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Can Cobalamin prevent Oxaliplatin induced peripheral neuropathy?

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Abstract

Background and objectives: Peripheral neuropathy induced by oxaliplatin is one of the main reasons for discontinuing chemotherapy. In this article, we evaluated the role of vitamin B12 in the prevention of oxaliplatin-induced peripheral neuropathy. **Methods:** A prospective randomized interventional study was done from 1st January 2018 to 30th December 2018, in which patients who were diagnosed with gastrointestinal cancer in Rizgary and Nanakali teaching hospitals that have been scheduled to receive oxaliplatin-based regimen were enrolled. Patients were divided into two groups: control group received chemotherapy only and prophylaxis group received chemotherapy with vitamin B12; each group included fifteen patients with no significant differences between the groups regarding age and gender. The prophylaxis group received vitamin B12 injection in scheduled periods. All Patients received at least a cumulative dose of 500 mg/m^2 of oxaliplatin. Patients were evaluated by nerve conduction study, B12 level, and other laboratory tests. **Results:** Twenty-one patients completed the study. There was a significant decrease in the serum vitamin B^{12} level (601.84±398.43 to 363±337.31) post-chemotherapy among the control group. Among the prophylaxis group, the mean value of serum vitamin B12 increased significantly after chemotherapy. To summarize, there was a significant decrease in the amplitude of nerve conduction study in the control group as compared to the prophylaxis group especially in left (11.85±6.84 to 8.14±5.36) and right (14.01±6.05 to 9.52±6.08) Sural nerves. **Conclusions:** Vitamin B12 injection had an important role in the prevention of development of chronic oxaliplatin-induced peripheral neuropathy.

Key words: Oxaliplatin, Oxaliplatin-induced peripheral neuropathy, Vitamin B12.

Introduction

Millions of colorectal and gastric cancer cases are diagnosed annually and considered highly prevalent worldwide as it's the fourth leading cause of cancer related death[1]. Advanced neoplastic agents have increased the survival rate significantly. Third-generation platinum compound like oxaliplatin demonstrated a significant role in the treatment of colorectal cancer in the adjuvant or metastatic setting, as well as other indications for pancreatic and gastric cancer management[2-4].

Oxaliplatin (OXA) exhibits its mechanism of action mainly through damaging DNA by forming a DNA lesion which leads to blocking of its replication and transcription resulting in cell death and immunological reaction through a different mechanism[5-7]. Oxaliplatin is usually administered in combination of either 5-fluorouracil plus leucovorin or capecitabine: which provides the optimal impact on progression-free and overall survival rate[2,4]. Oxaliplatin-induced peripheral neuropathy (OXLIPN) ranks among one of the most frequent side effects, secondary to hematological toxicity, whose clinical syndrome is in the form of acute and chronic neuropathy[8]. Acute neuropathy is resulting in paresthesia and dysesthesia of the feet and hand induced by cold, which occurs hours or days after oxaliplatin-based chemotherapy infusion. This is usually self-limiting after a week and disappears for the next cycle, but repetition of chemotherapy cycle will result in chronic neuropathy that is associated with paresthesia, numbness, sensory ataxia, and functional impairment, which can take up to 18 months or longer to recover, with the intensity of the symptoms increasing over time[9]. Both neuropathies are major dose limiting factors which impact the treatment regimen of the cancer patients and it can cause long-lasting, or even permanent symptoms, which detriment cancer survivors' life quality[10].

Over the years there have been many attempts to treat OXLIPN prophylactically; recent clinical studies included calcium and magnesium injection before and after OXA,

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pregabalin, vitamin E, venlafaxine and antihyperalgesic, but none have achieved significant results[11–14]. The American society of clinical oncology guideline only suggests pain management[15] for chemotherapy induced peripheral neuropathy (CIPN) cases, but does not advice the following: acetyl-L carnitine, amifostine, amitriptyline, nimodipine, all-trans retinoic acid, recombinant human leukemia inhibitory factors, and others for prevention of CIPN.

Vitamin B12 deficiency is associated with neurological symptoms and accounts for peripheral neuropathies. B12 has been prescribed for treatment and management of peripheral neuropathy (PN) especially in chronic diabetes mellitus patients and other causes in general [16,17]. The result of previous study on vitamin B group in general has shown that B12 has a role in CIPN[18].

The study was carried out to evaluate B^{12} level in patients receiving oxaliplatin as the main chemotherapy regimen for management of gastrointestinal tract (GIT) cancer and the therapeutic efficacy of B12 in reducing the incidence of chronic OXLIPN.

Patients and Methods

A prospective randomized interventional study was done to evaluate the effect of B12 on the OXLIPN. The study was carried out at Rizgary, Nanakali, and Hawler teaching hospitals from 1st of January 2018 to 30th of December 2018, after getting the ethical approval from the ministry of higher education and scientific researches in Erbil, Kurdistan region of Iraq.

The inclusion criteria of the study were patients >18 years of age and newly diagnosed with GIT cancer scheduled to receive oxaliplatin-based chemotherapy (at least a cumulative dose of 500 mg/m^2), while excluding criteria of chronically diseased (diabetes, significant peripheral vascular disease, uremia, progressive or degenerative neurologic disorders (e.g. B12 deficiency), hypertension) patients with history of radiculopathy or previously diagnosed PN, patients with prior exposure to neurotoxic agents (ethanol, pyridoxine, colchicine, allopurinol, phenytoin, chemotherapy drugs, vinca alkaloids (vincristine), cisplatin, paclitaxel, podophyllotoxins (etoposide and tenoposide), and those who are receiving antiepileptic medications.

Thirty patients were randomized into two groups regardless of their B^{12} serum level (B12 level above 300 pg/mL is considered normal), 15 patients enrolled as control group, and the other 15 as prophylaxis group that received methyl-cobalamin injection intramuscularly as follows: 1000 µg daily for one week, 1000 µg weekly for four weeks, and 1000 µg monthly for 3 months[19], with the treatment starting one day before receiving oxaliplatin-based chemotherapy. Blood samples were collected 10 days after the last injection of the monthly interval that consisted of 3 months.

Blood samples were taken from all the patients before and after receiving chemotherapy, with all samples tested in the same specialized laboratory for these parameters: B^{12}, haemoglobin, white blood cell (WBC) count, platelet (PLT) count, and bilateral nerve conduction studies performed by the same neurophysiologist for sensory branches of Median, Ulnar, and Sural nerves that were done during the first and the last observation, according to hospital standardized protocol at Hawler teaching hospital. Chronic OXLIPN was defined as a clinical syndrome characterized by the persistence of symptoms for at least two subsequent cycles that were without any symptoms free intervals. Chronic OXILPN was diagnosed clinically according to the sign and symptoms of numbness, tingling, and pain in their hands and feet that were interfering with their daily life activity with the acute symptoms of paresthesia and dysesthesia persisting for at least two subsequent cycles without any symptom free intervals [20]. Oxaliplatin-induced peripheral neuropathy was diagnosed neurophysiologically according to reduced amplitude of the nerve action potential[21].

Data was analyzed using the Statistical Package for Social Sciences (SPSS, version 22). Student's t-test of two independent samples was used to compare two means and Paired t-test was used to compare means before and after treatment. Chi square test of association was used to compare proportions between the two studied groups; when the expected count of cells was less than 5 in more than 20% of the table, Fisher's exact test was used and Pearson's test was used for correlation. Values were expressed as N (%) or Mean±SD. The p- value ≤ 0.05 was considered statistically significant.

Results

Twenty-one non-smoking patients with no drinking habits completed the study; the patients' flow in the study stages is illustrated in the, Figure 1.

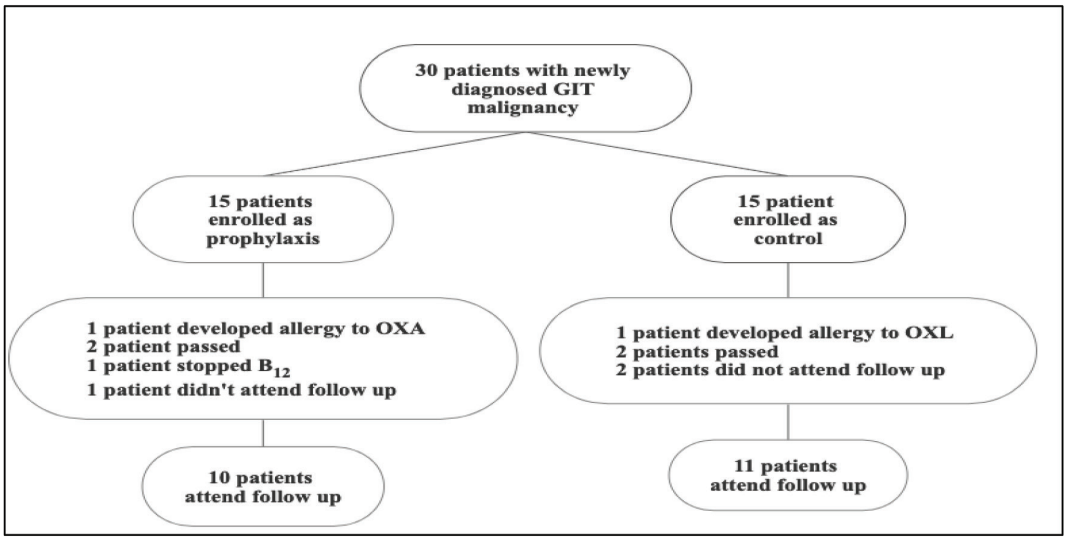

Figure (1): Flow diagram of the patients through stages of the study.

Table 1 shows the demographic characteristics of the patients without significant differences in the selection of the two groups regarding age ($p = 0.164$), gender ($p > 0.999$).

Table (1): Patients demographic characteristics.

Characteristics		Prophylaxis	Control	p-value
Age	< 40	1 (9.1%)	3 (30.0%)	0.164
	40-49	4 (36.4%)	0 (0.0%)	
	50-59	1 (9.1%)	3 (30.0%)	
	>60+	5 (45.5%)	4 (40.0%)	
Gender	Male	6 (54.5%)	5 (50.0%)	>0.999
	Female	5 (45.5%)	5 (50.0%)	

Table 2 shows type, stage, and treatment of GIT cancer, without significant difference between the groups.

Table (2): Patients disease and treatment characteristics.

Characteristics		Prophylaxis	Control	p-value
Type of GIT cancer	Upper digestive	3 (30.0)	6 (54.5)	0.387
	Lower digestive	7 (70.0)	5 (45.5)	
Stage of cancer	II	2(20.0%)	0 (0.0%)	
	III	5 (50.0%)	8 (72.7%)	0.453
	IV	3 (30.0%)	3 (27.3%)	
Treatment regimen*	EOX	1 (10.0%)	1 (9.1%)	
	FOLFOX	1 (10.0%)	2 (18.2%)	
	XELOX	5 (50.0%)	7 (63.6%)	0.404
	FOLOX+XELODA	0 (0.0%)	1 (9.1%)	
	FOLFOX+ Avastin	3 (30.0%)	0 (0.0%)	
Cumulative dose (Mean±SD)		749.5± 177.1	846.8± 232.2	0.297

*EOX (Epirubicin, Oxaliplatin, and Xeloda), FOLFOX (Folinic acid, 5-Fluorouracil Oxaliplatin), XELOX (Oxaliplatin and Xeloda)

Serum B12 level was significantly (p<0.001) increased in the prophylaxis group, while mean level of serum B12 in the control group showed significant (p=0.022) reduction from 601.84 pg/mL before chemotherapy vs 363 pg/mL after chemotherapy, which indicate that B12 is highly effected by oxaliplatin-based chemotherapy. When we correlated serum B12 level with the cumulative dose of OXA, we found a strong negative correlation between them (r=-0.688, p=0.019). When evaluating the hematological result of the two groups, the prophylaxis group showed no significant decrease in hemoglobin (p = 0.816) nor WBCs (p = 0.149); whereas in the control group, there were significant decrease in the means of hemoglobin (p= 0.013), WBC count (p-value = 0.018), and PLT (p-value =0.001). However, when comparing the result of the two groups, although the prophylaxis group had the better outcome, there was only a statistical significant difference between the two groups in serum B12 level (p-value < 0.001) as shown in Table 3.

Table (3): Laboratory measurement before and after chemotherapy.

Parameters	Prophylaxis			Control			p-value*
	Before	After	p-value	Before	After	p-value	
B_{12} (pg/mL)	357.15 ±118.31	1092.57 ±326.56	< 0.001	601.84 ±398.43	363 ±337.31	0.022	< 0.001
Hemoglobin (g/dL)	11.83 ±2.03	11.64 ±1.07	0.816	12.4 ±1.84	11.03 ±1.92	0.013	0.201
WBC (10^3 / µL)	10.86 ±8.03	6.8 ±3.10	0.149	6.90 ±2.02	4.50 ±1.77	0.018	0.532
PLT (10^3 / µL)	379.3 ±170.93	232.7 ±116.23	0.009	265.91 ±79.84	123.73 ±42.44	0.001	0.933

*P-value between the groups.

The nerve conduction study of prophylaxis group who received B12 injection showed no significant change in all three nerves except the right Ulnar nerve. There was a significant reduction in the mean amplitude: 28.6 µv before treatment vs 23.94 µv after treatment (p-value = 0.012), but the reduction was within normal range value. While in the control group, there was a significant reduction in the amplitude: the mean amplitude of the right Median nerve significantly decreased from 22.16 µv, before oxaliplatin treatment, to 14.47 µv, after oxaliplatin treatment (p-value = 0.012). There was also a significant decrease in the amplitude of the left and right Ulnar nerves as well as the left and right Sural nerves after treatment, compared with the mean before treatment. Those abnormalities were consistent with sensory neuropathy, which is linked to chronic OXLIPN. Significant differences were noted between the groups in the left Ulnar (p-value =0.013) and left Sural (p-value =0.049) nerves, as shown in Table 4.

Table (4): Nerve conduction study before and after chemotherapy.

Nerve	Prophylaxis			Control			p-value*
Amplitude†	Before	After	P-value	Before	After	p-value	
Left median	27.41 ±11.77	23.93 ±12.2	0.107	25.73 ±12.43	15.86 ±7.07	0.051	0.178
Right median	23.52 ±9.86	18.51 ±12.35	0.055	22.16 ±12.04	14.47 ±7.57	0.012	0.432
Left ulnar	26.25 ±10.19	25.22 ±11.73	0.697	28.43 ±11.17	16.99 ±9.62	0.002	0.013
Right ulnar	28.6 ±8.22	23.94 ±10.6	0.012	27.02 ±10.88	16.32 ±11.34	0.002	0.057
Left sural	11.87 ±4.97	14.96 ±7.65	0.333	11.85 ±6.84	8.14 ±5.36	0.028	0.049
Right sural	11.88 ±6.14	14.3 ±7.8	0.430	14.01 ±6.05	9.52 ±6.08	0.021	0.053

*p-value between the groups. †Normal values for the sensory amplitude (µv) is as fallow; Median nerve ≥ 20 µv, Ulnar nerve≥17 µv and Sural nerve≥ 10 µv (Hospital reference)

Most of the patient suffered from acute neuropathic symptoms of paresthesia and/or dysesthesia induced after oxaliplatin infusion, except two patients in the prophylaxis group who had no symptoms. The other eight patients had acute symptoms lasting for only three days. In the control group, the symptoms lasted for fourteen days or with incomplete regression between cycles along with paresthesia and/or dysesthesia accompanied by functional impairment in almost all of the patients. When the patient asked for the symptom experienced, most of them presented with tingling, numbness, and pain, which interfered with their daily life activity, but had significantly more severe symptoms in the control group.

At the end of the study, patients were diagnosed with peripheral neuropathy according to the patients' nerve conduction study results and the prolonging acute symptoms. Also, 30.0% of patients in the prophylaxis group had developed PN, while 90.9% patients in the control group developed PN, with significant difference (p-value=0.008) between the groups as shown in Table 5.

Table (5): Development of peripheral neuropathy after chemotherapy.

Neuropathy	prophylaxis	Control	Total	p-value
Yes	3 (30.0)	10 (90.9)	13 (61.9)	0.008
No	7 (70.0)	1 (9.1)	8 (38.1)	
Total	10 (100.0)	11 (100.0)	21 (100.0)	

Discussion

Limited understanding of the mechanism of OXLIPN has led to limiting scientific suggestion for prevention and treatment of OXLIPN or CIPN in general, leading to dose reduction, cycle postponing, and in some cases, treatment change, which makes it a daily challenge in clinical oncology practice[22,23].

In this clinical trial, we found that serum B12 was significantly reduced in post-chemotherapy (p-value=0.022) and most of the patients who developed neuropathy were in the control group. As shown in our study, B12 level was decreased with increasing cumulative doses (r= -0.688 p-value = 0.019), which may add to the neurotoxic effect of OXA and lead to increased progression of peripheral neuropathy. B12 level should be evaluated and corrected during chemotherapy to prevent the development of OXLIPN, in a randomized placebo-controlled trial which assesses the efficacy of oral vitamin B groups in the prevention of CIPN by Schloss et al[24]. Although the group which received the vitamin B complex was not superior to the placebo group, the study showed that B12 level was decreased post chemotherapy and showed the potential benefit and relation of B12 with CIPN, which reduced the total neuropathy score significantly (p-value= 0.024) post-chemotherapy.

The question to answer is whether decreased level of B12 is causative for the symptoms of neuropathy and is it necessary to be corrected by the end or during chemotherapy cycles? If serum B12 is at level of 250 pg/ml or less, it is recommended to be corrected while in cases of patients scheduled to receive neurotoxic OXA it should be corrected at a level of 350 pg/mL as suggested by Schloss et al[25], this was the case in the current study where one of the patient had normal serum B12 level of 250 pg/mL and was found to have abnormal nerve conduction study before receiving chemotherapy and the patient was asymptomatic, but upon receiving B12 injection along with oxaliplatin-based chemotherapy the nerve conduction study became normal upon follow up, this may indicate that neuropathy presented due to the patient's B12 level. And since B12 deficiency have been recognized medically as a causative of PN and possible risk factor for development of CIPN[26]. Therefore, the neurological side effects from B^{12} deficiency could be avoided and according to this study it might help to prevent the development of OXLIPN.

This study has found that B12 reduced the risk of development of sensory nerve neuropathy during OXA chemotherapy. There was a significant difference between prophylaxis and control groups in the duration of acute neuropathy, where the control group had prolonged symptoms of paresthesia and/or dysesthesia, lasting for either more than two weeks or with no regression between the cycles. Also, 90.9% of the patients had developed peripheral neuropathy related to OXA diagnosed as chronic sensory neuropathy, which is not aggravated by cold as shown in other studies[2, 27,28]. In the prophylaxis group, there was a non-significant increase in amplitude post-chemotherapy bilaterally, while the amplitudes of Sural nerve in control group post-chemotherapy significantly reduced bilaterally

and there were significant differences (p-value=0.049) in left Sural nerve amplitude in the prophylaxis group compared to the control group, while in the right Sural nerve the difference was non-significant (p-value=0.053). There was a significant reduction in the amplitude of Ulnar and Median nerve post-chemotherapy in the control group, while the prophylaxis group was fairly protected, reflecting the benefits of B12 injection on the symptoms and nerve conduction study results. In a study conducted by Krishnan et al[29], the nerve conduction study was routinely performed for 16 patients who have been treated for advanced colorectal cancer; the abnormalities kept with sensory symptom, but there was reduction in sensory amplitude in the Sural and Median nerves, especially in the symptomatic patients when compared with asymptomatic patients. The mean amplitudes of both nerves were reduced when compared with normal control and with no change in the motor study.

Vitamin B12 deficiency may cause hematologic abnormalities, namely anaemia, thrombocytopenia, and leukopenia. Oxaliplatin also causes the same hematologic abnormality which relates to bone marrow suppression[30,31]. Anaemia is recognized as one of the predisposing risk factors for increased incidence of PN due to OXA chemotherapy[32]. This study showed that B12 injections prevented a significant reduction of haemoglobin level. The control group had significant reduction p-value= 0.013, with no significant difference between the two groups p-value=0.201, which can reduce the chances of PN due to secondary causes.

Like any other study, this study has some limitations: patient's compliance with treatment, follow up attendance, and short duration of follow up due to time limitation to complete this study. Without these hindrances, we would have a larger sample size and probably end with different study results.

Conclusions

Vitamin B12 injections might prevent the development of peripheral neuropathy, induced by oxaliplatin. It may also have a role in preventing further progression of neuropathy and reducing hematologic toxicity; therefore, evaluation of the patient's vitamin B12 level during courses of oxaliplatin based chemotherapy and early correction of its level can reduce the risk of peripheral neuropathy, secondary to its neurotoxic effects.

References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 2018; 68(6): 394-424.

2. De Gramont A, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol. 2000; 18(16): 2938–47.

3. Alcindor T, Beauger N. Oxaliplatin: a review in the era of molecularly targeted therapy. Curr Oncol. 2011; 18(1): 18–25.

4. Schmoll H, Cartwright T, Tabernero J, et al. Phase III trial of capecitabine plus oxaliplatin as adjuvant therapy for stage III colon cancer: a planned safety analysis in 1,864 patients. J Clin Oncol. 2007; 25(1): 102–9.

5. Faivre S, Chan D, Salinas R, et al. DNA strand breaks and apoptosis induced by oxaliplatin in cancer cells. Biochem Pharmacol. 2003; 66(2): 225–37.

6. Todd RC, Lippard S.J. Inhibition of transcription by platinum antitumor compounds. Metallomics. 2009; 1(4): 280–91.

7. Tesniere A, Schlemmer F, Boige V, et al. Immunogenic death of colon cancer cells treated with oxaliplatin. Oncogene. 2010; 29(4):482–91.

8. Argyriou A, Bruna J, Marmiroli P, et al. Chemotherapy-induced peripheral neurotoxicity (CIPN): an update. Crit Rev Oncol Hematol. 2012; 82(1): 51–77.

9. Zedan A, Hansen T, Fex Svenningsen A, et al. Oxaliplatin-induced neuropathy in colorectal cancer: many questions with few answers. Clin Colorectal Cancer. 2014; 13(2): 73–80.

10. Cavaletti G, Marmiroli P. Chemotherapy-induced peripheral neurotoxicity. Nat Rev Neurol. 2010; 6(12): 657–66.

11. Loprinzi C, Qin R, Dakhil S, et al. Phase III Randomized, Placebo-Controlled, Double-Blind Study of Intravenous Calcium and Magnesium to Prevent Oxaliplatin-Induced Sensory Neurotoxicity (N08CB/Alliance). JCO. 2013; 32(10): 997–1005.

12. De Andrade D, Teixeira M, Galhardoni R, et al. Pregabalin for the Prevention of Oxaliplatin-Induced Painful Neuropathy: A Randomized, Double-Blind Trial. The oncologist. 2017; 22(10): 1154-e105.

13. Zimmerman C, Atherton P, Pachman D, et al. MC11C4: a pilot randomized, placebo-controlled, double-blind study of venlafaxine to prevent oxaliplatin-induced neuropathy. Support Care in Cancer. 2016; 24(3): 1071–8.

14. Salehi Z, Roayaei M. Effect of Vitamin E on Oxaliplatin induced Peripheral Neuropathy Prevention: A Randomized Controlled Trial. International Journal of Preventive Medicine. 2015; 6 (1): 104.

15. Hershman D, Lacchetti C, Dworkin R, et al. Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. JCO. 2014; 32(18):1 941–67.

16. Sun Y, Lai MS, Lu CJ. Effectiveness of vitamin B12 on diabetic neuropathy: systematic review of clinical controlled trials. Acta Neurologica Taiwanica. 2005; 14(2):48-54.

17. Zhang M, Han W, Hu S, et al. Methylcobalamin: a potential vitamin of pain killer. Neural Plasticity. 2013; 2013: 424651.

18. Schloss J, Colosimo M. B. vitamin complex and chemotherapy-induced peripheral neuropathy. Current Oncology Reports. 2017; 19 (12): 76.

19. Vidal-Alaball J, Butler C, Cannings-John R, et al. Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency. Cochrane Database of Systematic Reviews. 2005; (3):CD004655

20. Attal N, Bouhassira D, Gautron M, et al. Thermal hyperalgesia as a marker of oxaliplatin neurotoxicity: a prospective quantified sensory assessment study. PAIN. 2009;144(3): 245-52.

21. Argyriou A, Polychronopoulos P, Iconomou G, et al. A review on oxaliplatin-induced peripheral nerve damage. Cancer Treatment Reviews. 2008; 34(4):368-77.

22. Balayssac D, Ferrier J, Descoeur J, et al. Chemotherapy-induced peripheral neuropathies: from clinical relevance to preclinical evidence. Expert Opinion on Drug Safety. 2011; 10(3): 407–17.

23. Beijers A, Mols F, Vreugdenhil G. A systematic review on chronic oxaliplatin-induced peripheral neuropathy and the relation with oxaliplatin administration. Support Care in Cancer. 2014; (7): 1999–2007.

24. Schloss J, Colosimo M, Airey C, et al. A randomised, placebo-controlled trial assessing the efficacy of an oral B group vitamin in preventing the development of chemotherapy-induced peripheral neuropathy (CIPN). Support Care in Cancer. 2017;25(1): 195–204.

25. Schloss JM, Colosimo M, Airey C, et al. Chemotherapy-induced peripheral neuropathy (CIPN) and vitamin B12 deficiency. Supportive Care in Cancer. 2015; 23(7): 1843–50.

26. Armstrong T, Almadrones L, Gilbert M. Chemotherapy-induced peripheral neuropathy. In Oncology nursing forum 2005;32 (2):305-11

27.Vincenzi B, Frezza A, Schiavon G, et al. Identification of clinical predictive factors of oxaliplatin-induced chronic peripheral neuropathy in colorectal cancer patients treated with adjuvant Folfox IV. Support Care in Cancer. 2013; 21(5): 1313–9.

28.Grothey A. Oxaliplatin-safety profile: neurotoxicity. In Seminars in oncology 2003; 30 (4): 5-13.

29.Krishnan A, Goldstein D, Friedlander M, et al. Oxaliplatin-induced neurotoxicity and the development of neuropathy. Muscle & Nerve: Official Journal of the American Association of Electrodiagnostic Medicine. 2005;32 (1):51-60.

30. Green R. Vitamin B12 deficiency from the perspective of a practicing hematologist. Blood. 2017; 129(19): 2603–11.

31. Block KI, Koch AC, Mead MN, et al. Impact of antioxidant supplementation on chemotherapeutic toxicity: a systematic review of the evidence from randomized controlled trials. Int J Cancer. 2008; 123(6): 1227–39.

32. Jardim DL, Rodrigues CA, Novis YA. et al. Oxaliplatin-related thrombocytopenia. Ann Oncol. 2012; 23(8): 1937–42.