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Research Article *Volume 5 Issue 1*

To Study the Clinical Correlation between Chemotherapy Induced Peripheral Neuropathy (CIPN) and Deficiency of Vitamin B12, and Vitamin D3

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Abstract

Background: The prevalence of CIPN has been estimated to be 68.1% in the 1st month after administration of platinum (oxaliplatin/ carboplatin) or taxane based antineoplastic agents (paclitaxel/ Docetaxel). These agents have increased the overall survival rate of cancer patients but with development of debilitating side effects like motor and sensory symptoms-numbness, paraesthesia, dysaesthesias, loss of balance, muscle weakness and burning pain which poses a great challenge for oncologists to warrant a reduction in the dosage or stop the chemotherapeutic course to mitigate CIPN symptoms. Therefore, it is of at most importance to develop prophylactic measures to prevent CIPN so that the patients can be cancer free and not suffer from debilitating neuropathy induced by cancer treatment.

Aim: Improvement in chemotherapy induced neuropathic pain symptoms on VAS scale and SLANSS scale through selective nutritional supplementation.

Materials and Methods: A total of 103 patients receiving platinum, taxane and vinca-alkaloids based chemotherapy with clinically diagnosed chemotherapy induced peripheral neuropathy were enrolled in the study. After taking informed consent, a baseline workup of vitamin B12 and vitamin D3 was done. Those with deficiency of either vitamin were given Gabapentin with the deficient nutritional supplement likewise the other group was receiving gabapentin alone. They were subsequently followed up for a period of 3 months and 6 months with SLANSS scale and VAS scale. All the inclusion and exclusion criteria were checked before enrolment of the patient into the study. No patient had lost to follow up or expired during the study period.

Results: Comparative Statistical Analysis Among Intervention Groups was done Visual analogue scale calculated at 6 months in different intervention groups, the mean score of Gabapentin alone treated was found to be 3.73±1.26 (Mean±SD), Gabapentin and Vitamin D3 groups 3.30±0.823 (Mean±SD), Gabapentin and Vitamin B12 3.1 ±1.31 (Mean±SD), Gabapentin Vitamin D3 and Vitamin B12 2.5±1.31 (Mean±SD) respectively, which showed that the VAS score improvement in intervention groups as compared to Gabapentin alone groups. Mean value of two independent groups were compared using the Independent Samples t Test. The difference in mean VAS score at 6 months between the 'Gabapentin Alone' and 'Gabapentin and Vitamin D3' groups was not statistically significant. The difference in mean VAS score at 6 months between the 'Gabapentin Alone' and 'Gabapentin and Vitamin B12' groups, 'Gabapentin Alone' and 'Gabapentin, vitamin D3 and Vitamin B12' groups was statistically significant with

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p value less than 0.05. SLANSS score calculated at 6 months in different intervention groups, the mean score of Gabapentin alone treated was found to be 8.84±3.9 (Mean±SD), Gabapentin and Vitamin D3 groups 8.60±5.02 (Mean±SD), Gabapentin and Vitamin B12 groups 5.46±3.0 (Mean±SD), Gabapentin, Vitamin D3 and Vitamin B12 was 5.06±.68 (Mean±SD) respectively, which showed that the SLANSS score improvement in Vitamin supplementations groups as compared to Gabapentin alone groups. Mean value of two independent groups were compared using the Independent Samples t Test. The difference in mean SLANSS score at 6 months between the 'Gabapentin Alone' and 'Gabapentin and Vitamin D3' groups was not statistically significant. The difference in mean VAS score at 6 months between the 'Gabapentin Alone' and 'Gabapentin and Vitamin B12' groups, 'Gabapentin Alone' and 'Gabapentin, vitamin D3 and Vitamin B12' groups was statistically significant with p value less than 0.05.

Conclusion: Gabapentin and Vitamin D3 supplementation did not show significant improvement in the neuropathic pain component in CIPN patients as measured by VAS score and SLANSS score from baseline to 6 months follow-up. Gabapentin and Vitamin B12 and Gabapentin + Vitamin B12 + Vitamin D3 supplementation in CIPN shows significant improvement in reduction of neuropathic pain as compared to Gabapentin alone cases at 3 months and 6 months follow-up. Therefore, we can recommend the use of vitamin B12 and vitamin D3 supplementation with Gabapentin to mitigate the CIPN symptoms in cancer patients.

Keywords: CIPN symptoms in Cancer; Gabapentin Alone; Vitamin D3; Vitamin B12; Antineoplastic Agents

Abbreviations: S-LANSS: Self-Reported Leeds Assessment of Neuropathic Symptoms and Signs; VAS: Visual Analog Scale; PIS: Participant Information Sheet; CIPN: Chemotherapy Induced Peripheral Neuropathy.

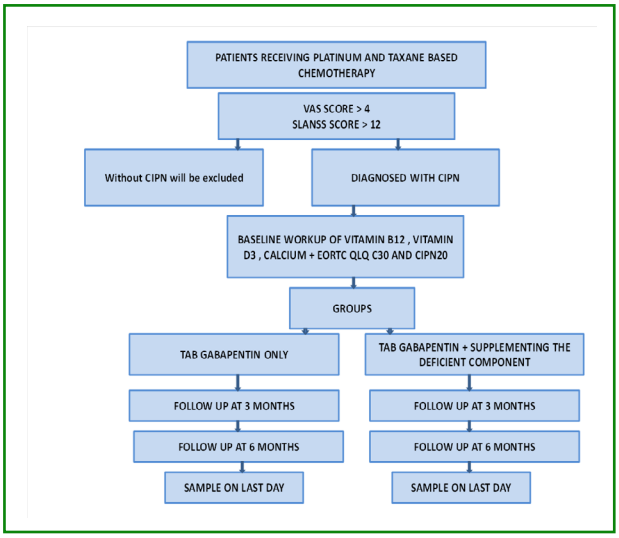
Introduction

The prevalence of CIPN has been estimated to be 68.1% in the 1st month after administration of platinum (oxaliplatin/ carboplatin) or taxane based antineoplastic agents (paclitaxel/ Docetaxel). These agents have increased the overall survival rate of cancer patients but with development of debilitating side effects like motor and sensory symptoms-numbness, paraesthesia, dysaesthesias, loss of balance, muscle weakness and burning pain which poses a great challenge for oncologists to warrant a reduction in the dosage or stop the chemotherapeutic course to mitigate CIPN symptoms. Therefore, it is of at most importance to develop prophylactic measures to prevent CIPN so that the patients can be cancer free and not suffer from debilitating neuropathy induced by cancer treatment.

Methodology of Study

The prospective observational study was done on patients registered at the Pain Clinic/ Medical Oncology clinic (Breast Clinic, Lung clinic and GI clinic), IRCH, AIIMS New Delhi. Patients who are receiving in-patient or out-patient platinum/ taxane and vinca alkaloids-based chemotherapy regimens from the Department of Onco-Anesthesia and Palliative Medicine/ Medical Oncology was approached to participate in the study. Those meeting the study selection criteria were provided with the Participant Information Sheet (PIS) that will provide details about the objectives of the study and study procedure. Those willing to provide the written informed consent were included in the study. Then the study subjects were been assessed using the study questionnaires. The study subjects were assessed by the following tools:

- Self-Reported Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) scale- It aims to identify neuropathic pain using SLANSS questionnaires without the need for doing clinical examination [1].
- Visual Analog Scale (VAS) - It consists of a 10cm line, the patient places a mark on the point on the line corresponding to the patients rating of pain intensity, and the line usually signifies the following 1-3 Mild pain, 3-6 Moderate pain and more than 7-Severe pain. The line can be depicted with a horizontal or vertical orientation usually the horizontal line is preferred [1].

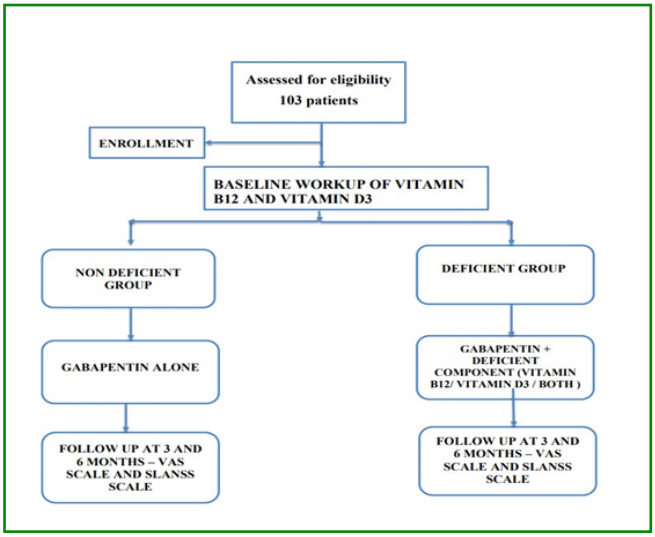


Results and Analysis

A total of 103 patients receiving platinum, taxane and vinca-alkaloids based chemotherapy with clinically diagnosed chemotherapy induced peripheral neuropathy was enrolled in the study. After taking informed consent a baseline workup of vitamin B12 and vitamin D3. Those with deficiency of either vitamin were given Gabapentin with the deficient nutritional supplement likewise the other group was receiving gabapentin alone. They were subsequently followed up for a period of 3 months and 6 months with SLANSS scale and VAS scale respectively. All the inclusion and exclusion criteria were checked before enrolment of the patient into the study. No patient had lost to follow up or expired during the study period.

Study Protocol

A Prospective Observational Study Design



Demographic Profile of Patients

Age Distributions: Total 103 patients were enrolled in the study between the age group of 20 years to 82 years, out of which 12 patients were between the age of 20-30 years, 25 patients were between 31-40 years, 24 patients were between 41-50 years and 42 patients were above 50 years of age group. The mean age of the patients was 47.15 ± 12.24years (mean ± SD).

Age Distributions (in years)	Frequency	Percentage
20-30	12	11.70%
31-40	25	24.30%
41-50	24	23.30%
>50	42	40.80%
Total	103	100.00%

Table 1: Showing Age Distributions (in years).

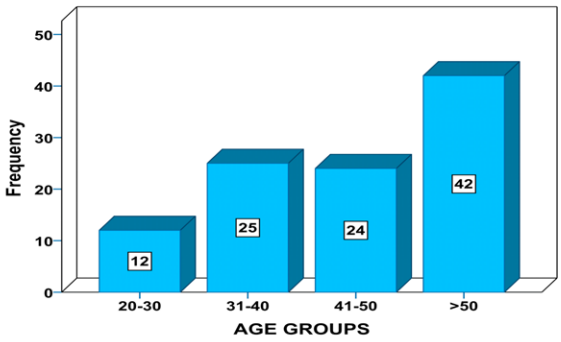


Figure 1: Bar Diagram Showing Age Distribution (in years).

Sex Distribution: In this study, total 103 patients were enrolled, out of which 31 were males and 72 were females.

Gender Distribution	Frequency	Percent
FEMALE	72	69.90%
MALE	31	30.10%
TOTAL	103	100.00%

Table 2: Showing Gender Distribution.

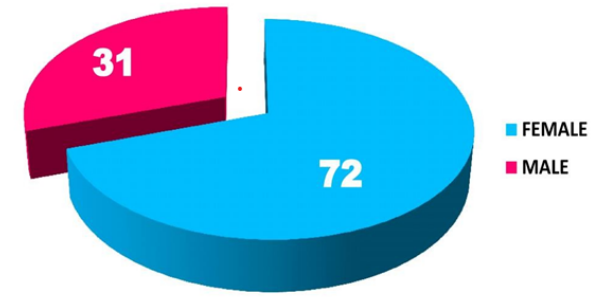


Figure 2: Pie Chart Showing Gender Distribution.

Diagnosis: In 103 patients enrolled in the study, 49 cases were diagnosed with Carcinoma Breast (including primary and metastatic), 35 cases were Carcinoma Lung, whereas 19 cases were Carcinoma Ovary.

Diagnosis	Frequency	Percent
CA Breast	49	47.6
CA Lung	35	34
CA Ovary	19	18.4
Total	103	100

Table 3: Showing Diagnosis.

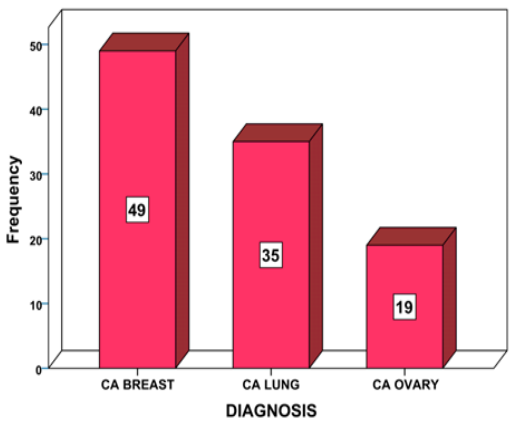


Figure 3: Bar Diagram Showing Distribution of Diagnosis.

Chemotherapy Received

Diagnosis	Frequency	Percent
CA Breast	49	47.6
CA Lung	35	34
CA Ovary	19	18.4
Total	103	100

Table 4: Showing Percentage of Chemotherapy Received.

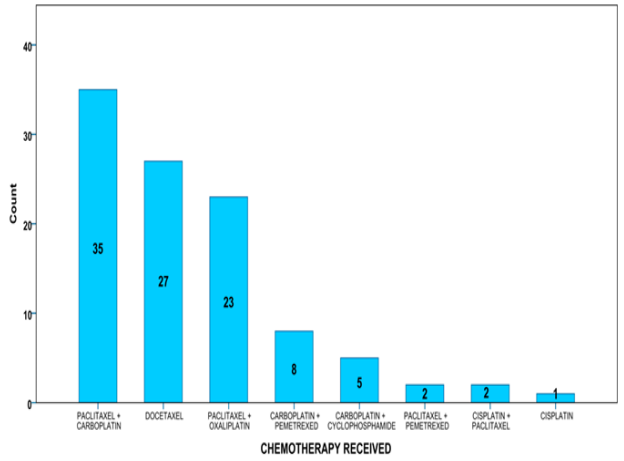


Figure 4: Bar Chart Showing Frequency of Chemotherapy Received.

Duration: The mean duration of Chemotherapy received in study population was 2.56±1.34 (Mean±SD).

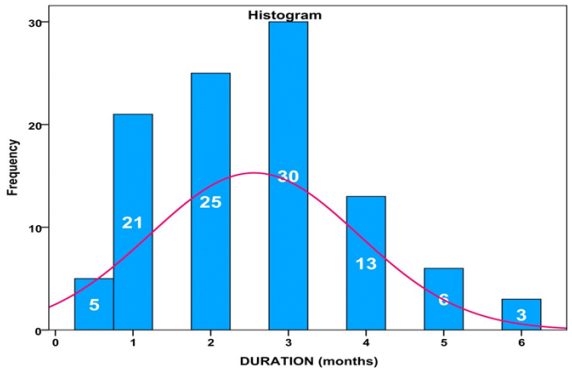


Figure 5: Histogram Showing Frequency of Duration of Chemotherapy.

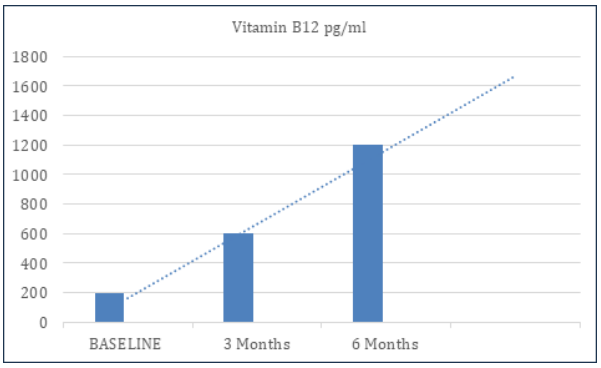


Figure 6: Serum Vitamin B12 Levels at Baseline, 3 Months and 6 Months after Vitamin B12 Supplementation.

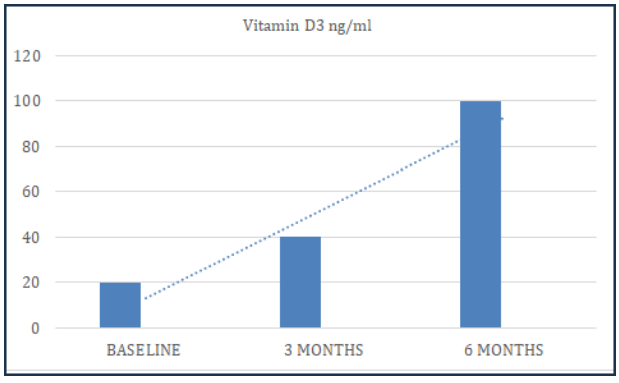


Figure 7: Serum Vitamin D3 Levels at Baseline, 3 Months and 6 Months after Vitamin D3 Supplementation.

S-LANSS Score

In the study population, total of 103 cases were analyzed, it was noted that almost all the patients had signs and

symptoms of tingling, pins and needle like sensation in either lower limb or upper limb associated with burning pain like sensation. Around 60 cases reported to have electric shock like sensation in the toes or fingers, 25 cases reported to have weakness of the either limb, 23 cases had skin discoloration post chemotherapy while 15 cases of patients complained to have allodynia.

Symptoms	Frequency
Tingling/pin/needles like	103
Burning Pain	103
Electric shock like	60
Weakness	25
Skin Discoloration	23
Allodynia	15

Table 6: Showing Symptom Assessment on SLANSS Scale.

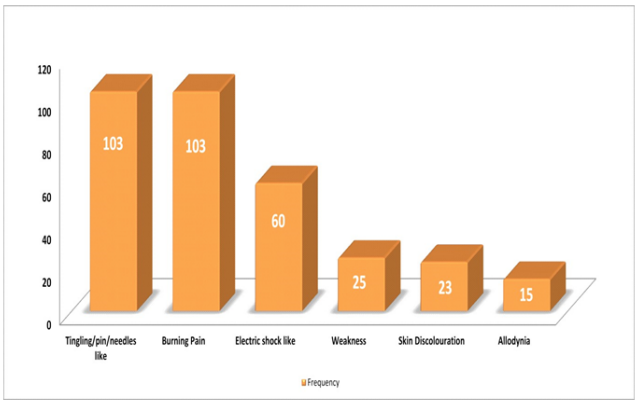


Figure 8: Bar diagram Showing Symptom Assessment on SLANSS Scale.

Pre-Interventional Evaluations

Baseline SLANSS Score: The mean baseline SLANSS score was 15.39±2.4 (Mean±SD). The baseline SLANSS score was ranging from a minimum 12 to maximum 23. A score of 12 or more suggests pain of predominantly neuropathic origin, therefore all the patients with SLANSS score above >12 were analyzed in the study.

Mean	Standard Deviation
15.39	2.4

Table 7: Mean baseline SLANSS Score.

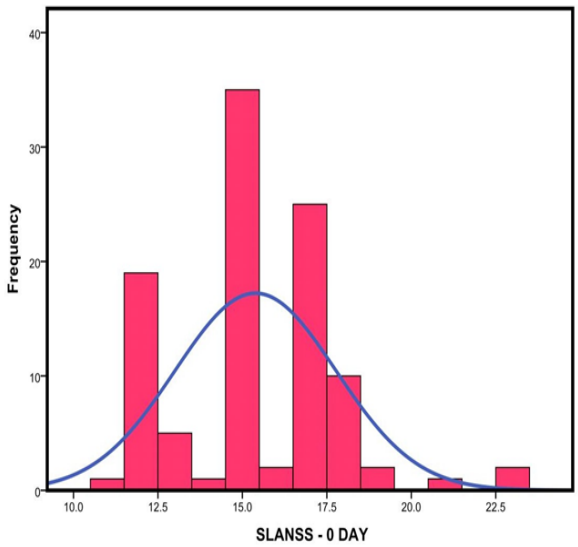


Figure 9: Histogram Showing Normal Distribution of Baseline SLANSS Score.

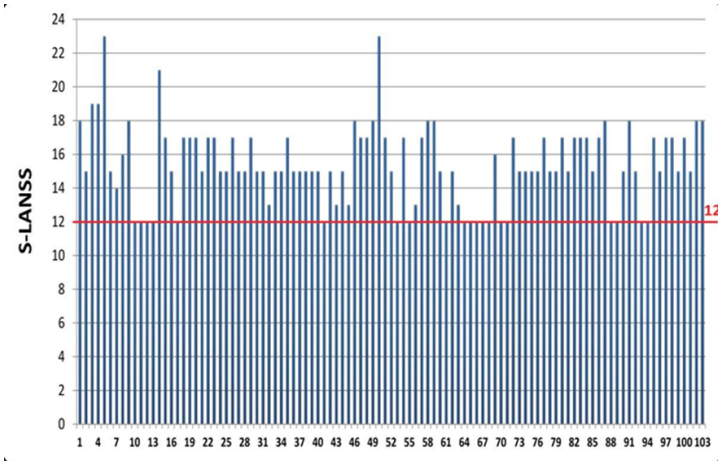


Figure 10: Bar diagram showing baseline SLANSS score.

Baseline VAS Scale: The mean baseline VAS score was 6.66±1.06 (Mean ± SD). The baseline VAS score was ranging from a minimum 4 to maximum 9. Patients with minimum VAS scale of >4 were analyzed in the study.

Mean	Standard deviation
6.66	1.06

Table 8: Mean Baseline VAS Score.

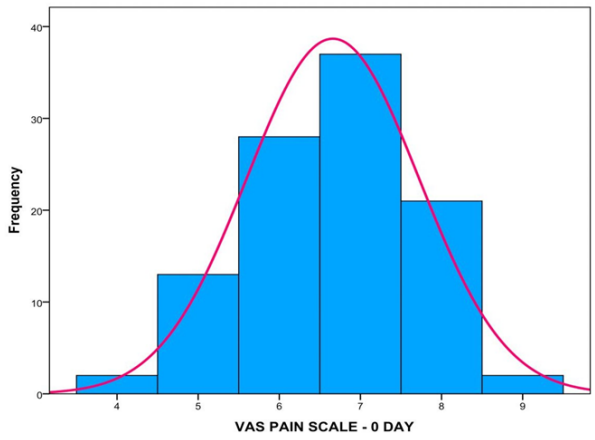


Figure 11: Histogram Showing Distribution of Baseline VAS scale.

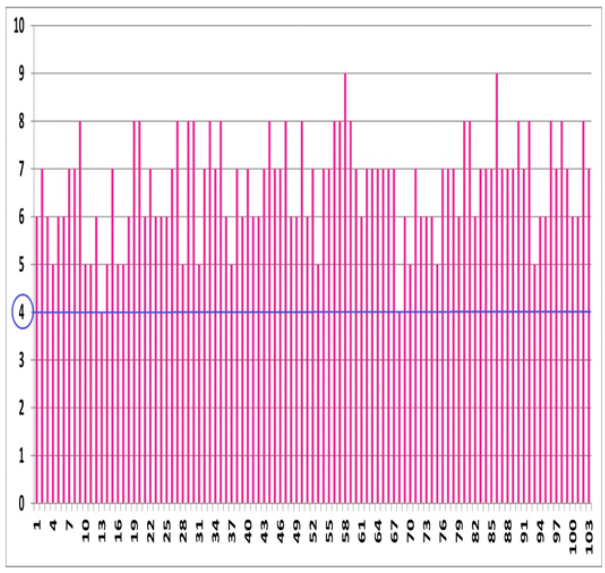


Figure 12: Bar Diagram Showing Baseline VAS scale of all Patients.

Clinical Evaluation: For the purpose of Chemotherapy induced peripheral neuropathy evaluation, subjective scoring was done with the following: Self-reported Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) questionnaire and the Visual Analogue Scale for pain. Subjective scoring was done prior to the intervention as a baseline value and post-intervention scores at the following intervals: SLANSS (3months and 6 months) and VAS score (3 months and 6 months) and the results of the above-mentioned evaluations are discussed below:

Visual Analogue Scale (VAS): We quantified the pain level using the Visual Analogue Scale with a vertical line on a 10cm horizontal line.

Baseline Visual Analogue Scale: The Baseline Visual Analogue Scale observed in the study population had a mean value of 6.66 ±1.06 (Mean±SD) ranging from a minimum of 4 to a maximum of 9.

Post- Intervention Visual Analogue Scale: The Post-Intervention Visual Analogue Scale observed in the study population at various intervals of follow up has been discussed below:

- At 3 months - Mean value of 4.88±.921 (Mean±SD) ranging from a minimum of 2 to a maximum of 7.
- At 6 months - Mean value of 3.33±1.31 (Mean±SD) ranging from a minimum of 1 to a maximum of 7.

Follow Up	Visual Analogue Scale for Pain (10mm)		
	Minimum	Maximum	Mean±SD
Baseline Value	4	9	6.66±1.06
3 months	2	7	4.88±.921
6 months	1	7	3.33±1.31

Table 9: Descriptive Statistics (trends) of VAS Over Period of Time.

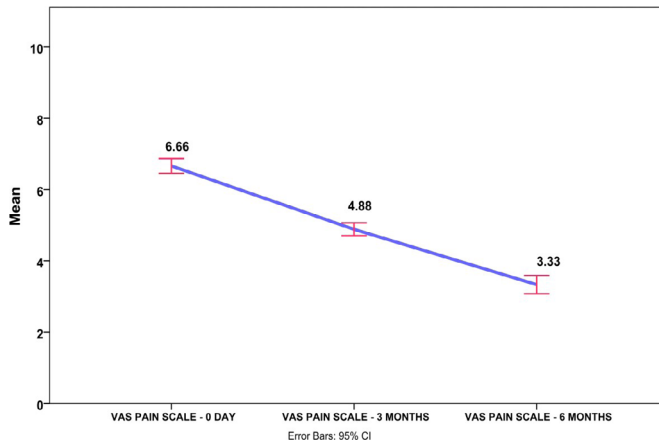


Figure 13: Graphical Representation of Mean VAS over Period of Time.

SLANSS Score

Baseline SLANSS Score: The Baseline SLANSS Score

observed in the study population had a mean value of 15.4 ±2.39 (Mean±SD) ranging from a minimum of 12 to a maximum of 23.

Post- Intervention SLANSS Score: The Post- Intervention SLANSS Score observed in the study population at various intervals of follow up has been discussed below:

- At 3 months - Mean value of 10.75 ± 3.83 (Mean±SD) ranging from a minimum of 4 to a maximum of 21.
- At 6 months - Mean value of 7.3± 3.8 (Mean±SD) ranging from a minimum of 2 to a maximum of 21.

Follow Up	Visual Analogue Scale for Pain (10mm)		
	Minimum	Maximum	Mean±SD
Baseline Value	4	9	6.66±1.06
3 months	2	7	4.88±.921
6 months	1	7	3.33±1.31

Table 10: Descriptive Statistics (trends) of SLANSS Score over Period of Time.

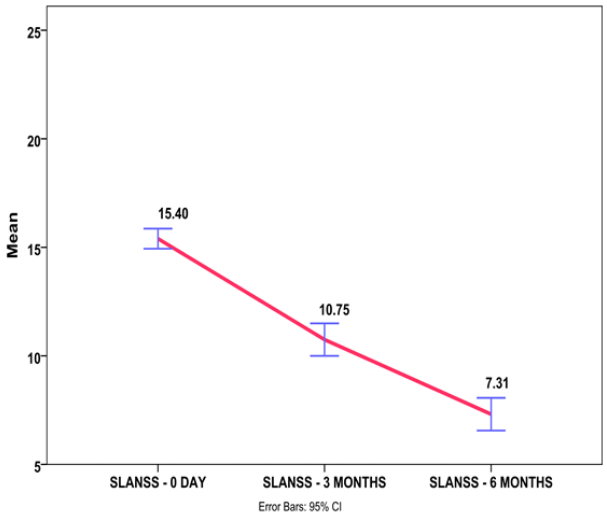


Figure 14: Graphical Representation of SLANSS Scale over Period of Time.

Descriptive Analysis

Outcomes Score in Different Intervention Groups
Visual Analogue Scale

Intervention Groups	Count	Visual Analogue Scale (MEAN±SD)		
		Baseline	3 months	6 months
Gabapentin	49	6.45±1.08	5.02±0.87	3.73±1.26
Gabapentin and vitamin D3	10	7.30±0.16	5.10±0.738	3.30±0.823
Gabapentin and vitamin B12	28	6.64±0.98	4.64±0.95	3.1±1.31
Gabapentin, vitamin B12 and vitamin D3	16	6.94±0.93	4.75±1.06	2.5±1.31

Table 11: Mean VAS Scale in Different Intervention Groups.

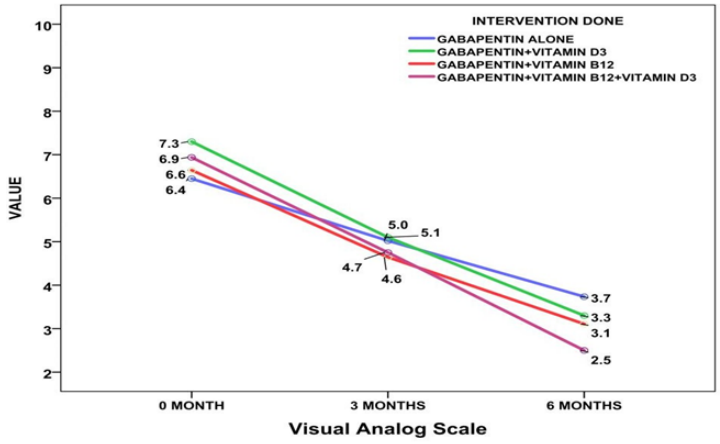


Figure 15: Line Diagram Representing Trend of VAS Scale in Different Intervention Groups.

SLANNS Score

Intervention Groups	Count	SLANSS Score (MEAN±SD)		
		Baseline	3 Months	6 Months
Gabapentin	49	15.65±2.32	11.96±3.75	8.84±3.9
Gabapentin and vitamin D3	10	16.20±3.36	12.80±4.36	8.60±5.02
Gabapentin and vitamin B12	28	14.7±2.03	9.14±3.6	5.46±3.0
Gabapentin, vitamin B12 and vitamin D3	16	15.3±2.28	8.56±1.3	5.06±.68

Table 12: Mean SLANSS Scale in Different Intervention Groups.

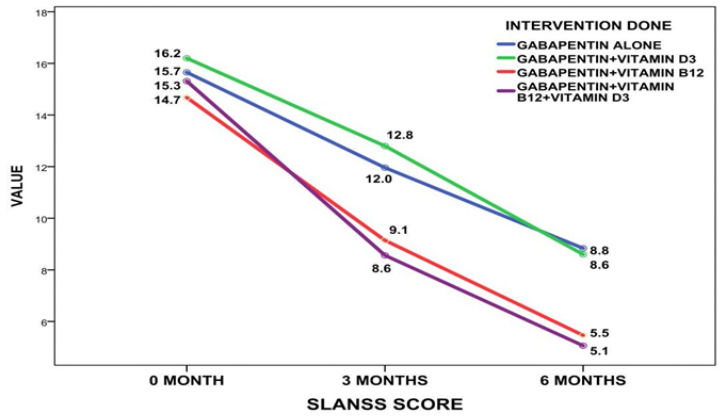


Figure 16: Line Diagram Representing Trend of SLANSS Score in Different Intervention Groups.

Comparative Statistical Analysis among Intervention Groups with Visual Analogue Scale at 6 Months: Visual analogue scale calculated at 6 months in different intervention groups, the mean score of Gabapentin alone treated was found to be 3.73±1.26 (Mean±SD), Gabapentin and Vitamin D3 groups 3.30±0.823 (Mean±SD), Gabapentin and Vitamin B12 3.1 ±1.31 (Mean±SD), Gabapentin Vitamin D3 and Vitamin B12 2.5±1.31 (Mean±SD) respectively, which showed that the VAS score improvement in intervention groups as compared to Gabapentin alone groups. Mean value of two independent groups were compared using the Independent Samples t Test.

S. No	VAS Score AT 6 Months	Mean±SD	T Score	P value
1	Gabapentin Alone	3.73±1.26		
	Gabapentin and Vitamin D3	3.30±0.823	1.047	P <.30
2	Gabapentin Alone	3.73±1.26		
	Gabapentin and Vitamin B12	3.1±1.31	2.075	P<.041
3	Gabapentin Alone	3.73±1.26		
	Gabapentin, Vitamin D3 and Vitamin B12	2.5±1.31	3.377	P<.001

Table 13: Showing Comparative Statistical Analysis of VAS score.

The difference in mean VAS score at 6 months between the 'Gabapentin Alone' and 'Gabapentin and Vitamin D3' groups was not statistically significant. The difference in mean VAS score at 6 months between the 'Gabapentin Alone' and 'Gabapentin and Vitamin B12' groups, 'Gabapentin Alone' and 'Gabapentin, vitamin D3 and Vitamin B12' groups was statistically significant with p value less than 0.05.

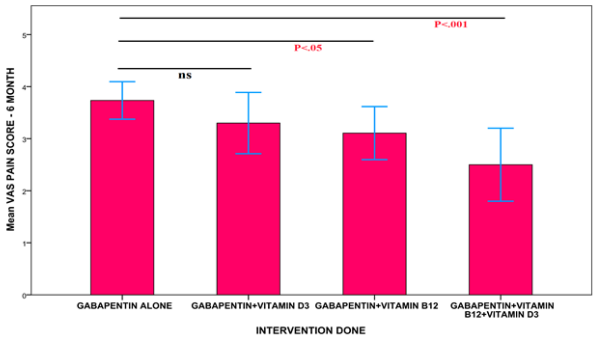


Figure 17: Histogram Showing Statistical Analysis among Intervention groups with VAS Score at 6 months.

Comparative Statistical Analysis among Intervention Groups with SLANSS Score at 6 months: SLANSS score calculated at 6 months in different intervention groups, the mean score of Gabapentin alone treated was found to be 8.84±3.9 (Mean±SD), Gabapentin and Vitamin D3 groups 8.60±5.02 (Mean±SD), Gabapentin and Vitamin B12 groups 5.46±3.0 (Mean±SD), Gabapentin, Vitamin D3 and Vitamin B12 was 5.06±.68 (Mean±SD) respectively, which showed that the SLANSS score improvement in Vitamin supplementations groups as compared to Gabapentin alone groups. Mean value of two independent groups were compared using the Independent Samples t Test.

S. No	SLANSS Score AT 6 Months	Mean±SD	T Score	P value
1	Gabapentin Alone	8.84±3.9		
	Gabapentin and Vitamin D3	8.60±5.02	0.167	P <.86
2	Gabapentin Alone	8.84±3.9		
	Gabapentin and Vitamin B12	5.46±3.0	3.96	P<.001
3	Gabapentin Alone	8.84±3.9		
	Gabapentin, Vitamin D3 and Vitamin B12	5.06±.68	3.86	P<.001

Table 14: Showing Comparative Statistical Analysis of SLANSS Score.

The difference in mean SLANSS score at 6 months between the 'Gabapentin Alone' and 'Gabapentin and Vitamin D3' groups was not statistically significant. The difference in mean VAS score at 6 months between the 'Gabapentin Alone' and 'Gabapentin and Vitamin B12' groups, 'Gabapentin Alone' and 'Gabapentin, vitamin D3 and Vitamin B12' groups was statistically significant with p value less than 0.05.

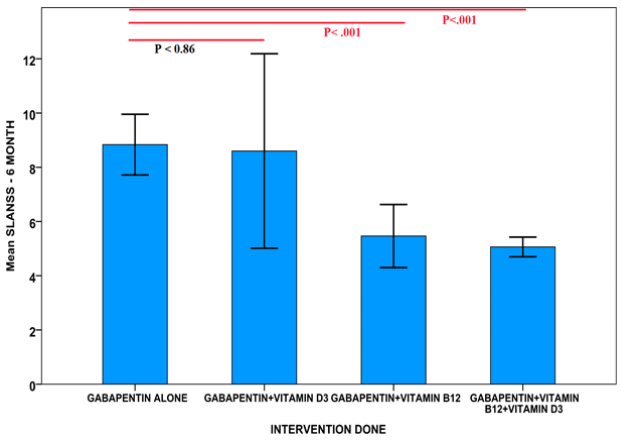


Figure 18: Histogram Showing Statistical Analysis among Intervention Groups with SLANSS Score at 6 month.

Discussion

Chemotherapy Induced Peripheral Neuropathy (CIPN) is a common dose limiting side effect of patients receiving treatment of cancer. Approximately 30-40% of patients treated with neurotoxic chemotherapy will develop CIPN, it is often sensory predominant with pain and may lead to long term morbidity in cancer survivors. CIPN prevalence was estimated to be 68.1% when measured in the 1st month of chemotherapy, 60.0% at 3 months and 30.0% at 6 months. It is therefore very crucial to estimate the incidence, grade of severity and identify the patients at high risk of developing CIPN so as to mitigate the long-term side effects and improve the overall quality of life in cancer patients.

There are no recent studies suggesting correlation of CIPN with vitamin B12 and Vitamin D3 deficiency, all the previous studies were related to use to multivitamins to eliminate the signs and symptoms of CIPN which warrant exploration to the individual vitamin supplementation as measures to reduce the impact on quality of life in cancer patients receiving chemotherapeutic agents.

Quite a number of studies has been conducted over the years to address the incidence of CIPN, signs and symptoms of CIPN, prophylactic measures to prevent the development

of CIPN and various drugs used to reduce the symptoms of CIPN for increasing the overall quality of life in cancer patients .Since the demographic and patients characteristics differ widely all over the world, it is important to establish data for this specific group of population for future research.

Through by the means of this study we have assessed the incidence of developing CIPN with the following antineoplastic drugs like -platinum based anti-neoplastics (oxaliplatin, carboplatin and cisplatin) and Taxanes (Paclitaxel and Docetaxel).

We have assessed the importance of early detection and prophylactic intervention using nutritional supplementation in chemotherapy induced peripheral neuropathy. It is emphasized that the patients receiving neurotoxic chemotherapeutic agents needs to undergo relevant investigations to identify the vitamin deficiencies like: Vitamin B12/ Vitamin D3/ Calcium and should be supplemented with the deficient component to mitigate the development of early CIPN signs and symptoms. It is also recommended to treat the neuropathic pain component using gabapentinoids in CIPN patients.

We have been successful in proving the clinical significance between CIPN and deficiency of vitamin B12 and vitamin D3. However, in our study population, all the patients had a normal calcium value (Normal reference range: 8.7-10.4 mg/dl) during the baseline and subsequent follow-up visits, suggesting that calcium values did not show any significant relationship with chemotherapeutic agents or cummulative doses administered.

Our study was conducted on 103 patients with confirmed clinical diagnosis of CIPN (SLANSS score >12 and VAS score >4). The mean age in our study was 47.15 ± 12.24 years which comprised of 31% males and 72% females, which was comparable to the previous studies done by Simon et al (October 2017) and Shah A, et al. [2,3] where the mean ages were 56.7 years (SD 11.8) and 58.1±16.4 respectively. All of these studies, assessing the prevalence and incidence of CIPN were conducted in England and USA depicting the average age group was more than >50 years indicating that the most affected age group to develop CIPN symptoms were the elderly population [2,3].

All the patients in our study were on regular follow-up at 3 and 6 months respectively and the minimum follow-up period was 6 months. During the follow-up visits -A blood investigation was sending to assess the status of: vitamin B12, Vitamin D3 and calcium levels of each patient, if found deficient they were been given the specific deficient component. All participants were also screened for CIPN signs and symptoms using - VAS scale and S-LANSS questionnaires, which were subsequently recorded and compared to the baseline scores.

In our study population, 49 cases were diagnosed with Carcinoma breast, 35 cases had carcinoma lung and 19 cases had carcinoma ovary. The mean duration of chemotherapy received in the study population was 2.56±1.34 (Mean±SD) in which maximum patients had received paclitaxel and carboplatin based chemotherapy (34%),docetaxel (6.2%),paclitaxel and oxaliplatin (22.3%), carboplatin and pametrexed (7.8%), carboplatin and cyclophosphamide (4.9%), paclitaxel and pametrexed (1.9%), cisplatin and paclitaxel (1.9%) and cisplatin alone (1%), these results were comparable to the study conducted by Mazilu L, et al. [4] where it was concluded that the highest incidence of chemotherapy induced peripheral neuropathy was associated with taxane based chemotherapy-paclitaxel (73.14%), oxaliplatin (72.22%), cisplatin (30%) and docetaxel (23.07%) [4].

Similarly, Pereira S, et al. [5] suggested that chemotherapy induced peripheral neuropathy was strongly associated with taxane based regimen like Docetaxel, signs and symptoms persisted for at least 6 months in most of the patients but the severity was comparatively low and had no impact on patient reported outcome, these results were also comparable to our current study suggesting that higher incidence of CIPN was seen in taxane based chemotherapeutic agents [5].

Symptom assessment was done using the SLANSS questionnaire: six most common symptoms found affecting our study population were: Tingling/ pins/ needle like sensation (103%), burning pain (103%), electric current like sensation (60%), weakness (25%), skin discoloration(23%) and allodynia (15%).

Magnowska M, et al. [6] conducted a study in patients treated with taxane and platinum group of anti-neoplastic drugs to analyse the effectiveness of gabapentinoids in CIPN , it was concluded that patients who were qualified to undergo gabapentin treatment had better neuropathic symptom improvement($p<0.027$) , pain ($p<0.027$) and neurological deficient ($p<0.0002$).Similarly, in our study the baseline VAS score was (6.45±1.08), after gabapentin treatment was initiated, there was a substantial decrease in the VAS score at 3 months(5.02±0.87) and 6 months(3.73±1.26) respectively, which was comparable to the values mentioned in their study. However, these studies cannot be compared with our current study due to difference in sample size, study design, and study settings [6].

Aghili M, et al. [7] suggested that gabapentin 300mg thrice daily given to patients treated with paclitaxel based chemotherapy in breast cancer is efficient in preventing intermediate to high grade neuropathies both objectively

and subjectively, these results could not be compared to our study as the study design and methods were different from our current study, however we can emphasis the effectiveness of gabapentin in reducing the signs and symptoms of CIPN through this study [7].

In the current study, we have divided the study population into four groups: Gabapentin alone, Gabapentin + Vitamin D3, Gabapentin + Vitamin B12 and Gabapentin + Vitamin B12 + Vitamin D3 respectively. They were compared using VAS score and SLANSS subjective outcome score.

In case of vitamin D3 nutrient supplementation group, it was noted that there is a decreasing trend in VAS score at 3 month and 6 months. So we conducted a comparative study using the paired T test for Gabapentin alone group (Mean 3.73+1.26) and Gabapentin + Vitamin D3 group (Mean 3.30+0.823) , it was noted that there was no significant difference in VAS score at 6 month (T=1.047, p = <0.30). Similarly SLANSS score was compared with the same groups (Gabapentin alone(8.84+3.9) and Gabapentin + Vitamin D3 group (8.60+5.02) , it was noted that there was no significant difference in SLANSS score at 6 months. (T= 0.167, p<0.86). So we can conclude that Vitamin D3 supplementation does not significantly improve the CIPN signs and symptoms.

However the study conducted by Grim J, et al. [8] to analyze the possible deficiencies in nutritional supplementation that can be used as a prophylactic measure in future to prevent the development of CIPN. It was noted that supplementation of vitamin D before chemotherapy could be an efficient neuro-protective in chemotherapy induced peripheral neuropathy prophylaxis, as significantly lower levels of 25OH derivative of vitamin D were observed in the chemotherapy induced peripheral neuropathy group throughout the study period. Vitamin D levels in the group without chemotherapy induced peripheral neuropathy were estimated to be 38.2nmol/L whereas in group with chemotherapy induced peripheral neuropathy was 25.6nmol/L. These results were conflicting with our study as the VAS score and SLANSS score calculated at 6 months follow-up was not statistically significant suggesting that there was no significant clinical improvement in CIPN signs and symptoms with vitamin D3 supplementation [8].

In vitamin B12 nutrient supplementation group, it was noted that there is a decreasing trend in VAS scores at 3 month and 6 months. So we conducted a comparative study using the paired T test for Gabapentin alone group (Mean 3.73+1.26) and Gabapentin + Vitamin B12 group (Mean 3.1+1.31) , it was noted that there was significant difference in VAS score at 6 month (T=2.075 , p = <0.041). Similarly, SLANSS score was compared with the same groups (Gabapentin alone(8.84+3.0) and Gabapentin + Vitamin B12 group (5.46+3.0) , it was noted that there was significant difference in SLANSS score at 6 months. (T= 3.96, p<0.001). So we can conclude that Vitamin B12 supplementation can significantly improve the CIPN signs and symptoms.

These results were comparable to the retrospective study conducted by Solomon LR, et al. [9] to evaluate the deficiency of Vitamin B12 in cancer patients, it was noted that both the functional vitamin B12 deficiency and neurological abnormalities had clinical improvement in CIPN signs and symptoms after vitamin B12 therapy. Vitamin B12 values were increased (>900 pg/ml) in 30 % and decreased (≤300 pg/ml) in 17 % of subjects tested. Increased levels of methylmelonic acid (>250 nmol/l) and homocysteine levels (>12.1 μmol/l) was present in 38% and 23 % of subjects respectively and at least one of the metabolite was increased in 54% of evaluated subjects, even when the values of B12 were ≥1500 pg/ml (n = 36), increased methylmelanic acid and homocysteine values occurred in 31 and 23 % of subjects. In all the four subjects B12 therapy decreased methylmelonic acid values and improved neurologic findings in the three subjects's tested. It was concluded in his study that the signs and symptoms of chemotherapy induced peripheral neuropathy were present in all four patients and improved in all three patients who were intervened with Vitamin B12 therapy.

Likewise, in the Vitamin B12 + Vitamin D3 nutrient supplementation group, it was noted that there is a decreasing trend in VAS score and SLANSS score at 3 month and 6 months respectively. A comparative study using the paired T test for Gabapentin alone group (Mean 3.73+1.26) and Gabapentin + Vitamin B12 + Vitamin D3 group (Mean 2.5+1.31), it was noted that there was significant difference in VAS score at 6 month (T=3.377, p=<0.001)). Similarly SLANSS score was compared with the same groups Gabapentin alone (8.84+3.9) and Gabapentin + Vitamin B12 group + Vitamin D3 group (5.06+0.68), it was noted that there was significant difference in SLANSS score at 6 months. (T=3.86, p =<0.001). So we can conclude that Vitamin B12 + Vitamin D3 supplementation can significantly improve the CIPN signs and symptoms.

Gary RZ, et al. [10] had conducted a DELCap questionnaire based study in breast cancer patients receiving doxorubicin, cyclophosphamide and paclitaxel to analyse the supplement use of multivitamins like vitamin D, vitamin C, vitamin B6, vitamin E, folic acid, vitamin B12, calcium, iron, omega 3 fatty acids and glucosamine before and at the diagnosis in chemotherapy induced peripheral neuropathy. The supplement use was evaluated in relation to CIPN with the help of NCI CTCAE v3.0 and FACT/GOG-Ntx subscales. It was noted in his study that the multivitamin use before the diagnosis was associated with reduced CIPN symptoms,

therefore it was further concluded that multivitamins use may be associated with reduced risk of developing signs and symptoms of chemotherapy induced peripheral neuropathy although individual dietary supplement use did not appreciably affect the risk. These results cannot be directly compared to our study as the study design, methods, questionnaires and the multivitamins used were different from our current study; however we can emphasis the effectiveness of multivitamin use before or during the administration of chemotherapeutic agents in mitigating the signs and symptoms of CIPN [10].

Therefore, with the above results we can recommend the need of good quality RCT in the future to establish the clinical correlation between chemotherapy induced peripheral neuropathy with deficiency of vitamin B12, vitamin D3 and calcium, symptom burden and quality of life [11-18].

Conclusion

- Gabapentin + Vitamin D3 supplementation did not show significant improvement in the neuropathic pain component in CIPN patients as measured by VAS score and SLANSS score from baseline to 6 months follow-up [19-28].
- Gabapentin + Vitamin B12 and Gabapentin + Vitamin B12 + Vitamin D3 supplementation in CIPN shows significant improvement in reduction of neuropathic pain as compared to Gabapentin alone cases at 3 months and 6 months follow-up [29-37].
- Therefore, we can recommend the use of vitamin B12 and vitamin D3 supplementation with Gabapentin to mitigate the CIPN symptoms in cancer patients [38-46].

References

1. Bennett MI, Smith BH, Torrance N, Potter J (2005) The S-LANSS score for identifying pain of predominantly neuropathic origin: validation for use in clinical and postal research. J pain 6(3): 149-158.

2. Shah A, Hoffman EM, Mauermann ML, Loprinzi CL, Windebank AJ, et al. (2018) Incidence and disease burden of chemotherapy-induced peripheral neuropathy in a population-based cohort. Journal of Neurology, Neurosurgery & Psychiatry 89(6): 636-641.

3. Simon NB, Danso MA, Alberico TA, Basch E, Bennett AV (2017) The prevalence and pattern of chemotherapy-induced peripheral neuropathy among women with breast cancer receiving care in a large community oncology practice. Quality of Life Research 26(10): 2763-2772.

4. Mazilu L, Stanculeanu DL, Gheorghe AD, Voinea F, Suceveanu AP, et al. (2019) Incidence of chemotherapy-induced peripheral neuropathy in cancer patients in clinical practice. Age. 67(3): 472-476.

5. Pereira S, Fontes F, Sonin T, Dias T, Fragoso M, et al. (2016) Chemotherapy-induced peripheral neuropathy after neoadjuvant or adjuvant treatment of breast cancer: a prospective cohort study. Supportive Care in Cancer 24(4): 1571-1581.

6. Magnowska M, Izycka N, Kapola CJ, Romała A, Lorek J, et al. (2018) Effectiveness of gabapentin pharmacotherapy in chemotherapy-induced peripheral neuropathy. Ginekologia polska 89(4): 201-205.

7. Aghili M, Zare M, Mousavi N, Ghalehtaki R, Sotoudeh S, et al. (2019) Efficacy of gabapentin for the prevention of paclitaxel induced peripheral neuropathy: A randomized placebo controlled clinical trial. The breast journal 25(2): 226-231.

8. Grim J, Ticha A, Hyspler R, Valis M, Zadak Z (2017) Selected risk nutritional factors for chemotherapy-induced polyneuropathy. Nutrients 9(6): 535.

9. Solomon LR (2016) Functional vitamin B12 deficiency in advanced malignancy: implications for the management of neuropathy and neuropathic pain. Supportive Care in Cancer 24(8): 3489-3494.

10. Zirpoli GR, McCann SE, Sucheston CLE, Hershman DL, Ciupak G, et al. (2017) Supplement use and chemotherapy-induced peripheral neuropathy in a cooperative group trial (S0221): the DELCaP study. JNCI: Journal of the National Cancer Institute 109(12).

11. Sangeetha P, Das UN, Koratkar R, Suryaprabha P (1990) Increase in free radical generation and lipid peroxidation following chemotherapy in patients with cancer. Free Radical Biology and Medicine 8(1): 15-19.

12. Look MP, Musch E (1994) Lipid peroxides in the polychemotherapy of cancer patients. Chemotherapy 40(1): 8-15.

13. Weijl NI, Hopman GD, Wipkink BA, Lentjes EG, Berger HM, et al. (1998) Cisplatin combination chemotherapy induces a fall in plasma antioxidants of cancer patients. Annals of Oncology 9(12): 1331-1337.

14. Bulua AC, Simon A, Maddipati R, Pelletier M, Park H, et al. (2011) Mitochondrial reactive oxygen species promote production of proinflammatory cytokines and are elevated in TNFR1-associated periodic syndrome (TRAPS). Journal of Experimental Medicine 208(3): 519-533.

15. Areti A, Yerra VG, Naidu VG, Kumar A (2014) Oxidative stress and nerve damage: role in chemotherapy induced peripheral neuropathy. Redox biology 2: 289-295.

16. Canta A, Pozzi E, Carozzi VA (2015) Mitochondrial dysfunction in chemotherapy-induced peripheral neuropathy (CIPN). Toxics 3(2): 198-223.

17. Flatters SJ, Bennett GJ (2006) Studies of peripheral sensory nerves in paclitaxel-induced painful peripheral neuropathy: evidence for mitochondrial dysfunction. Pain 122(3): 245-257.

18. Siau C, Bennett GJ (2006) Dysregulation of cellular calcium homeostasis in chemotherapy-evoked painful peripheral neuropathy. Anesthesia and analgesia 102(5): 1485-1490.

19. Carozzi VA, Canta A, Chiorazzi A (2015) Chemotherapy-induced peripheral neuropathy: What do we know about mechanisms. Neuroscience letters 596: 90-107.

20. Jordan B, Jahn F, Beckmann J, Unverzagt S, Muller TC, et al. (2016) Calcium and magnesium infusions for the prevention of oxaliplatin-induced peripheral neurotoxicity: a systematic review. Oncology 90(6): 299-306.

21. Kidd JF, Pilkington MF, Schell MJ, Fogarty KE, Skepper JN, et al. (2002) Paclitaxel affects cytosolic calcium signals by opening the mitochondrial permeability transition pore. Journal of Biological Chemistry 277(8): 6504-6510.

22. Boyette DJ, Xin W, Zhang H, Dougherty PM (2011) Intraepidermal nerve fiber loss corresponds to the development of taxol-induced hyperalgesia and can be prevented by treatment with minocycline. PAIN 152(2): 308-313.

23. Boehmerle W, Huehnchen P, Peruzzaro S, Balkaya M, Endres M (2014) Electrophysiological, behavioral and histological characterization of paclitaxel, cisplatin, vincristine and bortezomib-induced neuropathy in C57Bl/6 mice. Scientific reports 4(1): 6370.

24. Sittl R, Lampert A, Huth T, Schuy ET, Link AS, et al. (2012) Anticancer drug oxaliplatin induces acute cooling-aggravated neuropathy via sodium channel subtype NaV1. 6-resurgent and persistent current. Proceedings of the National Academy of Sciences 109(17): 6704-6709.

25. Zitvogel L, Apetoh L, Ghiringhelli F, Kroemer G (2008) Immunological aspects of cancer chemotherapy. Nature reviews immunology 8(1): 59-73.

26. Makker PG, Duffy SS, Lees JG, Perera CJ, Tonkin RS, et al. (2017) Characterisation of immune and neuroinflammatory changes associated with chemotherapy-induced peripheral neuropathy. PloS one 12(1): e0170814.

27. Howell SB, Safaei R, Larson CA, Sailor MJ (2010) Copper transporters and the cellular pharmacology of the platinum-containing cancer drugs. Molecular pharmacology 77(6): 887-894.

28. Dasari S, Tchounwou PB (2014) Cisplatin in cancer therapy: molecular mechanisms of action. European journal of pharmacology 740: 364-378.

29. Alcindor T, Beauger N (2011) Oxaliplatin: a review in the era of molecularly targeted therapy. Current oncology 18(1): 18-25.

30. Todd RC, Lippard SJ (2009) Inhibition of transcription by platinum antitumor compounds. Metallomics 1(4): 280-291.

31. Tesniere A, Schlemmer F, Boige V, Kepp O, Martins I, et al. (2010) Immunogenic death of colon cancer cells treated with oxaliplatin. Oncogene 29(4): 482-491.

32. Deuis JR, Zimmermann K, Romanovsky AA, Possani LD, Cabot PJ, et al. (2013) An animal model of oxaliplatin-induced cold allodynia reveals a crucial role for Nav1.6 in peripheral pain pathways. Pain 154(9): 1749-1757.

33. Huang R, Murry DJ, Kolwankar D, Hall SD, Foster DR (2006) Vincristine transcriptional regulation of efflux drug transporters in carcinoma cell lines. Biochemical pharmacology 71(12): 1695-1704.

34. Gregory RK, Smith IE (2000) Vinorelbine-a clinical review. British journal of cancer 82(12): 1907-1913.

35. Cavaletti G, Marmiroli P (2010) Chemotherapy-induced peripheral neurotoxicity. Nature Reviews Neurology 6(12): 657-666.

36. Argyriou AA, Cavaletti G, Briani C, Velasco R, Bruna J, et al. (2013) Clinical pattern and associations of oxaliplatin acute neurotoxicity: a prospective study in 170 patients with colorectal cancer. Cancer 119(2): 438-444.

37. Sereno M, Gutierrez GG, Rubio JM, Apellaniz RM, Sanchez BL, et al. (2017) Genetic polymorphisms of SCN9A are associated with oxaliplatin-induced neuropathy. BMC cancer 17(1): 63.

38. Seretny M, Currie GL, Sena ES, Ramnarine S, Grant R, et al. (2014) Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: a

systematic review and meta-analysis. Pain 155(12): 2461-2470.

39. Andersen HE, Pitz M, Shay B (2019) Neuropathic pain in taxane-induced peripheral neuropathy: evidence for exercise in treatment. Neurorehabilitation and neural repair (10):792-799.

40. Reyes-Gibby C, Morrow PK, Bennett MI, Jensen MP, Shete S (2010) Neuropathic pain in breast cancer survivors: using the ID pain as a screening tool. Journal of pain and symptom management 39(5): 882-889.

41. Schloss JM, Colosimo M, Airey C, Vitetta L (2015) Chemotherapy-induced peripheral neuropathy (CIPN) and vitamin B12 deficiency. Supportive Care in Cancer 23(7): 1843-1850.

42. Jennaro TS, Smith EM, Vangipuram K, Kidwell KM, Burness ML, et al. (2020) Vitamin D insufficiency and risk of paclitaxel-induced peripheral neuropathy 180(3): 707-714.

43. Ishibashi K, Okada N, Miyazaki T, Sano M, Ishida H (2010) Effect of calcium and magnesium on neurotoxicity and blood platinum concentrations in patients receiving mFOLFOX6 therapy: a prospective randomized study. International journal of clinical oncology 15(1): 82-87.

44. Wolf S, Barton D, Kottschade L, Grothey A, Loprinzi C (2008) Chemotherapy-induced peripheral neuropathy: prevention and treatment strategies. European journal of cancer 44(11): 1507-1515.

45. Muto O, Ando H, Ono T, Itagaki H, Kobayashi Y, et al. (2007) Reduction of oxaliplatin-related neurotoxicity by calcium and magnesium infusions. Cancer & chemotherapy 34(4): 579-581.

46. Pachman DR, Barton DL, Watson JC, Loprinzi CL (2011) Chemotherapy-induced peripheral neuropathy: prevention and treatment. Clinical Pharmacology & Therapeutics 90(3): 377-387.