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Original Scientific Paper

IMPACT OF CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY ON THE QUALITY OF LIFE IN CANCER PATIENTS

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SUMMARY – The aim of the study was to investigate the correlation between chemotherapy-induced peripheral neuropathy (CIPN) and quality of life, as well as to establish whether there was a difference in peripheral neuropathy symptoms and their effect on the quality of life depending on the type of agents applied. The study encompassed 156 patients treated at the Department of Oncology from March to May 2017. Data were collected through self-reported questionnaires issued by the European Organization for Research and Treatment of Cancer (EORTC QLQ-C30) and by Chemotherapy-Induced Peripheral Neuropathy module (CIPN20). The results showed sensory and motor neuropathy to be statistically significantly correlated with the general quality of life variables of pain, tiredness, diarrhea, insomnia and breathing difficulty. Oxaliplatin had a significantly greater effect on the onset of motor and sensory neuropathy than taxane and cisplatin/carboplatin. Nursing interventions based on specific characteristics of certain chemotherapeutic agents should be developed for CIPN alleviation.

Key words: *Cancer; Oncology; Nursing; Neuropathy; Oxaliplatin; Taxane; Cisplatin*

Introduction

The progress made in the treatment of malignant diseases in recent years and the implementation of early detection programs have contributed to the prolonged life of patients suffering from malignant diseases. Consequently, cancer has become a chronic disease requiring long-term treatment. The main goal of cancer treatment as a chronic illness is to optimally exploit the possibilities for sustained survival while maximizing the quality of life[1,2]. Many chemotherapeutic agents are neurotoxic, and neuropathy may be a limiting factor for the use of chemotherapy[3]. The incidence of chemotherapy-induced peripheral neuropathy (CIPN) is 30%-40%[4]. CIPN most commonly manifests itself as pure sensory neuropathy with symmetric symptoms typically including numbness, loss of proprioceptive sense, tingling, pins and needles sensation, hyperalgesia or allodynia in the hands or feet in a stocking-glove distribution[5]. The commonly used chemotherapeutic agents causing CIPN include taxanes (paclitaxel, docetaxel) and platinum compounds (cisplatin, carboplatin, oxaliplatin).

Cisplatin causes decay of neurons in dorsal sensory ganglia and degeneration of thick sensory fibers. Damage depends on the dose. Neuropathy develops in 60% of patients with cumulative doses[6] of 225-500 mg/m^2.

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Cisplatin-induced neuropathy is reversible, but recovery is long-lasting and often incomplete[7]. Carboplatin is a less neurotoxic drug than cisplatin, but in extremely high doses (600 mg/m^2) it causes sensory neuropathy similar to that caused by cisplatin[6].

Shortly after application, oxaliplatin can induce acute pain sensory neuropathy in over 90% of patients[3]. The chronic form of peripheral neuropathy caused by oxaliplatin is induced by morphological and functional changes in dorsal ganglia neurons, which are due to the deposition and accumulation of oxaliplatin[6]. In about 35% of patients, the presence of toxic oxaliplatin-induced neuropathy was found even 5 to 6 years after treatment discontinuation[8,9].

Paclitaxel-induced neuropathy is frequently manifested as sensory neuropathy. In the case of high doses of taxane, apart from sensory symptoms, development of motor symptoms can occur in the form of weakness of proximal musculature[7,10]. Apart from specific chemotherapeutic agents, their doses *per* application, cumulative doses, as well as the duration of treatment, neuropathy may be provoked by other factors such as age, alcoholic beverage consumption, use of other neurotoxic drugs, and simultaneous presence of other diseases such as hypertension, chronic kidney disease and diabetes mellitus[3]. A study of the life quality related to CIPN after treatment with platinum- and taxane-based drugs showed very little impact on sensory, motor and autonomic scales. However, motor scale items were rated lower than those concerning sensory functioning[11].

Although most studies pointed to the correlation between CIPN and reduced quality of life[12,13], there also were contradictory results[14,15]. Two guidelines, Euro PEP (Putting Evidence into Practice) guidelines by the Oncology Nursing Society to improve health care of oncologic patients and the American Society of Clinical Oncology Clinical Practice Guidelines provide recommendations to improve the management of symptoms in the care of oncologic patients. Important parts of health care include evidence-based interventions to prevent or relieve neuropathic symptoms, injuries, education and support, as well as patient safety[16,17]. However, these guidelines do not include possible fine differences in the appearance of neuropathy in patients treated with various agents. In a recent study, there was a difference in the frequency and intensity of neuropathy symptoms in patients treated with oxaliplatin and docetaxel[18].

In spite of a growing amount of data concerning CIPN, the impact of peripheral neuropathy on the quality of life in patients treated with different chemotherapeutic agents has not yet been sufficiently researched, especially from the point of view of a potential nursing intervention.

Therefore, the aims of this study were to examine the following: association between CIPN and quality of life; whether there is any difference in the effect of the investigated neurotoxic agents on the quality of life in patients with respect to other risk factors; and whether there is a difference in the symptoms of peripheral neuropathy and their impact on the quality of life in patients depending on the type of chemotherapeutic agent.

Patients and Methods

Patients

This quantitative cross-sectional research was conducted at the Department of Oncology, Zagreb University Hospital Center, from March to May 2017. The main criterion for selecting study patients was treatment with a chemotherapeutic agent known for its high potential for peripheral neuropathy occurrence, i.e., taxanes, cisplatin/carboplatin, or oxaliplatin. The sample consisted of 156 patients divided into three groups of 52 patients according to the type of chemotherapeutic agent applied. Group 1 included patients who received cisplatin and carboplatin, group 2 patients treated with oxaliplatin, and group 3 patients treated with taxanes. All study patients were in the process of treatment and they agreed to participate by signing an informed consent form.

Data collection

Data were collected through three questionnaires. The first questionnaire was designed for the purpose of this research with the aim of collecting demographic and patient history data (age, gender, alcohol consumption, chronic kidney disease, diabetes mellitus, hypertension, type and frequency of chemotherapeutic agent applied). The second questionnaire was the European Organization for Research and Treatment of Cancer EORTC QLQ-C30 (Core Quality of Life Questionnaire of the European Organization for Research and Treatment of Cancer) version 3.0 for self-assessment of the quality of life in patients suf-

fering from malignant diseases. The quality of life assessment refers to the seven days preceding the test day. The questionnaire consists of 5 functional scales, overall health status/quality of life scales, and 9 scales of symptoms. All results were converted into a 0-100 scale. Higher results on functional scales indicated better functioning, and more common symptoms on the scales of symptoms. The third questionnaire was an additional module for the evaluation of CIPN, EORTC QLQ-CIPN20 (chemotherapy-induced peripheral neuropathy module) that was administered with the prior approval by EORTC[19,20]. The questionnaire consists of sensory and motor neuropathy scales, autonomic scales for dizziness, blurred vision, and erectile dysfunction. The results obtained were converted into a 0-100 scale, with higher results indicating a higher degree of peripheral neuropathy[21].

Ethical considerations

Prior to the research, it was approved by the Ethics Committee of the Zagreb University Hospital Center (class: 8.1-17/23-2, number: 02/21 AG). All patients were informed on the purpose of the research and signed an informed consent form. The study was conducted in accordance with the Declaration of Helsinki.

Data analysis

Category data are shown as absolute and relative frequencies. Differences in categorical variables among the examined groups were tested by χ^2, and continuous variables by the ANOVA test. Correlations between variables were determined by Pearson correlation coefficient and correlation pair distribution test. On multivariate analysis of parameters collected by questionnaire and independent variables, clinical parameters and their interactions, the ANOVA test with linear model was used. Numerical data were expressed as arithmetic mean and standard deviation. Differences of numeric variables among the three independent groups were tested by ANOVA test with linear regression model. The level of significance was set at α=0.05. All p values were two-sided. Statistical package R was used on statistical analysis[22].

Results

General and clinical characteristics of patients are shown in Table 1. There was no significant difference among the study groups except for gender, alcohol consumption and number of chemotherapy cycles. Men were more represented in the group treated with oxaliplatin and cisplatin/carboplatin, whereas women were predominant in the group treated with taxanes. Hypertension was the most common of the studied risk factors that might contribute to the development of peripheral neuropathy in all three groups.

The distribution of patient answers to the EORTC QLQ-C30 and QLQ-CIPN20 questionnaires according to the Likert scale is shown in Figure 1a,b,c.

The correlation of all variables of the quality of life, peripheral neuropathy, risk factors and types of chemotherapy agents is illustrated in Figure 2. There was a statistically significant positive correlation of sensory and motor neuropathy and dizziness with general quality of life variables of pain, tiredness, diarrhea, insomnia and impaired breathing. The correlation with physical, business, emotional functioning, and general health status was negative.

On multivariate analysis, hypertension had a statistically significant effect on as many as 8 life quality scales, and in combination with the type of chemotherapy agents, it influenced sensory neuropathy (Fig. 3). A greater number of chemotherapy cycles also had a statistically significant effect on sensory neuropathy. On the contrary, alcohol consumption and the presence of renal disease did not have a statistically significant effect on the quality of life scales for peripheral neuropathy.

The effect of oxaliplatin on sensory and motor neuropathy was statistically significantly higher than the effect of taxane and cisplatin/carboplatin. Taxane and cisplatin/carboplatin had a greater effect on motor neuropathy than on sensory neuropathy (Fig. 4).

Discussion

Numerous studies have shown frequent occurrence of peripheral neuropathy in patients treated with cisplatin/carboplatin, oxaliplatin, and taxanes[6,7,9,10]. The aim of this study was to examine the quality of life in patients with CIPN and to determine whether there was a difference in clinical presentation of peripheral neuropathy and its effect on the patient quality of life with regard to the type of chemotherapeutic agent used.

As it had been previously shown that the occurrence and intensity of peripheral neuropathy was of-

ten correlated with the number of cycles administered and the cumulative dose of the agent, as well as the existence of comorbidities (diabetes mellitus, chronic kidney disease, hypertension)[23] and habits such as alcohol consumption[3], we investigated whether there were differences among the study groups with respect to the above mentioned characteristics. In this study, a statistically significant difference in gender distribution was established among the study groups with respect to the agent used. A possible explanation of this finding is the high proportion of women in the taxane group (67.3%), which is most likely due to the fact that taxane is frequently used in the treatment of breast cancer, a disease that is significantly more common in women than in men. Men were more represented in the remaining two groups treated with oxaliplatin and cisplatin/carboplatin because it was about treating malignant diseases, which are more common in males. In addition, there was a statistically significant difference among the study groups in the number of chemotherapy cycles and alcohol consumption. Five and more chemotherapy cycles were administered in 80.7%, 46.1% and 50% of patients treated with oxaliplatin, cisplatin/carboplatin and taxanes, respectively. A greater number of cycles received in the oxaliplatin group could potentially have resulted in more periph-

Table 1. Profile of study patients (N=156)

		Oxaliplatin n (%)	Cisplatin/ carboplatin n (%)	Taxane n (%)	Total n (%)	p*
Gender	Male Female	30 (57.7) 22 (42.3)	36 (69.2) 16 (30.8)	17 (32.7) 35 (67.3)	83 (53.2) 73 (46.8)	**p<0.001**
Age (yrs)	33-44 45-54 55-64 65-74 75-84	2 (3.9) 5 (9.6) 14 (26.9) 23 (44.2) 8 (15.4)	8 (15.4) 10 (19.2) 12 (23.1) 21 (40.4) 1 (1.9)	8 (15.4) 12 (23.1) 11 (21.2) 17 (32.7) 4 (7.7)	18 (11.5) 27 (17.3) 37 (23.2) 61 (39.1) 13 (8.3)	p=0.085
Diabetes mellitus	No Yes	41 (78.8) 11 (21.2)	46 (88.5) 6 (11.5)	46 (88.5) 6 (11.5)	133 (85.3) 23 (14.7)	p=0.279
Hypertension	No Yes	29 (55.8) 23 (44.2)	33 (63.5) 19 (36.5)	31 (59.6) 21 (40.4)	93 (59.6) 63 (40.4)	p=0.726
Chronic renal disease	No Yes	48 (92.3) 4 (7.7)	52 (100.0) 0 (0.0)	49 (94.2) 3 (5.8)	149 (95.5) 7 (4.5)	p=0.143
Alcohol consumption	No Yes	51 (98.1) 1 (1.9)	47 (90.4) 5 (9.6)	52 (100) 0 (0.0)	150 (96.2) 6 (3.8)	**p=0.026**
Treatment cycles	1-4 5-10 >10	10 (19.2) 28 (53.8) 14 (26.9)	28 (53.9) 19 (36.5) 5 (9.6)	26 (50.0) 16 (30.8) 10 (19.2)	64 (40.9) 63 (40.4) 29 (18.6)	**p=0.002**

*χ^2 -test

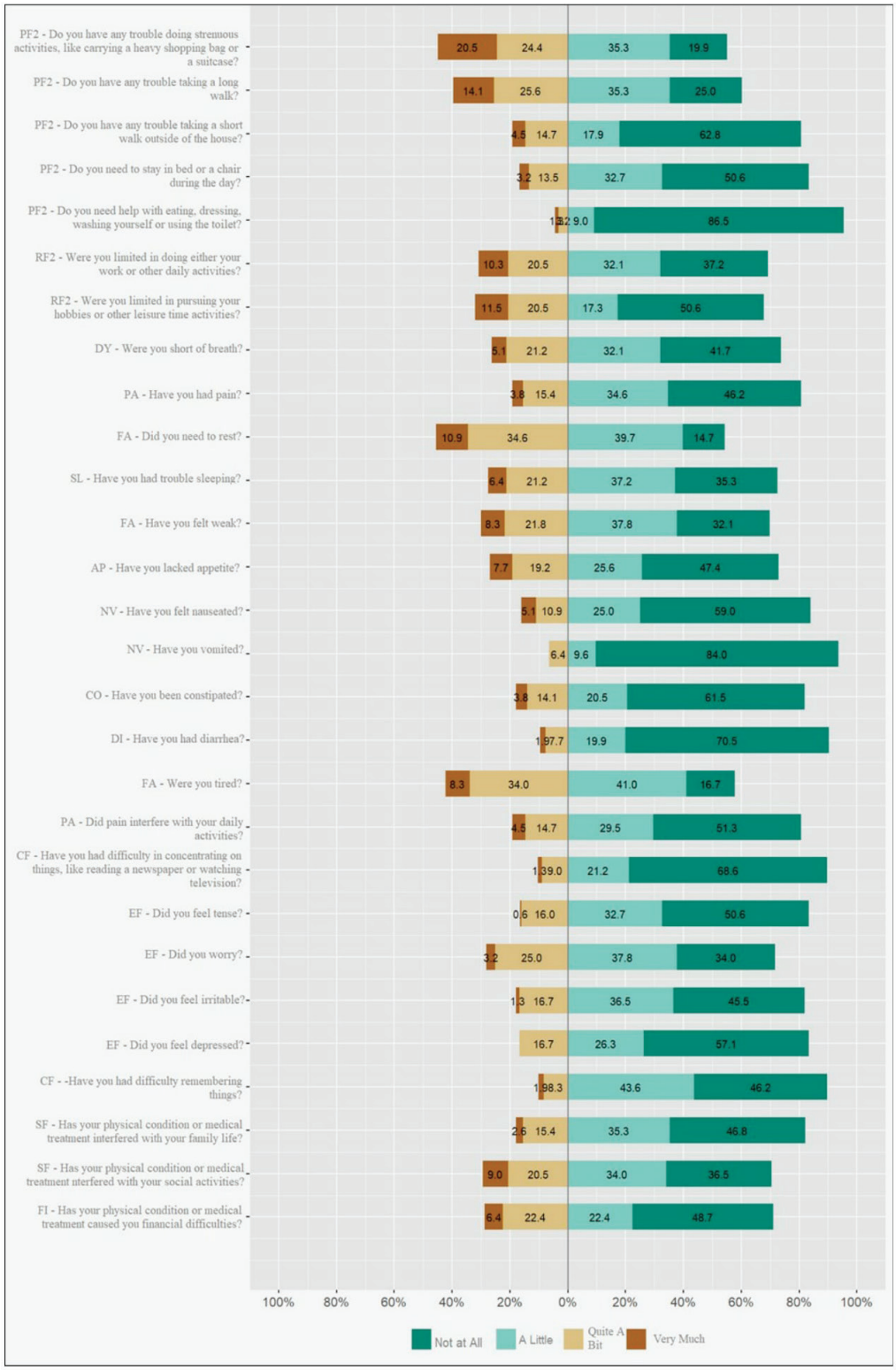

Fig. 1a. Distribution of patient responses to EORTC QLQ-C30 (Core Quality of Life Questionnaire of the European Organization for Research and Treatment of Cancer version 3.0) questions related to functional ability and symptoms.

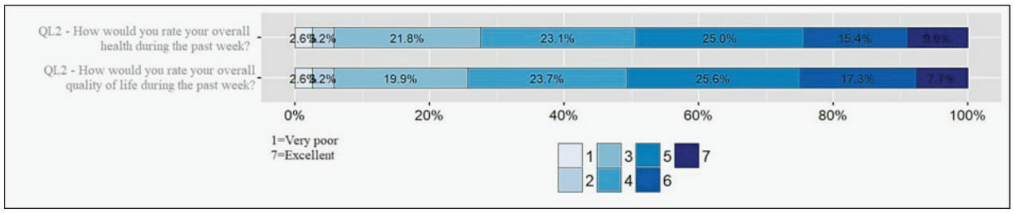

Fig. 1b. Distribution of patient responses to EORTC QLQ-C30 (Core Quality of Life Questionnaire of the European Organization for Research and Treatment of Cancer version 3.0) questions related to global health status.

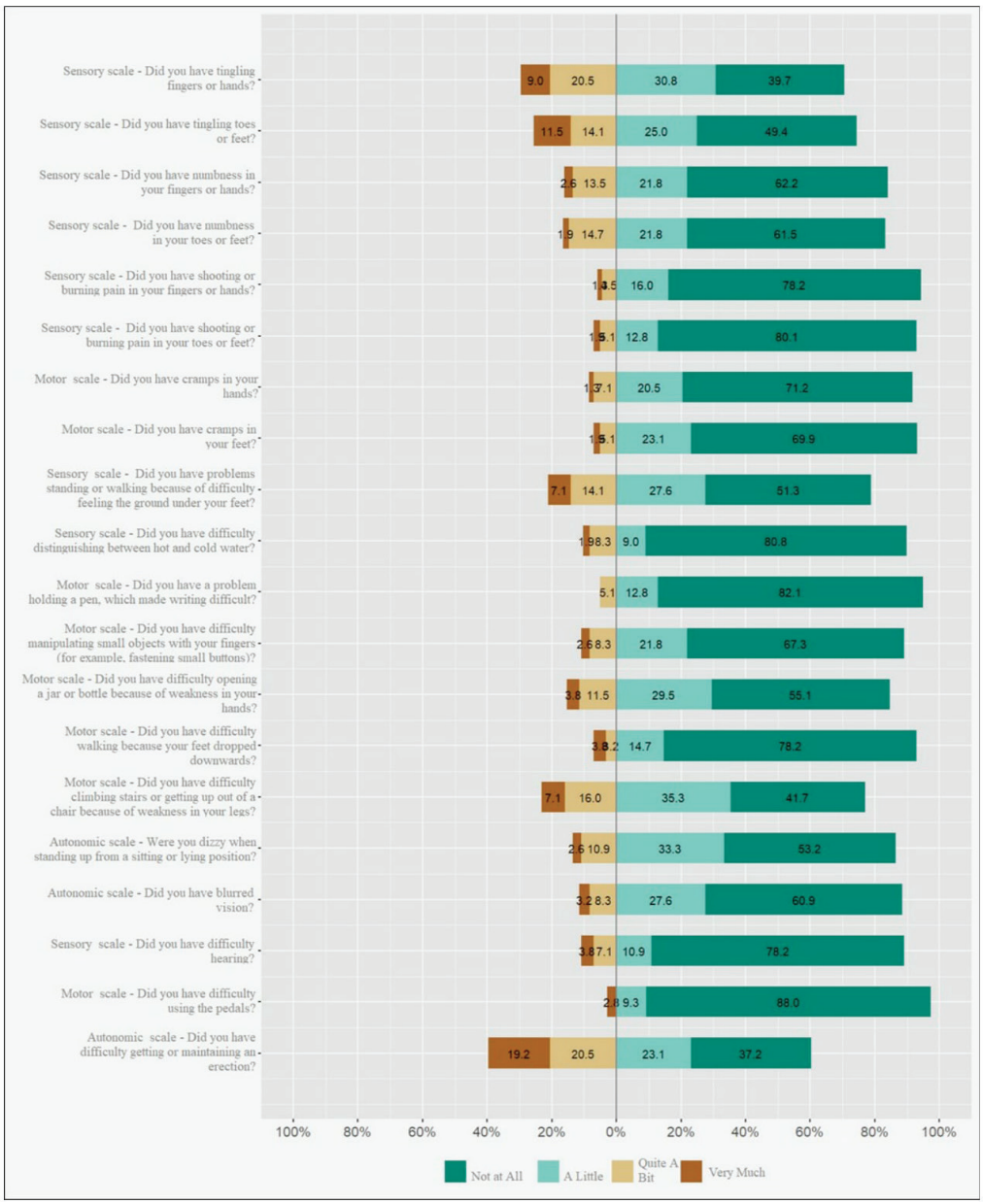

Fig. 1c. Distribution of patient responses to EORTC QLQ-CIPN20 scales (Core Quality of Life Questionnaire of the European Organization for Research and Treatment of Cancer Chemotherapy-Induced Peripheral Neuropathy module 20).

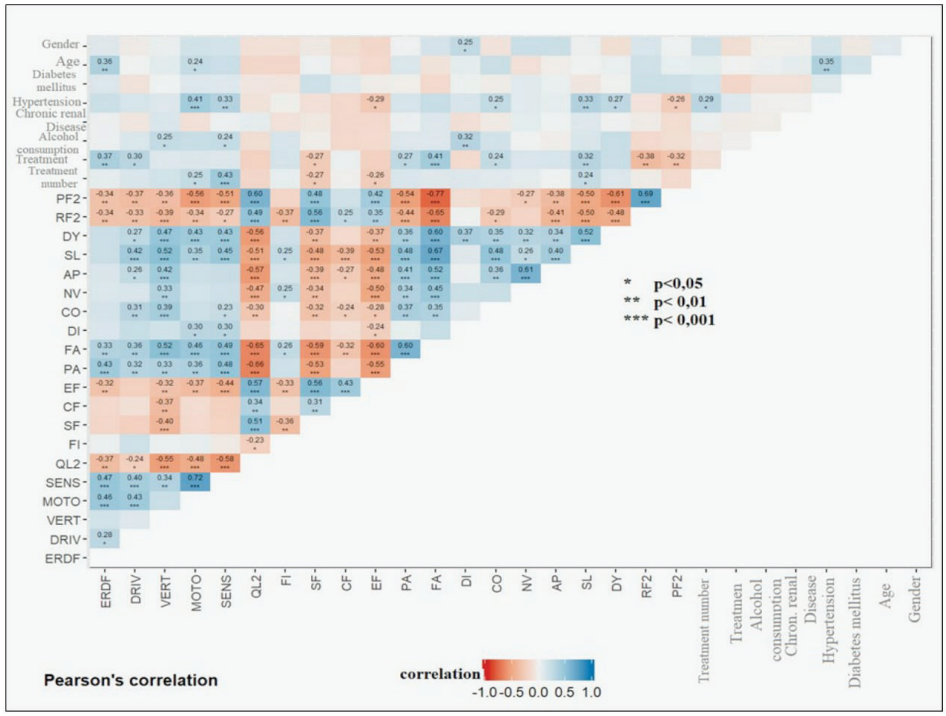

Fig. 2. Pearson's correlation of all items.

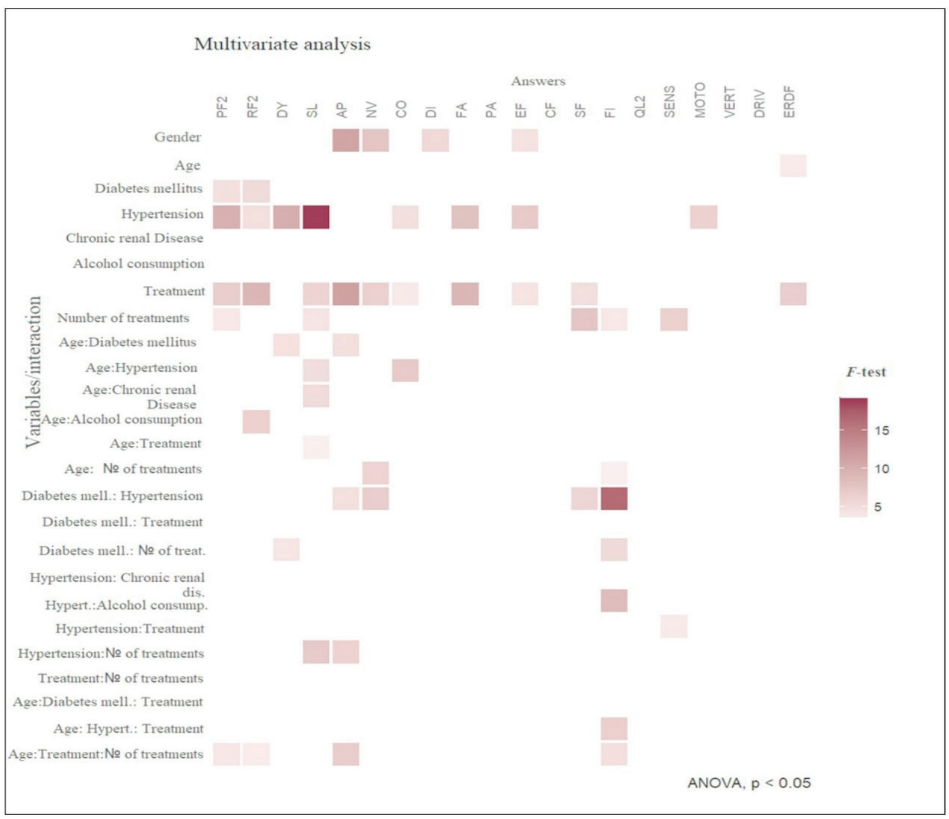

Fig. 3. Multivariate analysis of the effect of patient clinical characteristics on the quality of life.

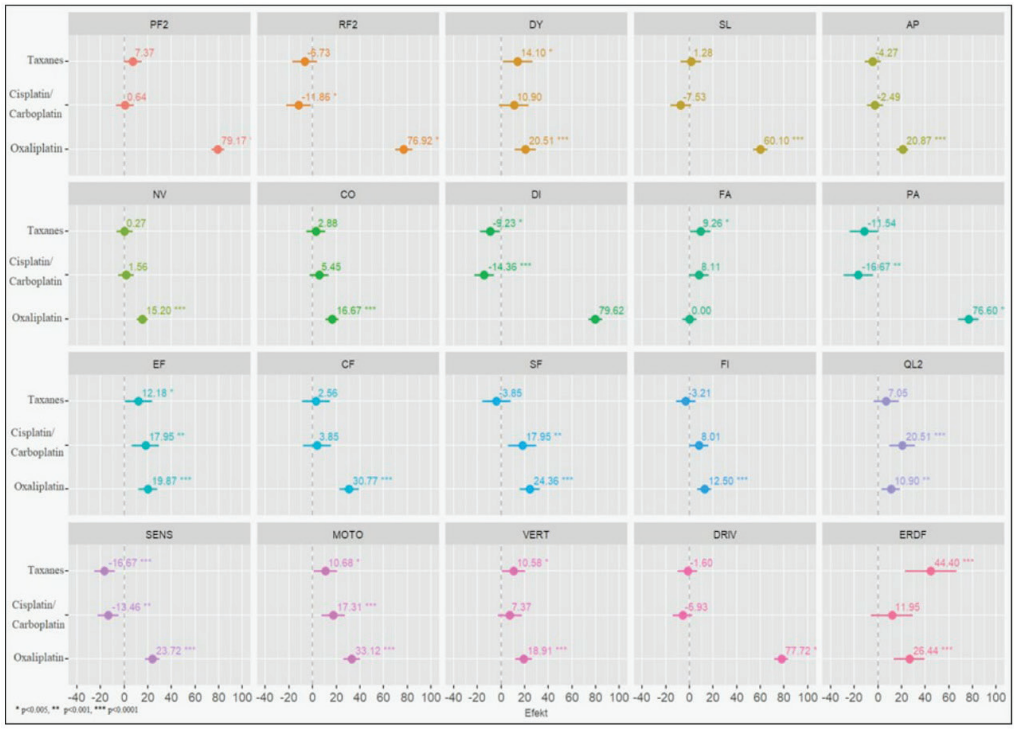

Fig. 4. Effect of different chemotherapeutic agents on the quality of life and peripheral neuropathy.

PF2 = physical functioning; RF2 = role functioning; EF = emotional functioning; CF = cognitive functioning; SF = social functioning; FA = fatigue; NV = nausea and vomiting; PA = pain; DY = dyspnea; SL = insomnia; AP = appetite loss; CO = constipation; DI = diarrhea; FI = financial difficulties; QLQ2 = global health status; SENS = sensory scale; MOTO = motor scale; VERT = dizziness; DRIV = drivers; ERDF = getting and maintaining erection

eral neuropathy, but according to the results of multivariate analysis, the type of chemotherapy agent applied and the number of cycles did not significantly affect the quality of life variables. Alcohol was most consumed in the cisplatin/carboplatin group (10%), but it should be emphasized that alcohol consumption data were based on self-assessment and honesty of the subjects.

This study found a statistically significant positive correlation of sensory and motor neuropathy and vertigo with general quality of life variables of pain, tiredness, diarrhea, insomnia, and breathing difficulty. However, the correlation with physical functioning, role functioning, emotional functioning, and general health status was negative.

The results of the quality of life testing factors in patients treated with chemotherapy in Ankara indicated that fatigue, anxiety, concern for the future and the family, difficulty in meeting basic requirements, and changes in physical image reduced the quality of life. Social support, economic security and faith in recovery improved the quality of life[24].

According to the results of this study, hypertension affected development of sensory neuropathy, while the number of chemotherapy cycles and alcohol consumption were not recognized as significant factors for the emergence of peripheral neuropathy. Hershman *et al.*[25] identified diabetes mellitus with complications as a significant predictor of neurotoxicity. Among our respondents, there were 14% of diabetics and there was no statistically significant effect on the development of neuropathy.

According to a study conducted in oncologic patients in Florida, the most common symptoms were sensitivity to cold, pain, burning and tingling. Peripheral neuropathy mostly affected everyday activities of patients such as walking, catching objects, driving a car, and hobbies[26].

The results of this study showed that oxaliplatin had a greater impact on the occurrence of sensory and motor neuropathy than taxane and cisplatin/carboplatin. This effect was particularly pronounced in sensory neuropathy. Therefore, patients treated with oxaliplatin suffered more the tingling in their hands and feet, felt insecurity on walking, and had more difficulty in distinguishing warm and cold, which is typical for sensory neuropathy.

The results of this study indicated that taxanes had greatest effect on erectile dysfunction, while oxaliplatin had lesser impact, and the effect of cisplatin/carboplatin was not significant. A possible explanation for this result is a small number of male study patients treated with taxanes.

The limitations of this study were patients with different diagnoses, different number of chemotherapy cycles at the time of testing, and an uneven distribution of subjects by gender within the study groups.

Conclusion

Chemotherapy-induced peripheral neuropathy was demonstrated to affect the quality of life of cancer patients in terms of pain, fatigue, diarrhea, insomnia, and breathing difficulty. A significant difference was observed in clinical manifestations of peripheral neuropathy and their effect on the quality of life among patients treated with oxaliplatin, taxanes and cisplatin/carboplatin. The use of oxaliplatin had greatest effect on sensory and motor neuropathy. Although the use of taxane and cisplatin/carboplatin was associated with more motor neuropathy than sensory neuropathy, this effect on motor neuropathy was still less than the effect of oxaliplatin. The knowledge of the symptoms induced by the use of a particular type of chemotherapy agent allows for developing nursing diagnosis, health care goals and specific nursing interventions aimed at facilitating the prevention and/or mitigating the CIPN symptoms.

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Sažetak

UTJECAJ KEMOTERAPIJOM IZAZVANE PERIFERNE NEUROPATIJE NA KVALITETU ŽIVOTA U BOLESNIKA S KARCINOMOM

M. Novak, J. Miličević i *V. Bišof*

Cilj je ovog istraživanja bio ispitati povezanost kemoterapijom izazvane periferne neuropatije (KIPN) i kvalitete života te postoji li razlika u simptomima periferne neuropatije i njihovu utjecaju na kvalitetu života ovisno o vrsti citostatika. Istraživanje je provedeno na 156 odraslih bolesnika na Klinici za onkologiju od ožujka do svibnja 2017. godine. Podatci o kvaliteti života prikupljeni su putem upitnika za samoprocjenu kvalitete života Europske organizacije za istraživanje i liječenje karcinoma (Core Quality of Life Questionnaire of the European Organization for Research and Treatment of Cancer, EORTC QLQ-C30) i putem modula za procjenu KIPN (CIPN20). Rezultati istraživanja su pokazali da su senzorna i motorna neuropatija bile u statistički značajnoj korelaciji s varijablama opće kvalitete života: boli, umorom, proljevom, nesanicom i otežanim disanjem. Oksaliplatin je imao značajno veći utjecaj na pojavu motorne i senzorne neuropatije od taksana i cisplatina/karboplatina. Potrebno je razviti sestrinske intervencije na temelju specifičnih karakteristika pojedinih citostatika radi ublažavanja KIPN.

Ključne riječi: *Karcinom; Onkologija; Sestrinstvo; Neuropatija; Oksaliplatin; Taksan; Cisplatin*