Journal of Current Biomedical Reports
Volume 3, Number 2, 2022
jcbior.com
eISSN: 2717-1906

Original research

The characterization of oxaliplatin-induced peripheral neuropathy using electromyography in gastrointestinal cancer patients

Babak Bakhshayesh Eghbali[1], Sara Ramezani[1], Hamid Saeidi Saedi[2], Nazanin Rahman Amlash[3], Ehsan Kazemnezhad Leili[4], Hamidreza Hatamian[1], Cyrus Emir Alavi[1,*]

[1]*Neuroscience Research Center, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran*
[2]*GI Cancer Screening and Prevention Research Center, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran*
[3]*Student Research Committee, Neuroscience Research Center, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran*
[4]*Road Trauma Research Center, School of Nursing and Midwifery, Guilan University of Medical Sciences, Rasht, Iran*

Abstract

Oxaliplatin-induced peripheral neuropathy (OIPN) is a common dose-dependent chemotherapy complication in gastrointestinal cancer (GIC). This side effect may restrict therapeutic dose elevation of oxaliplatin. Here, OIPN frequency and determinants of neuropathy appearance in oxaliplatin-treated GIC patients. A total of 102 GIC patients who underwent chemotherapy with fluorouracil, folinic acid and oxaliplatin (FOLFOX4) regimen participated in this longitudinal study. Electromyography (EMG) was accomplished for ulnar, radial, sural, peroneal nerves and superficial peroneal nerve (SPN) before, 3, and 6 months after treatment. National Cancer Institute-Common Toxicity Criteria V.3 and clinical version of the Total Neuropathy Score were used for the neuropathy diagnosis at six months after treatment onset. Of all entered patients, twelve people discontinued this study, and five patients passed away. About 85 patients remained three and six months after chemotherapy onset. Approximately 95% of patients three months after chemotherapy demonstrated OIPN manifestations. Finally, data for 81 patients having neuropathy were analyzed. Mean age of patient 64.0±10.9 years. There were about 3.7%, 30.9%, 63% grade III, II, I of neuropathy, respectively. Interestingly, a significant decrease in action potential (AP) amplitude of SPN, sural and radial nerves but not ulnar and peroneal was observed after treatment onset. However, only the ulnar nerve indicated a substantial deceleration of nerve conduction. Age, sex, weight, past medical diseases, smoking and acute neuropathy were not significantly associated with OIPN. The occurrence of OIPN is detectable by electrophysiological changes of SPN, radial, and sural nerves at three and six months after starting chemotherapy with the FOLFOX4 regimen.

Keywords: Oxaliplatin, Neuropathy, Gastrointestinal cancer, Chemotherapy, Electromyography

1. Introduction

Platinum compounds such as cisplatin, carboplatin, and oxaliplatin are among the alkaline agents that limit deoxyribonucleic acid (DNA) synthesis. Cisplatin is used to treat especially metastatic gastrointestinal cancers (GICs) [1-3]. Oxaliplatin is used as a platinum analog and as a major component of a standard chemotherapy approach

[*]**Corresponding author:**
Cyrus Emir Alavi, MD
Neuroscience Research Center, School of Medicine,
Guilan University of Medical Sciences, Rasht, Iran
Tel/Fax: +98 13 33325783/+98 13 33339842
Email: cyrusemiralavi@yahoo.com
https://orcid.org/0000-0003-1664-0822

Received: November, 22, 2021
Accepted: February, 12, 2022

with the composition of fluorouracil, folinic acid and oxaliplatin called FOLFOX4 regimen in a variety of malignancies such as metastatic GIC [4].

Oxaliplatin- induced peripheral neuropathy (OIPN) is one of the most common side effects of the FOLFOX4 regimen that occurs both during and after treatment and interferes with the chemotherapy process [5]. Chemotherapy-induced peripheral neuropathies (CIPNs) including sensory, motor, and autonomic neuropathies are defined as the damage, inflammation, and degeneration of the peripheral nerve caused by chemotherapy [6]. Based on the evidence, patients with CIPN experienced some symptoms such as numbness, tingling, proprioception disorders, pain, and weakness of limbs. Particularly, autonomic manifestations may be represented as some physiological abnormalities consisting of thermoregulation disturbance, blood pressure changes, and intestinal motility disorder and loss of involuntary reflexes [7]. The occurrence of CIPN is dependent on the length of the sensory nerve and can be observed in the axons of myelinated and unmyelinated neural fibers. Evidently, effective factors on the CIPN development include age, dosage, and cumulative dose, and treatment duration, concurrent usage with other neurotoxic chemotherapeutic agents, alcohol consumption and diabetes [7].

It seems that improvement of OIPN symptoms may be begotten very slowly and partially in the majority of FOLFOX4-treated patients. Likewise, restricting the dose increase of oxaliplatin is recommended immediately after OIPN symptoms appear to prevent the stabilization of OIPN manifestations. Accordingly, early diagnosis of OIPN possesses an especial clinical significance [4, 7].

Recently, some studies have shown a direct association of acute neuropathy development with the occurrence and severity of cumulative neurotoxicity [8, 9]. Reducing the dose of oxaliplatin is not an effective approach to decrease the severity of neuropathy because this approach is started when neuropathy has been stabilized. Besides, the detection of acute toxicity may be beneficial for the prediction of neuropathy development. However, there is very little evidence to support a direct link between serum levels of this oxaliplatin and neurotoxicity. Some studies have shown that there is no linear relationship between the blood level of the drug and the possibility of toxicity before cumulative dose occurrence, but after reaching the cumulative dose, the toxicity becomes dose-dependent [10].

Mechanistically, permanent neural transduction in the length of the axon brings about the continuous discharge of voltage-dependent sodium channels, leading to peripheral neuropathy due to platinum compounds [11]. Therefore, early diagnosis of neuropathy before the onset of clinical symptoms via electrodiagnostic test is very helpful [12].

Given the influence of genetic and environmental factors on the OIPN occurrence and severity, it seems that complications of FOLFOX4 may be different in several ethnicities and geographical areas. So far, it has been provided few reports on the OIPN in Iranian GIC patients. Hence, this study aimed to investigate the occurrence and severity of peripheral neuropathy in GIC patients treated with the FOLFOX4 regimen after three and six months of treatment onset. Here, the findings of the electrodiagnostic evaluation for the sensory and motor nerves before and after treatment were compared, as well.

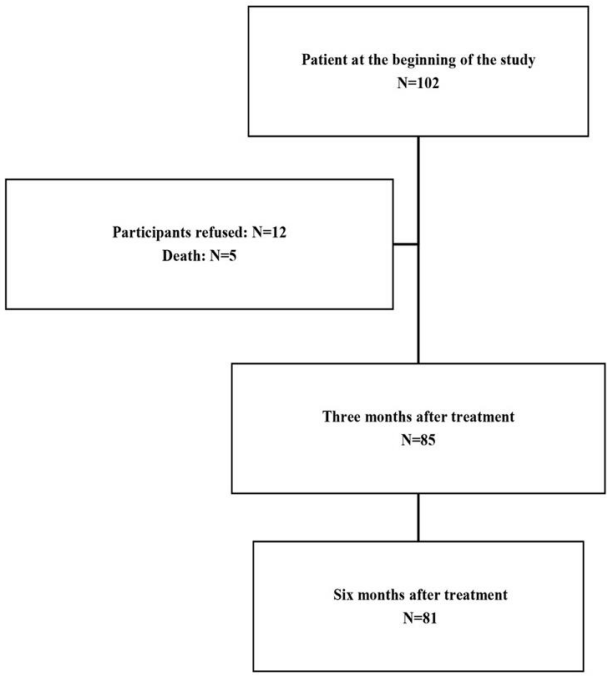

Figure 1. Flow chart of the longitudinal study for GIC patients referred to EMG unit

2. Materials and Methods

2.1 Study design and sample size

A longitudinal study was designed. We used a consecutive sampling method where all patients

presenting at a single institution were screened for study participation. The sample size was calculated based on the study of Argyriou et al. that reported the OIPN in GIC 64% of patients [13], taking into account the 95% confidence level and measurement error of 0.1. About 10% was added to the final sample size to compensate for possible dropout. Therefore, the final sample size was 102 who were entered in the study. However, twelve patients refused and five of those were dead. About 95% of 85 patients who remained in this study at three months after treatment onset reported the OIPN. At the end of the study period, data for 81 OIPN patients were analyzed (Figure 1).

2.2 Inclusion criteria of participants

All patients with GIC were treated with the FOLFOX4 chemotherapy regimen for the four treatment courses. Those continued this study until three months of chemotherapy onset. Participants were evaluated using EMG before chemotherapy began.

2.3 Exclusion criteria of study

The patients who passed away after three months of chemotherapy onset and the patients without available EMG data at three months after chemotherapy onset were excluded.

2.4 Study procedure

This study was approved by the Guilan University of Medical Sciences Ethics Committee (IR.GUMS.REC.1394.560) and was conducted in compliance with the guidelines of the Declaration of Helsinki. The written informed consent was obtained from the patients prior to their participation in the study. The study was conducted in Razi Educational, therapeutic and Research in 2017 Center. Before starting chemotherapy, patients were referred to the electromyography (EMG) unit to measure nerve conduction velocity (NCV) on the ulnar, radial, sural, and superficial peroneal nerve in an antidromic manner. Sensory nerve action potential (AP) amplitude and velocity were calculated. Motor conduction study of the common peroneal nerve, compound muscle AP amplitude and velocity assessment was also performed at the baseline (T0), at three months (T1) and six months (T2) of chemotherapy onset. Patients were evaluated for neuropathy by one neurologist using and clinical criteria after six months of starting the chemotherapy course. Neuropathy is clinically measured by two scales, National Cancer Institute-Common Toxicity Criteria V.3 (NCI-CTCv3) and the Clinical version of the Total Neuropathy Score (TNSc). During chemotherapy, patients were asked about the symptoms of acute neuropathy. Grade one, two and three of neuropathy were considered as mild, moderate and severe neuropathy.

2.5 Statistical analysis

After collecting the data, statistical analysis was performed using SPSS v21 (IBM, New York, USA). Fisher's exact and Pearson's chi-squared tests were applied for nominal and categorical variables. Independent t-test was used to compare continuous variables. The AP amplitude changes and NCV was compared over time via repeated-measures ANOVA. Post hoc analyses (Bonferroni pairwise comparisons) were subsequently performed for the pairwise comparison. The level of significance was set at 0.05 for all statistical procedures.

3. Results

In this study, after a dropout of about 16.7%, 81 FOLFOX4-treated GIC patients with neuropathy were studied in terms of electrodiagnostic properties of sensory and motor nerves before and after 3 and 6 months of treatment. 42% of the samples were female and 58% were male. The mean and standard deviation (SD) of the age and weight were 64±10.9 years and 69.5±8.8 kg, respectively.

Among the total patients, underlying diseases including diabetes (n=25), hypertension (n=16), hyperlipidemia (n=20), ischemic heart disease (n=13), smoking (n=15) and symptoms of acute neuropathy during treatment (n=17) has been reported.

Supplementary Figure 1 delineated the severity of neuropathic symptoms at six months of chemotherapy onset. It was reported that about 3.7% (n=3) grade three 30.86% (n=25), grade two, 62.96% (n=51) grade one and 2.47% (n=2) grade zero at six months after treatment onset, successively.

Based on the repetitive measure ANOVA test, a significant difference was shown in the AP amplitude mean of SPN, radial and sural nerves over time (P <0.001). There was no significant difference in the AP amplitude mean of the ulnar nerve (P=0.132) and

peroneal (*P*=0.624) nerve over time. See more information in Table 1.

Table 1. The AP amplitude mean of indicated nerves overtime in GIC patients with neuropathy induced by FOLFOX4 regimen

Variable	Time	Mean ± SD	P value*
Peroneal nerve	Baseline	4.09±2.29	0.624
	After 3 months	4.13±2.34	
	After 6 months	4.17±2.33	
SPN	Baseline	15.55±9.48	<0.001
	After 3 months	11.2±7.61	
	After 6 months	10.7±7.57	
Sural nerve	Baseline	18.74±12.09	<0.001
	After 3 months	13.45±10.13	
	After 6 months	13.01±9.91	
Ulnar nerve	Baseline	23.27±18.67	0.132
	After 3 months	22.8±18.42	
	After 6 months	22.08±17.85	
Radial nerve	Baseline	24.58±13.85	<0.001
	After 3 months	20.38±13.67	
	After 6 months	20.15±14.18	

*Repeated-measeure ANOVA

Supplementary Figure 2 depicts the mean of AP amplitude changes percentage of the nerves over times. It was revealed that the mean of AP amplitude changes percentage of SPN (23.99 ± 26.46), sural (25.72±29.04) and radial (16.53±27.02) nerves from T0 to T1 were dramatically different as compared to those in SPN (2.62±5.29), sural (3.48±2.91) and radial (2.35±1.43) from T1 to T2 (P <0.001). Similarly, a substantial difference was displayed in the mean of AP amplitude changes percentage of the same nerves from T0 to T2 relative to T1 to T2 (*P* <0.001). However, there was no a remarkable difference in the mean of AP amplitude changes percentage of SPN, sural and radial nerves from T0 to T1 in comparison with those in SPN (27.03±8.69), sural (27.89±9.66) and radial (17.98±5.4) nerves from T0 to T2 (*P* >0.05).

As shown in Table 2 There was no significant difference in NCV mean of peroneal (*P*=0.693), sural (*P*=0.263), radial (*P*=0.693), nerves, and SPN (*P*=0.849) over time. However, there was a substantial reduction (*P*=0.023) of the NCV mean for ulnar nerve after three (61.83±21.12) and six (60.67±20.03) months of chemotherapy onset relative to baseline (66.09±25.86). The results of pairwise comparisons illustrated a significant attenuation of NCV mean at three (*P*=0.042) and six months after treatment onset versus baseline (*P*=0.006).

According to Table 3, it was not found a significant association of severity of neuropathy with diabetes, hyperlipidemia, hypertension, acute neuropathy, and a history of ischemic heart disease and smoking (P >0.05), age (*P*=0.667), weight (*P*=0.441) and gender (*P*=0.555).

Table 2. The NCV mean of indicated nerves overtime in GIC patients with neuropathy induced by FOLFOX4 regimen

Variable	Time	Mean ± SD	P value
Peroneal nerve	Baseline	49.03±7.37	P=0.603 $P_{1,2}$=0.999 $P_{1,3}$=0.999 $P_{2,3}$=0.999
	After 3 months	48.95±7.30	
	After 6 months	49.25±7.25	
SPN	Baseline	71.67±33.47	P=0.849 $P_{1,2}$=0.999 $P_{1,3}$=0.999 $P_{2,3}$=0.999
	After 3 months	72.55±26.99	
	After 6 months	72.49±28.36	
Sural nerve	Baseline	73.28±30.07	P=0.163 $P_{1,2}$=0.365 $P_{1,3}$=0.421 $P_{2,3}$=0.999
	After 3 months	71.49±26.80	
	After 6 months	70.94±28.90	
Ulnar nerve	Baseline	66.09±25.86	P=0.023 $P_{1,2}$=0.142 $P_{1,3}$=0.042 $P_{2,3}$=0.006
	After 3 months	61.83±21.12	
	After 6 months	60.68±20.03	
Radial nerve	Baseline	55.44±9.59	P=0.693 $P_{1,2}$=0.999 $P_{1,3}$=0.999 $P_{2,3}$=0.999
	After 3 months	55.49±8.33	
	After 6 months	55.15±8.73	

4. Discussion

In this study, we investigated the effect of chemotherapy with FOLFOX4 on the electrodiagnostic features of sensory and motor nerves in GIC patients. According to the study of Velasco et al. [14], The mean age of the subjects was 64 years. In contrast to this prior study, the majority of patients in our study were male. The findings of our study indicated that the frequency of each of the underlying diseases was less than one-third of the total patients. About 21% of the patients of this study had acute neuropathy symptoms during treatment. According to NCI-CTCv3 and TNSc, 3.7% of patients had grade

Table 3. The association of neuropathy severity in FOLFOX4-treated GIC patients with underlying diseases and acute neuropathy

		NS status		
		Mild neuropathy	**Moderate to severe neuropathy**	**P-Value**
Age (Mean±SD)		63.6±11.2	64.7±10.6	0.667
Sex N (%)	Male	32(68.1)	15(31.9)	0.550
	Female	21(61.8)	13(38.2)	
Weight (Mean±SD)		68.9±8.1	70.5±9.9	0.441
Diabetes N (%)	Yes	18(72.0)	7(28.0)	0.406
	No	35(62.5)	21(37.5)	
Hypertension N (%)	Yes	8(50.0)	8(50.0)	0.147
	No	45(69.2)	20(30.8)	
Hyperlipidemia N (%)	Yes	11(55.0)	9(45.0)	0.258
	No	42(68.9)	19(31.1)	
Ischemic heart disease N (%)	Yes	7(53.8)	6(46.2)	0.338
	No	46(67.6)	22(32.4)	
Smoking N (%)	Yes	12(80.0)	3(20.0)	0.189
	No	41(62.1)	25(37.9)	
Acute neuropathy N (%)	Yes	12(70.6)	5(29.4)	0.615
	No	41(64.1)	23(35.9)	

three of neuropathy. These results corroborated previous reports in this regard [13, 14].

The percentage of the patients with grades two and three of neuropathy in our study was approximately 34%. However, another study exhibited grade two of neuropathy in almost 20% of GIC patients treated with the FOLFOX4 regimen [15]. Overall, the neuropathy rate in our study was 95% while others have reported the neuropathy incidence by 68% and 82% of total patients receiving FOLFOX4 chemotherapy [16]. An explanation for this result may be that various ethnicities may be differentially prone to experience the neuropathy presumably due to the differences in their diet, genetic and climate [17].

Another finding of our study was that hypertension and smoking increased by 20% and 18% the frequency of moderate and severe neuropathies in FOLFOX4-treated GIC patients, respectively. Diabetes, hyperlipidemia, and ischemic heart disease resulted in an enhancement of moderate and severe neuropathies frequency by less than 10%. Unexpectedly, we witnessed that the percentage of mild OIPN in the patients with a diabetes history was higher than that in non-diabetic patients. Nevertheless, there is no association of the severity of neuropathies with none of past medical histories in this study. This result of our study was inconsistence with some prior studies which have suggested an association between the incidence of clinical neuropathy and past medical diseases such as diabetes [18]. It is believed that high blood glucose can harm the peripheral nerves presumably through some pathophysiological mechanisms such as vascular dysfunction, hyperosmolarity and edema of the nerve trunk [19]. Albeit hyperglycemic instability and subsequently loss of axonal integrity due to preexisting diabetes may increase the risk of CIPN, it is thought that the CIPN severity might be influenced the rate of neural regeneration in cancer patients with diabetes history [20, 21]. Although some investigations showed a relationship between neuropathy and age [14], but there was no association between neuropathy severity and age, weight and gender of patients in the present study. The rate of acute neuropathy in this study was lower than in other studies [22, 23], which is possible to be related to ethnic discrepancies and geographic differences.

As an important finding of our study, a significant decrease was disclosed in AP amplitude of SPN, sural and radial nerves. However, NCV decrease was clarified only in the ulnar nerve. Herein, Park and his colleagues displayed the reduction of AP amplitude in the sural and radial nerves [12]. Decreased AP amplitude in these nerves can be suggested as determinants of high-grade neuropathy. According to the finding of our study, the previous studies have not

yet confirmed the clinical importance of NCV in the diagnosis of FOLFOX4-induced neuropathy. Oxaliplatin neurotoxicity in the FOLFOX regimen is known as a dose-limiting indicator. Dose reduction happens after neuropathy development and axon damage. Therefore, reducing the dose of the chemotherapeutic agent is useless. Moreover, it seems that the application of clinical examination and grading systems based on the NCI-CTCv3 and TNSc may underestimate neuropathy development in GIC patients receiving FOLFOX4 regimen [24, 25].

Accordingly, electrodiagnostic features might possess a clinical utility for the early detection of neuropathy in patients treated with oxaliplatin before the occurrence of toxicity induced by oxaliplatin.

Notably, performing EMG at least after 3 and 6 months of treatment onset may be suggested to detect seemingly healthy patients in terms of neurology. Electrophysiological property of peripheral nerves appears to be a sensitive measure for the diagnosis of neuropathy caused by chemotherapy. In addition, the electrodiagnostic findings may be a prognostic marker for oxaliplatin-induced neurotoxicity, refined treatment strategies, and facilitate neuroprotective strategies.

This study had some limitations. Our study was conducted with a little sample size. It is suggested to design a large-scale study in the future. Furthermore, we cannot investigate the serum levels of inflammation and oxidative stress markers in the patients. Besides, we did not measure chemotherapy-induced toxicity at various time points of study. It is seriously recommended to design a next study that incorporates the above considerations.

The occurrence of neuropathy due to the FOLFOX4 therapeutic approach can be detected by EMG at least three months after chemotherapy onset. The trend of AP amplitude changes for the sural and radial nerves, and SPN at various time points of treatment might be significant indicators of neuropathy development after chemotherapy before chemotherapy-induced toxicity happens. The data obtained from EMG may have a clinical utility to identify the patients treated with the FOLFOX4 regimen and are susceptible to neuropathy.

Supplementary files

Supplementary file 1.

Authors' contributions

Conception or design of the work: BBE, SR, HSS, NRA, CEA; Data collection: BBE, SR, HSS, NRA, HH; Data analysis and interpretation: EKL, SR, NRA; Drafting and critical revision of the manuscript: BBE, SR, HSS, NRA, and CEA. All authors read and approved the final version of the manuscript.

Conflict of interests

There is no conflict of interest.

Ethical declarations

All applicable international, national, and/or institutional guidelines for the study of human participants were performed by the authors. The study was approved by the ethics committee of Guilan University of Medical Sciences that conforms to the provisions of the Declaration of Helsinki.

Acknowledgments

The authors would like to thank the all staff of the Neuroscience Research Center and the Clinical Research Development Unit of Poursina Hospital at Guilan University of Medical Sciences, Rasht, who helped us in performing the data collection and study processes.

Financial support

This project was not funded

References

1. Dasari S, Tchounwou PB. Cisplatin in cancer therapy: molecular mechanisms of action. Eur J Pharmacol. 2014;740:364-78.
2. Johnstone TC, Suntharalingam K, Lippard SJ. The next generation of platinum drugs: targeted Pt (II) agents, nanoparticle delivery, and Pt (IV) prodrugs. Chem Rev. 2016;116(5):3436-86.
3. Köberle B, Schoch S. Platinum complexes in colorectal cancer and other solid tumors. Cancers. 2021;13(9):2073.
4. Haghighi S, Kasbkar H, Esmaeilpour K, Yasaei M. Oxaliplatin, 5fluorouracil and leucovorin (FOLFOX4) as first line chemotherapy in elderly patients with advanced gastric cancer. Asian Pac J Cancer Prev. 2016;17(7):3277-80.
5. Argyriou AA. Updates on oxaliplatin-induced peripheral neurotoxicity (OXAIPN). Toxics. 2015;3(2):187-97.
6. Zajączkowska R, Kocot-Kępska M, Leppert W, Wrzosek A, Mika J, Wordliczek J. Mechanisms of chemotherapy-induced peripheral neuropathy. Int J Mol Sci. 2019;20(6):1451.
7. Marshall TF, Zipp GP, Battaglia F, Moss R, Bryan S. Chemotherapy-induced-peripheral neuropathy, gait and fall risk in older adults following cancer treatment. J Cancer Res Pract. 2017;4(4):134-8.

8. Simão DAdS, Murad M, Martins C, Fernandes VC, Captein KM, Teixeira AL. Chemotherapy-induced peripheral neuropathy: review for clinical practice. Revista Dor. 2015;16(3):215-20.
9. Gordon-Williams R, Farquhar-Smith P. Recent advances in understanding chemotherapy-induced peripheral neuropathy. F1000Research. 2020;9.
10. Pasetto LM, D'Andrea MR, Rossi E, Monfardini S. Oxaliplatin-related neurotoxicity: how and why? Crit Rev Oncol Hematol. 2006;59(2):159-68.
11. Lazić A, Popović J, Paunesku T, Woloschak GE, Stevanović M. Insights into platinum-induced peripheral neuropathy–current perspective. Neural Regen Res.. 2020;15(9):1623.
12. Park SB, Lin CS, Krishnan AV, Goldstein D, Friedlander ML, Kiernan MC. Long-term neuropathy after oxaliplatin treatment: challenging the dictum of reversibility. Oncologist. 2011;16(5):708.
13. Argyriou AA, Polychronopoulos P, Iconomou G, Chroni E, Kalofonos HP. A review on oxaliplatin-induced peripheral nerve damage. Cancer Treat Rev. 2008;34(4):368-77.
14. Velasco R, Bruna J, Briani C, Argyriou AA, Cavaletti G, Alberti P, et al. Early predictors of oxaliplatin-induced cumulative neuropathy in colorectal cancer patients. J Neurol Neurosurg Psychiatry. 2014;85(4):392-8.
15. Shimizu T, Satoh T, Tamura K, Ozaki T, Okamoto I, Fukuoka M, et al. Oxaliplatin/fluorouracil/leucovorin (FOLFOX4 and modified FOLFOX6) in patients with refractory or advanced colorectal cancer: post-approval Japanese population experience. Int J Clin Oncol. 2007;12(3):218-23.
16. Kemeny N, Garay CA, Gurtler J, Hochster H, Kennedy P, Benson A, et al. Randomized multicenter phase II trial of bolus plus infusional fluorouracil/leucovorin compared with fluorouracil/leucovorin plus oxaliplatin as third-line treatment of patients with advanced colorectal cancer. J Clin Oncol. 2004;22(23):4753-61.
17. Tahrani AA, Altaf QA, Piya MK, Barnett AH. Peripheral and Autonomic Neuropathy in South Asians and White Caucasians with Type 2 Diabetes Mellitus: Possible Explanations for Epidemiological Differences. J Diabetes Res. 2017;2017:1273789.
18. Sempere-Bigorra M, Julián-Rochina I, Cauli O. Chemotherapy-induced neuropathy and diabetes: a scoping review. Curr Oncol. 2021;28(4):3124-38.
19. Dewanjee S, Das S, Das AK, Bhattacharjee N, Dihingia A, Dua TK, et al. Molecular mechanism of diabetic neuropathy and its pharmacotherapeutic targets. Eur J Pharmacol. 2018;833:472-523.
20. Hershman DL, Till C, Wright JD, Awad D, Ramsey SD, Barlow WE, et al. Comorbidities and Risk of Chemotherapy-Induced Peripheral Neuropathy Among Participants 65 Years or Older in Southwest Oncology Group Clinical Trials. J Clin Oncol. 2016;34(25):3014-22.
21. Khoshnoodi MA, Ebenezer GJ, Polydefkis M. Epidermal innervation as a tool to study human axonal regeneration and disease progression. Exp Neurol. 2017;287:358-64.
22. Tofthagen C, Donovan KA, Morgan MA, Shibata D, Yeh Y. Oxaliplatin-induced peripheral neuropathy's effects on health-related quality of life of colorectal cancer survivors. Support Care Cancer. 2013;21(12):3307-13.
23. Mizrahi D, Park SB, Li T, Timmins HC, Trinh T, Au K, et al. Hemoglobin, Body Mass Index, and Age as Risk Factors for Paclitaxel-and Oxaliplatin-Induced Peripheral Neuropathy. JAMA Netw Open. 2021;4(2):e2036695-e.
24. Gilchrist LS, Tanner L. The pediatric-modified total neuropathy score: a reliable and valid measure of chemotherapy-induced peripheral neuropathy in children with non-CNS cancers. Support Care Cancer. 2013;21(3):847-56.
25. Sałat K. Chemotherapy-induced peripheral neuropathy—part 2: focus on the prevention of oxaliplatin-induced neurotoxicity. Pharmacol Rep. 2020;72(3):508-27.