_{V2}-p_{V3}=0,681 p_{V1}-p_{V3}=0,037	4,3±1,3	4,5±1,3 p_{V1}-p_{V2}=0,52	4,9±1,2 p_{V2}-p_{V3}=0,056 p_{V1}-p_{V3}=0,033	0,6350
4. Freezing sensation, VAS, cm, m±SD	4,1±1,1	3,5±0,5 p_{V1}-p_{V2}=0,046	3,0±0,5 p_{V2}-p_{V3}=0,09 p_{V1}-p_{V3}=0,054	4,0±1,0	4,7±1,0 p_{V1}-p_{V2}=0,45	5,3±1,0 p_{V2}-p_{V3}=0,052 p_{V1}-p_{V3}=0,021	0,989

Notes: Acronyms: VAS — Visual Analog Scale

of the underlying disease (ρ = 0.092), mean duration of polyneuropathy (ρ = 0.38), as well as the studied clinical manifestations of polyneuropathy. During the follow-up period, we observed the following trend: a significant improvement in all the symptoms studied in the group of patients taking vitamins with a decrease in numbness as well as a subsidence of the painful sensation of cold, tingling, creeping sensation during V_3. At the same time, in the comparison group, an increase in all studied clinical symptoms was observed during V_2 with an increase in the VAS score, including during V_3.

Discussion

To date, most researchers working with the problem of polyneuropathy induced by chemotherapy in cancer patients note, first of all, its negative impact on QOL, limiting the patient's performance of everyday household functions while experiencing severe pain, numbness, and convulsions in the upper and/or lower extremities at the same time [13–15]. Our observations show that the number of patients experiencing acute and painful sensations is highly significant among all patients receiving chemotherapeutic drugs, regardless of the tumor localization. At the same time, the symptoms of polyneuropathy are extremely variable, which is due to the individual response of nerve fibers to the damaging effects of chemotherapy. Nevertheless, the main manifestations of polyneuropathy were represented by sensory disorders and pain sensations of a neuropathic nature. According to our data, the majority of patients have presented complaints that are consistent with damage to sensory fibers, including numbness and burning that is generally symmetrical. It is known that the symptoms of polyneuropathy, in some cases, may have a tendency to spontaneously subside after the completion of chemotherapy. However, in a number of cases, the symptoms increase and worsen [16]. This is especially true when the patient is taking such drugs as paclitaxel and thalidomide [17–19]. In our study, patients with breast and lung cancer who received paclitaxel reported acute symptoms of damage to the peripheral nerve fiber with a subsequent deterioration on the VAS in the 2nd group of patients. It was discovered that in the patients with colorectal cancer under the FOLFOX regimen, there is an extremely high incidence (from 70 to 90 %) of symptoms reflecting peripheral nerve fiber damage [20]. Our data also demonstrate the high incidence of polyneuropathy in this category of patients with predominant distal damage of the upper extremities. Moreover, it was noted that in patients undergoing chemotherapy cycles within the FOLFOX regimen, the appearance of a sensory deficit in the upper and lower extremities was noted quite early, starting from the initial courses of treatment. This result is also consistent with the results of previous studies [20]. The results of our study coincide with the data of a number of authors, which associate specifically oxaliplatin administration with the early onset of polyneuropathies, distal dysesthesia, allodynia, and burning pains.

In general, it can be said that manifestations of polyneuropathy in patients receiving chemotherapeutic drugs vary significantly, both in the severity of symptoms and in duration [21–23]. We noted significant differences in the manifestation of qualitative and quantitative characteristics of polyneuropathy with their level of variation in each patient, which is also reflected in the works of other authors [24]. The results of our study prove that the chemotherapy-induced polyneuropathy has a number of phenotypic features.

The second stage of the study was undertaken to directly study the possibility of correcting chemotherapy-induced disorders. According to the publications, methods to treat polyneuropathy induced in cancer patients by chemotherapy have not been sufficiently developed. Despite the fact that a considerable number of observations of such patients has been accumulated, the data on effective regimens for the treatment of polyneuropathy are limited and contradictory [25]. This may be due to the fact that each MP damages the peripheral nerve tissue in its own way, and may also be related to the individual characteristics of the patient. Vitamin B supplements have been proven to be highly effective in clinical practice for the treatment of polyneuropathies, including those primarily of diabetic and alcoholic origin. Few studies on the use and treatment results of this class of drugs in patients with chemotherapy have been conducted. The functional significance of vitamin B for human health is known and has been well studied. The

basic metabolic processes, the synthesis of neurotransmitters, and the activation of enzymatic processes are impossible in the central and peripheral nervous system without vitamin B complex. Deficiency of B_1, B_6 is directly associated with nervous dysfunction and nerve damage [26, 27]. The most significant connection is to vitamin B_{12} deficiency. Thus, the study presented by Soloman L. in 2016 demonstrated the association of peripheral neuropathy and neuropathic pain development in patients with a history of cancer [28]. Recent studies have shown that for patients undergoing chemotherapy, vitamin B_{12} deficiency rapidly increases during a short time from the start of treatment [29]. We have confirmed that patients receiving chemotherapy experience the following positive change: a decrease in manifestations of polyneuropathy while undergoing therapy with group B supplements followed by a sustained effect for two months. While in the comparison group there was a statistically significant increase in all studied clinical symptoms of polyneuropathy during V_2–V_3. In the absence of timely therapy, manifested sensory and painful disorders in the extremities were observed in patients in the 2nd group with delay, which indicated an increase in damage to the peripheral nervous system.

Further studies aimed at discovering the effective doses and therapy regimens for vitamin B supplements are underway. Nonetheless, we already possess the data on both meta-analyses and individual studies on the effectiveness of vitamin therapy in this group of patients. For example, the authors of the recently published review note that the vitamins B_3, B_6 and B_{12} demonstrate potential for helping patients to protect themselves from the development of polyneuropathy, and they indicate that further research is required [30]. Our observations represent an attempt not only to clarify the prevalence, localization, and variability of clinical manifestations of polyneuropathies in patients receiving chemotherapy, but they also indicate that vitamin B complex administration may have a positive clinical effect.

Conclusion

We recognize that our study has had some limitations due to the small sample group of patients. However, we found that the incidence of polyneuropathy among cancer patients receiving chemotherapy is extremely high. The phenotype of clinical manifestations and the severity of their symptoms and localization are probably determined by the used MP. When such patients are followed-up by a doctor at the outpatient stage of treatment, it is necessary to focus on the need for the use of pathogenetic therapy aimed at restoring the function of peripheral nerves. Our study demonstrated the effectiveness of the use of step-by-step therapy with group B supplements in order to reduce the clinical manifestations of polyneuropathy. The obtained data confirm that the problem is topical. It requires further study with a larger sample group of patients over a longer period of time. A study of such scope would allow us to make conclusions that would be valid for the general population about the early and late manifestations of polyneuropathy.

Conflict of interests

The authors declare no conflict of interests.

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ИНФОРМАЦИОННОЕ ПИСЬМО

Главное военно-медицинское управление МО РФ;
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Научно-практическое общество баротерапевтов
Санкт-Петербурга и Ленинградской области

17 — 18 мая 2018 года проводят

Юбилейную X Всеармейскую научно-практическую конференцию «БАРОТЕРАПИЯ В КОМПЛЕКСНОМ ЛЕЧЕНИИ И РЕАБИЛИТАЦИИ РАНЕНЫХ, БОЛЬНЫХ И ПОРАЖЁННЫХ»

Конференция состоится в Военно-медицинской академии имени С.М. Кирова по адресу: 194044, Санкт-Петербург, Военно-медицинская академия имени С.М. Кирова, ул. Академика Лебедева, д. 6. Проезд до станции метро «Площадь Ленина».

На конференции предполагается рассмотреть теоретические и прикладные вопросы лечения раненых, больных и пораженных; проблемы реабилитации человека со сниженной работоспособностью различными видами и методами баротерапии; теоретические и практические положения гипербарической физиологии и водолазной медицины.

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Военно-медицинская академия имени С.М. Кирова, Санкт-Петербург
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В исследовании по проблеме оптимальной дозы кислорода при гипербарической оксигенации принимали участие 88 практически здоровых мужчин в возрасте 24-34 лет...

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При ***необходимости*** в марте-апреле 2018 г. в адрес участников конференции будут направлены **Приглашения.**

Для участников конференции 18 мая планируется культурная программа.

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