Support Care Cancer
DOI 10.1007/s00520-016-3404-y

ORIGINAL ARTICLE

A randomised, placebo-controlled trial assessing the efficacy of an oral B group vitamin in preventing the development of chemotherapy-induced peripheral neuropathy (CIPN)

Janet M. Schloss[1,2] · **Maree Colosimo**[3] · **Caroline Airey**[4] · **Paul Masci**[1] · **Anthony W. Linnane**[5,6] · **Luis Vitetta**[5,6]

Received: 31 May 2016 / Accepted: 29 August 2016

Abstract

Introduction Chemotherapy-induced peripheral neuropathy (CIPN) is a debilitating side effect resulting from neurotoxic chemotherapeutic agents. This study aimed to assess the efficacy and safety of an oral B group vitamin compared to placebo, in preventing the incidence of CIPN in cancer patients undergoing neurotoxic chemotherapy.

Methods A pilot, randomised, placebo-controlled trial was conducted. Newly diagnosed cancer patients prescribed with taxanes, oxaliplatin or vincristine were invited to participate. A total of 71 participants (female 68 %, male 32 %) were enrolled into the study and randomised to the B group vitamin ($n = 38$) arm or placebo ($n = 33$). The data from 47 participants were eligible for analysis (B group vitamins $n = 27$, placebo $n = 22$). The primary outcome measure was the total neuropathy score assessed by an independent neurologist. Secondary outcome measures included serum vitamin B levels, quality of life, pain inventory and the patient neurotoxicity questionnaires. Outcome measures were conducted at baseline, 12, 24 and 36 weeks.

Results The total neuropathy score (TNS) demonstrated that a B group vitamin did not significantly reduce the incidence of CIPN compared to placebo ($p = 0.73$). Statistical significance was achieved for patient perceived sensory peripheral neuropathy (12 weeks $p = 0.03$; 24 weeks $p = 0.005$; 36 weeks $p = 0.021$). The risk estimate for the Patient Neurotoxicity Questionnaire (PNQ) was also statistically significant (OR = 5.78, 95 % CI = 1.63–20.5). The European Organisation of Research and Treatment of Cancer (EORTC) quality of life, total pain score and pain interference showed no significance ($p = 0.46$, $p = 0.9$, $p = 0.37$ respectively). A trend was observed indicating that vitamin B12 may reduce the onset and severity of CIPN.

Conclusion An oral B group vitamin as an adjunct to neurotoxic chemotherapy regimens was not superior to placebo ($p > 0.05$) for the prevention of CIPN. Patients taking the B group vitamin perceived a reduction in sensory peripheral neuropathy in the PNQ. Moreover, a robust clinical study is warranted given that vitamin B12 may show potential in reducing the onset and severity of CIPN.

Trial number: ACTRN12611000078954

Protocol number: UH2010000749

✉ Janet M. Schloss
janet.schloss@uqconnect.edu.au

Maree Colosimo
maree@qldoncology.com.au

Caroline Airey
caroline.airey@health.qld.gov.au

Paul Masci
p.masci@uq.edu.au

Anthony W. Linnane
tlinnane.cmbm@live.com.au

Luis Vitetta
luis.vitetta@sydney.edu.au

1 The University of Queensland, School of Medicine, Level 5, TRI, Princess Alexandra Hospital, Ipswich Road, Woolloongabba, Brisbane 4102, Australia

2 Endeavour College of Natural Health, Brisbane 4006, Australia

3 Medical Oncology Group of Australia, Clinical Oncology Society of Australia, Queensland Clinical Oncology Group, Brisbane 4000, Australia

4 Neurology Fellow at Queensland Health, Department of Neurology, Ned Hanlon Building, RBWH, Herston, Brisbane 4006, Australia

5 The University of Sydney, Sydney Medical School, Sydney 2006, Australia

6 Medlab Clinical Ltd, Sydney 2015, Australia

Published online: 09 September 2016

Keywords Chemotherapy-induced peripheral neuropathy · CIPN · B vitamins · Vitamin B12 · Taxanes · Vincristine

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN), numbness, tingling and pain in hands and feet is a debilitating clinical condition that represents a dose-limiting side effect from neurotoxic antineoplastic agents such as taxanes, platinum compounds, vinca alkaloids, proteasome inhibitors and other individual agents [1]. The incidence of CIPN has been reported with the administration of platinum drugs, cisplatin (60 %) and oxaliplatin (80 %), and anti-tubulin drugs such as paclitaxel (60 %) and vincristine (75 %) [2–7].

It is estimated that one third of all patients who undergo chemotherapy experience some form of CIPN [2]. Patients experiencing moderate to severe CIPN report a reduced quality of life [3], chronic discomfort [4] and disruption of physical abilities for general life activities which can be temporary or permanent [3]. Due to advanced medical treatment for cancer over the last five decades, there has been a threefold increase in the number of cancer survivors globally [1]. According to the World Health Organisation (2015), there are approximately 14.1 million new cases and 8.2 million cancer-related deaths in 2012 with the number of new cases expected to rise by about 70 % over the next two decades. In 2014, it was estimated that 65 % of cancer patients survived for 5 years and 15 % for 20 or more years [8]. It is therefore pertinent to decrease the incidence of neurotoxic side effects that may be permanent from treatment to improve patient quality of life (QoL).

The B group vitamins include thiamine (B1), riboflavin (B2), niacin (B3), pantothenic acid (B5), pyridoxine (B6), cobalamin (B12), folate, choline and biotin. These vitamins all function as coenzymes in their activated state for numerous intermediary metabolic pathways including neurotransmitter synthesis and neuronal membrane synthesis [9]. Deficiencies in B group vitamins can occur due to various reasons such as diet insufficiency and age-affected nutrient and medication-induced vitamin deficiency. A deficiency in certain B group vitamins such as B1, B6 and B12 is absorption associated with nerve dysfunction and nerve damage that can lead to peripheral neuropathy [10].

Vitamin B12 in particular has been identified to have an association with neuropathy and neuropathic pain particularly in advanced malignancy [10]. Traditionally, a vitamin B12 deficiency takes a long time to develop; however, studies have now found that vitamin B12 can decrease rapidly during chemotherapy exposure [10–12].

Vu et al. (1992) reported that a range of chemotherapeutic agents induce a temporary deficiency in blood vitamin B12 levels when they assessed holotranscobalamin II levels (Holo TC) [11]. Hence, it is possible that chemotherapy agents may induce a transient B vitamin deficiency or insufficiency, which may be a major causal factor for the development of CIPN in patients undergoing treatment with neurotoxic chemotherapy agents. The association between vitamin B12 insufficiency or deficiency and CIPN development is an area that does require further investigation.

The primary aim of this study was to assess the prevention of CIPN by a commercially available orally administered B group vitamin complex when compared to placebo.

Patients and methods

Study design

The trial was conducted according to a randomised, placebo-controlled design in the oncology unit at the Princess Alexandria Hospital, Australia. The study design complied with the Helsinki Declaration and was approved by the University of Queensland's Human Research Ethics Committee (UH 2010000749) and by the Princess Alexandra Hospital's Human Research Ethics Committee (HREC/10/QPAH/140). Participants who met the inclusion and exclusion criteria were then randomly assigned to one of the two treatment arms, i.e. B group vitamins or placebo. The endpoint classifications were efficacy and safety. Each participant received written and verbal explanations regarding their involvement in the study before signing an informed consent form. Participants commenced the intervention approximately 1 week before the initiation of the first cycle of chemotherapy and continued 12 weeks postchemotherapy cessation.

The subjects were followed up at 12, 24 and 36 weeks. Due to the possibility of delayed CIPN from a variety of chemotherapy agents [13], all participants were assessed 12 weeks postchemotherapy completion. Involvement for this clinical trial was between 24 to 36 weeks in duration depending on the chemotherapy regime.

Participant selection

Recruitment was conducted from June 2011 to January 2014. The study group comprised of 71 participants recently diagnosed with cancer (68 % female, 32 % male) who satisfied the inclusion and exclusion criteria. Participants were recruited from the Princess Alexandra (PA) Hospital in Brisbane, Queensland, through oncologists, haematology oncologists and cancer care coordinators. The participants were randomised into the intervention or placebo arms to be administered during their chemotherapy regimen.

Participants were included into the study if they were 18 years or older; newly diagnosed with a neoplastic disease and were being prescribed a chemotherapy regime that

included oxaliplatin, taxanes or vincristine. No restriction was given to ethnicity or social background. The exclusion criteria included patients who had or who previously had peripheral neuropathy, had been prescribed concurrent investigation products, had undergone previous chemotherapy with a neurotoxic agent, were pregnant or breast feeding, had established cognitive impairment, were a diagnosed alcoholic or had an intellectual disability or severe mental illness. Any prospective participant that was consuming multivitamins, nutritional and/or herbal supplements or fish oils and were not prepared to cease these supplementations were also excluded. Subjects found deficient in either serum vitamin B12 or folate at baseline, who had excessive vitamin B6 or who had an Eastern Cooperative Oncology Group (ECOG) score of 4 were also excluded from participation.

Intervention

Participants were randomised to a B group vitamin or placebo (1 capsule, b.i.d) taken with or after meals. The dose per capsule of the B vitamin complex included 50 mg of thiamine, 20 mg of riboflavin, 100 mg of niacin, 163.5 mg of pantothenic acid, 30 mg of pyridoxine, 500 μg of folate, 500 μg of cyanocobalamin, 500 μg of biotin, 100 mg of choline and 500 μg of inositol. The placebo was identical to the intervention and consisted of microcrystalline cellulose with a small amount of beta-carotene to colour the capsule. The dose administrated was two capsules daily, which was based on a literature search on the doses needed of vitamin B12, B6 and B1 to elicit nerve restoration from a state of deficiency [14–16].

Randomisation

Randomisation was conducted by an independent statistician using a computer-generated randomisation sequence based on a block randomisation process. Sealed envelopes containing the two groups were used to assign subjects to either the intervention or placebo arm. The allocation was conducted by the statistician and primary study coordinator with study investigators remaining blinded to the sequence.

Objectives and outcomes

The primary outcome measure was a change in the total neuropathy score (TNS) [17] to assess efficacy of B group vitamins in preventing CIPN. It was assessed by an independent neurologist at the Princess Alexandra Hospital who was blinded to randomisation and who conducted both clinical and electrophysiological evaluation of each patient at each time point.

The assessment time points included prechemotherapy commencement, after chemotherapy (2 to 4 weeks postchemotherapy completion) and 12 weeks postchemotherapy completion.

Secondary outcome measures

The secondary outcome measures consisted of three validated questionnaires that included (i) the MD Anderson Brief Pain Inventory [18], (ii) the European Organisation of Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire [19] and the (iii) Patient Neurotoxicity Questionnaire (PNQ) [20] that tracked a participant's perception of neuropathy progression. A patient diary for each 12-week period was given to the subjects upon follow-up. Secondary outcome measures were recorded at 12 weeks, 24 weeks and if the subject's chemotherapy was 6 months in duration, at 36 weeks. In addition, blood pathology tests were conducted prechemotherapy and postchemotherapy that included assays for vitamins thiamine, riboflavin, pyridoxine, red cell folate and holo TC (vitamin B12).

Assessment of safety

Oncologists, cancer care coordinators and a research assistant checked full blood count and blood chemistry results for all subjects during chemotherapy regimens. All adverse events were recorded and noted during the intervention stage of the clinical study and evaluated for any potential relationship to B group vitamin supplementation causality. All participants were encouraged to complete intervention diaries, which included reporting of any adverse events, changes in medication, hospitalisation or symptomology. At each follow-up visit, changes in symptoms and treatment compliance were recorded. Adverse events were also noted from inspections of patient medical charts and blood pathology reports.

Sample size

Sample size was determined from published data assessing nutraceuticals for the prevention of CIPN [21–27]. Calculations were based on comparison of two independent proportions of participants expected to have CIPN. The power of this study was set at 80 % and a two-sided significance level at 0.05. The average number of participants from previous studies was $n = 30$ for grade 1 and $n = 35$ for grade 2–4 CIPN. We therefore estimated that the requisite number for this pilot trial should be 90 participants plus 50 % attrition rate.

Statistical analysis

All available data was analysed as for intention-to-treat. Due to the nature of the dependent variables, the statistical analysis was based on t tests, analysis of variance, a mixed effects model and multiple logistic regression. To ascertain normal

or non-normal distribution of variables, a stem-and-leaf plot was carried out for baseline and postchemotherapy time points, for the variables TNS, cobalamin and pyridoxine. As the data was not normally distributed, a non-parametric approach was utilised to assess these variables. A non-parametric Levene's test was used to verify the equality of variances in the samples (from both the B group vitamin and placebo arms) thereby providing a more homogeneous variance (p = >0.05) [28, 29].

The analysis incorporated the comparison of evaluable participants in each arm who experienced CIPN compared to those who did not, comparison of TNS scores and the scores of the secondary outcomes using a mixed effects model. The neurologist's sensory and motor nerve function TNS score was assessed for significance with the chi-squared and Fischer's exact tests. Independent t tests and the Mann-Whitney test also assessed significance of the total TNS scores. The chi-squared and Fischer's exact tests were also employed to assess PNQ for sensory and motor nerve function. Odds ratio (risk estimate) was calculated for the PNQ at each time point for sensory and motor nerve function.

Blood pathology results were statistically analysed for normality, and the comparison between treatment arms was assessed with the Wilcoxon and Mann-Whitney U tests. All analysis were conducted with software from STATA for Windows version 11.0 (College Station, Texas) and IBM SPSS Statistics 20 (SPSS Inc., Chicago).

Results

In total, 121 participants were screened for eligibility and 50 of the subjects were excluded due to not meeting the inclusion/exclusion criteria, being too overwhelmed, transport issues and not attending neurological testing. Seventy-one participants were then randomised to either

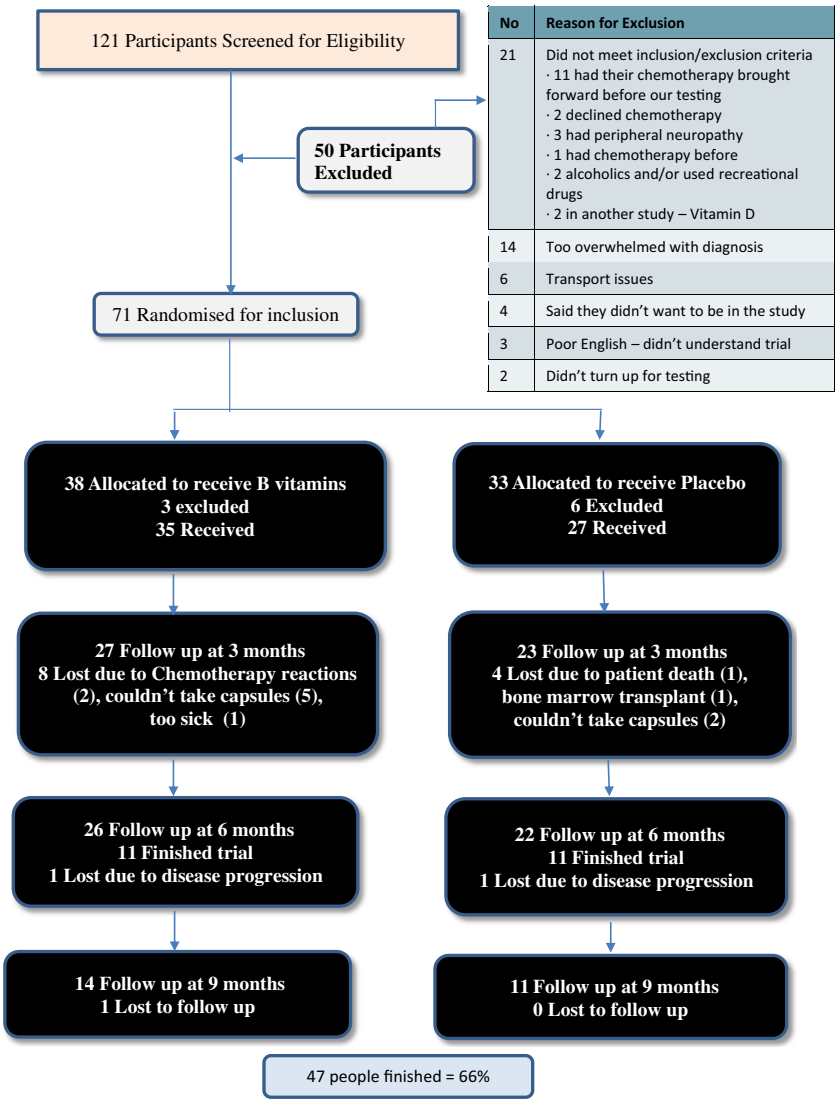


Fig. 1 CONSORT diagram

the B vitamin arm (n = 38) or placebo (n = 33). Of the participants randomised, three were excluded from the B vitamin arm and six from the placebo due to being deficient in vitamin B12 or failing the neurology test, leaving 35 participants to receive the B vitamins during chemotherapy treatment and 27 to receive placebo. By the completion of the trial, 47 participants (66.2 %) had completed all requirements for this study with an attrition rate of 14 %. See Fig. 1.

From those randomised, 68 % were female and the most frequent chemotherapy agent administered was the taxane class (66 %). Oxaliplatin recruitment was ceased after only four participants had been recruited within the year of trial commencement. The most common forms of cancer being treated in the study were breast cancer (51 %) and lymphoma (28 %). The subjects that consented to participate in the trial were predominantly of Caucasian ethnicity (82 %). Patients with type 2 diabetes mellitus (T2DM) who were recruited into

Table 1 Patient demographics and clinical characteristics

Characteristics	B vitamins n = 38		Placebo n = 31	
	No.	%	No.	%
Gender				
Female	28	73.68	20	60.6
Male	10	26.31	13	39.39
Chemotherapy agent				
Taxanes	26	68.4	21	63.64
Docetaxel	19	50	12	36.36
Paclitaxel	7	18.4	9	27.27
Vincristine	10	26.3	10	30.3
Oxaliplatin	2	5.26	2	6.06
Types of cancer				
Breast cancer	20	52.63	16	48.5
Lymphoma	10	26.31	10	30.3
Lung	4	10.5	5	15.15
Colon	2	5.26	2	6
Prostate	1	2.63		
Endometrial	1	2.63		
ECOG performance score				
0	24	63.16	21	63.64
1	12	31.58	9	27.27
2	2	5.26	1	3.03
3	0	0	2	6.06
Race				
Caucasian	31	81.6	27	81.8
New Zealand Maori	2	5.3	3	9.1
Indigenous	2	5.3	0	0
Italian	1	2.6	0	0
Asian	1	2.6	1	3
American Samoan	0	0	1	3
Chilean	1	2.6	0	0
Age				
Median		53.81		55.18
Range		29–75		33–75
<60		23		19
≥60		15		12
BMI				
Mean ± SD		29.4 ± 6.28		31.08 ± 7.23
Serum B vitamin levels at baseline				
Vitamin B1 (ref. 66–200 nmol/L)		174.21 ± 34.35		155.31 ± 28.39
Vitamin B2 (ref. 180–470 nmol/L)		321.05 ± 56.51		291.87 ± 43.58
Vitamin B6 (ref. 35–110 nmol/L)		167.83 ± 201.91		191.06 ± 624
Vitamin B12 (ref. >35 pmol/L)		86.79 ± 23.19		80.92 ± 25.46
Folate (ref. >900 nmol/L)		1873.35 ± 612.43		1870.6 ± 477.61
Serum B vitamin levels after chemotherapy				
Vitamin B1 (ref. 66–200 nmol/L)		203.92 ± 55.06		144.79 ± 38.66
Vitamin B2 (ref. 180–470 nmol/L)		301.42 ± 43.94		264.17 ± 42.31
Vitamin B6 (ref. 35–110 nmol/L)		656.92 ± 428.87		148.12 ± 253.79
Vitamin B12 (ref. >35 pmol/L)		101 ± 14.83		76.45 ± 24.98
Folate (ref. >900 nmol/L)		2456.62 ± 515.05		1814.37 ± 588.31

Table 2 Statistics for primary and secondary outcomes

Mixed effects model						
Outcomes	Placebo v B vits		Differences in time		Placebo v B vits over 3 time points	
Scores	T Score	P score	T score	P score	T score	P score
Primary outcome						
TNS	1.24	0.22	2.41	*0.02*	−0.35	0.73
Secondary outcomes						
PNQ sensory	0.85	0.4	0.61	0.55	0.84	0.4
PNQ motor	0.73	0.47	0.51	0.61	0.48	0.63
PNQ other	−0.05	0.96	−1.43	0.16	1.13	0.26
EORTC QoL	0.74	0.46	−0.67	0.5	0.28	0.78
Total pain score	−0.12	0.9	−0.35	0.73	0.56	0.58
Total pain interference	−0.9	0.37	−1.21	0.23	1.51	0.13

Italic indicates significance at <0.05

the trial did not demonstrate any symptoms of CIPN prior to chemotherapy commencement (T2DM $n = 6$). Information pertaining to demographics can be seen in Table 1.

The current medical treatment for CIPN during chemotherapy administration is dose reduction of the agent or complete cessation of the chemotherapy agent [2]. Due to the development of CIPN, $n = 3$ from the placebo arm ceased chemotherapy treatment and $n = 1$ in the B group vitamin reduced their chemotherapy dose by 20 % but did complete the prescribed regime.

The final analysis of the data found no statistical significance for B group vitamin over placebo for the prevention of CIPN. When comparing the TNS scores between the B group vitamin and placebo, using a mixed effects model (MEM) analysis reported non-significance ($p = 0.22$; T score 1.24). When comparing the two groups at each time point, no significant difference was observed for the neurological assessments ($p = 0.73$; T score = −0.35). CIPN is known to be an accumulative side effect and this was found in the final neurological assessment [5]. All other analysis using the MEM for secondary outcomes found no statistical significance (see Table 2). Analysis comparing the TNS scores and demographic data from the two groups also found no correlation. This indicated that gender, age, culture, type of cancer, chemotherapy, alcohol and caffeine consumption and smoking was found to not influence neurotoxic effects. Results of the analysis using the ANOVA procedure are presented in Table 3.

A statistical analysis of the sensory and motor functions of the TNS scores using the chi-squared and Fisher's exact tests showed no statistical significance between the two groups (24 weeks: sensory $p = 0.11$ motor $p = 0.79$; 36 weeks: sensory $p = 0.96$ motor $p = 0.46$). Independent sample t test and the Mann-Whitney tests were also conducted for the TNS scores with no statistical significance observed (Independent sample t test: 24 weeks $p = 0.376$, T score = −0.89; 36 weeks $p = 0.579$, T score = −0.559; Mann Whitney: 12 weeks $p = 0.329$; 36 weeks $p = 0.424$) (see Fig. 2).

Statistical significance was observed in the PNQ for sensory neuropathy by participants in the B group vitamin arm (12 weeks $p = 0.03$; 24 weeks $p = 0.005$; 32 weeks $p = 0.021$). In addition, the risk estimate for the PNQ was also statistically significant at both 24 weeks OR = 5.78, 95 % CI = [1.63–20.5] and 32 weeks OR = 8.1, 95 % CI = [1.23–53.2]. Statistical significance was achieved for the participant's perception of sensory peripheral neuropathy prevention (see Table 4).

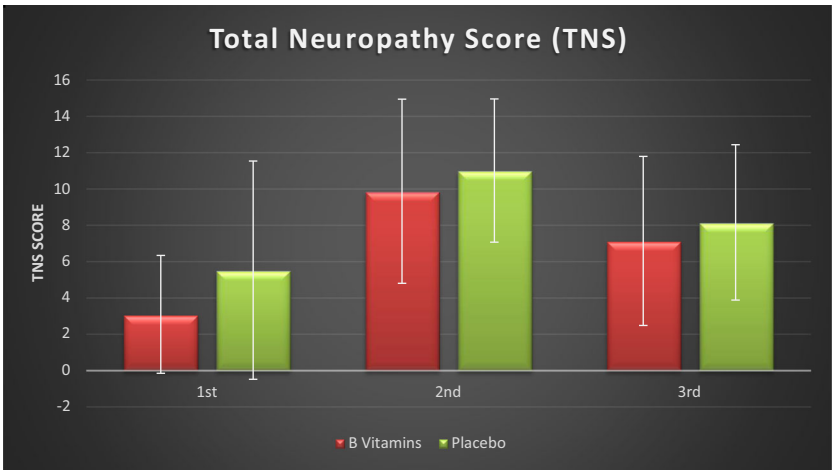
Blood pathology results showed that supplementation with a B group vitamin during chemotherapy increased blood levels of thiamine, pyridoxine, cobalamin and folate when compared to placebo, see Table 1. The only B vitamin that was found to show statistical difference between baseline and postchemotherapy when compared between the two groups was cobalamin ($p = 0.770$ and $p = 0.024$, respectively). The results found that the TNS at baseline and postchemotherapy were not statistically significant, but the trend was in the right direction for a benefit ($p = 0.760$; $p = 0.300$ respectively).

Table 3 TNS results from both arms compared to demographic information

Demographic Information	p Values (ANOVA)[a]
Gender	0.308
Age	0.465
Race/culture	0.836
Type of cancer	0.68
Chemotherapy	0.94
Alcohol consumption per week	0.60
Caffeine consumption per day	0.52
Smoking per day	0.638

[a] These p values reflect the results of the ANOVA analysis undertaken for each group comparing baseline TNS to after chemotherapy TNS and 3-month TNS results

Fig. 2 Results of the total TNS



	Total TNS		
	Baseline	After Chemo	3 mths f/u
B vitamins	3.05 ± 3.25	9.86 ± 5.08	7.12 ± 4.67
Placebo	5.5 ± 6.02	11 ± 3.96	8.14 ± 4.29

To ascertain if vitamin B12 has a relationship with CIPN, the vitamin B12 results were correlated to the TNS results. It was found that baseline was not statistically significant ($p = 0.770$); however, the postchemotherapy was statistically significant ($p = 0.024$). Pyridoxine was also correlated but not found to be statistically significant before or postchemotherapy ($p = 0.938$; $p = 0.948$ respectively). This is due to the high standard deviation found in the pyridoxine results (for total cohort: baseline SD = 513.19; postchemotherapy SD = 442.29 indicated by normality tests).

In addition, one breast cancer participant was found deficient in vitamin B12 3 weeks postchemotherapy cessation and presented with moderate to severe form of CIPN. After vitamin B12 administration both orally for 12 weeks and an intramuscular injection, CIPN was reduced to a mild form according to the TNS and neurological assessment [12].

Therefore, the primary outcome of the TNS demonstrated that B group vitamins did not statistically decrease the incidence of CIPN ($p = 0.22$; T score = 1.24). The patient's perception that sensory peripheral neuropathy was decreased by B vitamins was statistically significant (12 weeks $p = 0.03$; 24 weeks $p = 0.005$; 32 weeks $p = 0.021$). The risk estimate for patient's perception of sensory neuropathy was also statistically significant for both after chemotherapy cessation and at 12 weeks follow up (OR = 5.78, 95 % CI = [1.63–20.5] and 32 weeks OR = 8.1, 95 % CI = [1.23–53.2]).

Table 4 PNQ assessment of CIPN at each 3-month follow up

Y/N results: Patient Neurotoxicity Questionnaire: *p* values			
		p values (chi-square test)*	*p* values (Fisher exact test)**
Baseline	Sensory	0.077	0.082
	Motor	*0.004*	*0.005*
12 weeks	Sensory	*0.03*	*0.029*
	Motor	0.477	0.336
24 weeks	Sensory	*0.005*	*0.005*
	Motor	0.656	0.437
36 weeks	Sensory	*0.021*	*0.027*
	Motor	0.383	0.325

Italics indicate significance at <0.05

[a] These *p* values reflect the results of the chi-square analysis undertaken for each data point throughout the study

[b] These *p* values reflect the results of the Fisher exact test undertaken for each data point throughout the study

Limitations of the clinical trial

The major limitation identified in this study was the low number of participants recruited resulting in a study that was underpowered. This was due to poor recruitment that led to extended study duration. Poor recruitment was predominantly due to the strict inclusion/exclusion criteria that resulted in 50 participants from 121 screened being excluded. The number of chemotherapy agents assessed increased the complexity of data analysis and in hindsight a more judicious approach would have been to select one agent only for analysis. Also, the assessment tools for CIPN to date do not have a gold standard that can assess and compare peripheral neuropathy results with other studies.

Discussion

This clinical trial found that although there was a trend in favour of the B vitamins in reducing the prevalence of CIPN, the difference between the test and placebo groups were not statistically significant. The study was based on the hypothesis that the administration of an oral B vitamin complex formulation could prevent CIPN when vincristine and the taxane class neurotoxic compounds were administered to patients diagnosed with a cancer.

Oncologists are aware that CIPN is a common and debilitating side effect associated with neurotoxic chemotherapeutic agents. Such agents have both detrimental physical and mental health effects that need to be addressed while maintaining therapeutic efficacy with chemotherapy treatments. To alleviate CIPN, a number of treatments have been prescribed by clinicians or have been independently tried by patients, despite the limited availability of evidence [1, 30].

Blood pathology results showed that serum B vitamin levels increased for thiamine, pyridoxine, cobalamin and folate. The results also demonstrated that participants allocated to the B group vitamin arm and that subsequently developed CIPN could not reverse the peripheral neuropathy regardless of continued supplementation with B group vitamins. In addition, B group vitamin supplementation did not protect against small nerve damage or reflex loss. Furthermore, the increased B vitamin blood levels were not associated with the prevention of CIPN when correlated to the TNS results. Interestingly, elevated serum levels of pyridoxine were observed in four participants in the B group vitamin arm with the concomitant development of mild CIPN. This result, largely unexpected, warrants further research, given that perhaps in susceptible individuals higher serum levels of pyridoxine during chemotherapy administration may be associated with increased risk for CIPN.

We also observed that blood vitamin B12 levels were decreased from baseline in participants allocated to the placebo group (Holo TC average 81 ± 25 pmol/L at baseline to 76 ± 25 pmol/L postchemotherapy). However, levels were not low enough to induce a neurological response (neurological signs and symptoms may occur at Holo TC <35) or below 221 pmol/L in serum vitamin B12 [31]). Only one participant was found deficient in blood vitamin B12 levels postchemotherapy, and this participant displayed severe CIPN. The severity of CIPN experienced by this participant was a result of both the chemotherapy administration and a deficiency in vitamin B12. This was evident by the administration of one IM vitamin B12 and an oral B vitamin over 3 months that reduced the severity of the CIPN from grade 4 to grade 1 as assessed from the National Cancer Institute common toxicity criteria.

The pain interference projection found that participants administered the B group vitamin supplement experienced significantly ($p < 0.05$) less pain interference with daily activity compared to the subjects who were administered a placebo. No other differences were recorded for quality of life or pain. B group vitamins may be associated with overall reduction of pain during chemotherapy, this allowing the subjects to engage in daily activities.

When stratifying the subjects in the B vitamin group for different cancer types, we observed a sensory neuropathy benefit in patients diagnosed with a lymphoma that were undergoing the chemotherapy regimen R-CHOP for eight cycles, three weekly and lung cancer patients undergoing paclitaxel and carboplatin weekly.

Patients undergoing chemotherapy can experience numerous and severe symptoms that can contribute to overall symptom burden. As expected, such symptom profiles tend to be associated with a significant reduction in quality of life [32]. Hence, cancer patients undergoing chemotherapy present a complex picture. Therefore, supplementation with an oral B vitamin may not be appropriate for some patients due to difficulties encountered in swallowing capsules or the odour of B vitamins excreted in the urine. When patients are administered emetogenic chemotherapy regimens, unpleasant odours such as those produced by B vitamins may trigger further unpleasant behaviour that possibly can exacerbate chemotherapy-induced nausea and vomiting. Therefore, the administration of intramuscular (IM) vitamin B12 is a prudent option for patients undergoing chemotherapy and who have been also diagnosed with a blood vitamin B12 deficiency.

If patients present with a blood vitamin B12 deficiency prior to chemotherapy administration, continual intramuscular injections of vitamin B12 may need to be administered throughout the chemotherapy cycles. Consensus on how often an IM B12 should be administered requires further verification. Considering that vitamin B12 was found to be statistically significant in this trial, further research into vitamin B12 during chemotherapy regimens is certainly warranted.

Conclusion

B vitamin supplementation was not statistically significantly better at reducing the development of CIPN when compared to placebo. Patient perception for the prevention of sensory neuropathy with B vitamins was statistically significant as was the odds ratio for after chemotherapy and follow up. One patient was found deficient in vitamin B12 postchemotherapy presenting with moderate to severe CIPN and benefited from vitamin B12 administration. This is clinically relevant and further studies are required to confirm vitamin B12 status in CIPN development. Patients with moderate to severe CIPN should be tested for vitamin B12 deficiency as the severity of peripheral neuropathy could be due to both the chemotherapy neurotoxicity and blood vitamin B12 deficiency.

Acknowledgments We would like to thank Bio Concepts Pty Ltd. for supplying the supplemental product and assisting the research position to conduct this trial. Acknowledgement also goes to all the oncology and neurological staff at the Princess Alexandra Hospital and the members of the former Centre for Integrative and Clinical Medicine at the University of Queensland for their assistance during the study. A special acknowledgement goes to Dr. Samantha Coulson for her detailed editing of the manuscript and assistance with this manuscript.

Compliance with ethical standards

Ethics statement The study design complied with the Helsinki Declaration and was approved by the University of Queensland's Human Research Ethics Committee (UH 2010000749) and by the Princess Alexandra Hospital's Human Research Ethics Committee (HREC/10/QPAH/140).

Funding The authors have received no financial support for the research, authorship and/or publication of this article.

Conflicts of interest Luis Vitetta has received National Institute of Complementary Medicine and National Health and Medical Research Council of Australia competitive funding and industry support for research into nutraceuticals and herbal medicines. The authors declare no other potential conflicts of interest with respect to research, authorship and/or publication of this article.

References

1. Park SB, Goldstein D, Krishnan AV, et al. (2013) Chemotherapy-induced peripheral neurotoxicity: a critical analysis. CA Cancer J Clin 63:419–437
2. Bhagra A, Rao RD (2007) Chemotherapy-induced neuropathy. Curr Oncol Rep 9:290–299
3. Cavaletti G, Nicolini G, Marmiroli P (2008) Neurotoxic effects of antineoplastic drugs: the lesson of pre-clinical studies. Front Biosci 13:3506–3524
4. Cavaletti G, Marmiroli P (2004) Chemotherapy-induced peripheral neurotoxicity. Expert Opin Drug Saf 3:535–546
5. Armstrong T, Almadrones L, Gilbert MR (2005) Chemotherapy-induced peripheral neuropathy. Oncol Nurs Forum 32:305–311
6. Cersosimo RJ (1989) Cisplatin neurotoxicity. Cancer Treat Rev 16: 195–211
7. Roelofs RI, Hrushesky W, Rogin J, et al. (1984) Peripheral sensory neuropathy and cisplatin chemotherapy. Neurology 34:934–938
8. Cancer Treatment & Survivorship Facts & Figures 2014-2015. (2015) http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-042801.pdf
9. Scott J, Weir D (1994) Folate/vitamin B12 inter-relationships. Essays Biochem 28:63–72
10. Soloman L. (2016) Functional vitamin B12 deficiency in advanced malignancy: implications for the management of neuropathy and neuropathic pain. Support Care Cancer. March.
11. Vu T, Amin J, Ramos M, et al. (1993) New assay for the rapid determination of plasma holotranscobalamin II levels: preliminary evaluation in cancer patients. Am J Hematol 42:202–211
12. Schloss J, Colosimo M, Airey C, Vitetta L (2015) Chemotherapy-induced peripheral neuropathy (CIPN) and vitamin B12 deficiency. Support Care Cancer 23(7):1843–1850
13. Kim HI, Hyung WJ, Song KJ, Choi SH, Kim CB, Noh SH (2011) Oral vitamin B12 replacement: an effective treatment for vitamin B12 deficiency after total gastrectomy in gastric cancer patients. Ann Surg Oncol 18(14):3711–3717
14. Ghavanini AA, Kimpinski K (2014) Revisiting the evidence for neuropathy caused by pyrdioxine deficiency and excess. J Clin Neuromuscul Dis 16(1):25–31
15. Ang CD, Alviar MJ, Dans AL, Bautista-Velz GG, et al. (2008) Vitamin B for treating peripheral neuropathy. Cochrane Database Syst Rev 16(3):CD004573
16. Cavaletti G, Alberti P, Frigeni B (2011) Chemotherapy-induced neuropathy. Curr Treat Options Neurol 13:180–190
17. Smith EM, Beck SL, Cohen L (2008) The total neuropathy score: a tool for measuring chemotherapy-induced peripheral neuropathy. Oncol Nurs Forum 35:96–102
18. Cleeland CS. (1989) Measurement of pain by subjective report. In: Chapman CR, Loeser JD, editors. Issues in pain measurement. Advances in pain research and therapy, vol. 12. New York: Raven Press. P391–403
19. Groenvold M, Klee MC, Sprangers MAG, Aaronson NK (1997) Validation of the EORTC QLQ-C30 quality of life questionnaire through combined qualitative and quantitative assessment of patient-observer agreement. J of Clin Epid 40(4):441–450
20. Shimozuma K, Ohashi Y, Takeuchi A, Aranishi T, Satoshi M, et al. (2009) Feasibility and validity of the patient neurotoxicity questionnaire during taxane chemotherapy in a phase III randomized trial in patients with breast cancer: N-SAS BC 02. Support Care Cancer 17: 1483
21. Argyriou AA, Chroni E, Koutras E, et al. (2005) Vitamin E for prophylaxis against chemotherapy-induced neuropathy: a randomized controlled trial. Neurology 64:26–31
22. Wang WS, Lin JK, Lin TC, et al. (2007) Oral glutamine is effective for preventing oxaliplatin-induced neuropathy in colorectal cancer patients. Oncologist 12:312–319
23. Pace A, Giannarelli D, Galie E, et al. (2010) Vitamin e neuroprotection for cisplatin neuropathy: a randomized, placebo-controlled trial. Neurology 74:762–766
24. Argyriou AA, Chroni E, Koutras A, et al. (2006) A randomized controlled trial evaluating the efficacy and safety of vitamin E supplementation for protection against cisplatin-induced peripheral neuropathy: final results. Support Care Cancer 14:1134–1140
25. Gamelin L, Boisdron-Celle M, Delva R, et al. (2004) Prevention of oxaliplatin-related neurotoxicity by calcium and magnesium infusions: a retrospective study of 161 patients receiving oxaliplatin combined with 5-fluorouracil and leucovorin for advanced colorectal cancer. Clin Cancer Res 10:4055–4061

26. Gedlicka C, Scheithauer W, Schull B, et al. (2002) Effective treatment of oxaliplatin-induced cumulative polyneuropathy with alpha-lipoic acid. J Clin Oncol 20:3359–3361
27. Milla P, Airoldi M, Weber G, et al. (2009) Administration of reduced glutathione in FOLFOX4 adjuvant treatment for colorectal cancer: effect on oxaliplatin pharmacokinetics, Pt-DNA adduct formation, and neurotoxicity. Anti-Cancer Drugs 20: 396–402
28. Nordstokke DW, Zumbo B, Cairns SL, et al. (2011) The operating characteristics of the nonparametric Levene test for equal variances with assessment and evaluation data. Practical Assessment Research Evaluation. 16:ISSN 1531–7714.
29. Nordstokke DW, Zumbo B (2010) A new nonparametric Levene test for equal variances. Psicológica 31:401–430
30. Schloss JM, Colosimo M, Airey C, Masci PP, Linnane AW, Vitetta L (2013) Nutraceuticals and chemotherapy induced peripheral neuropathy (CIPN): a systematic review. Clin Nutr 32(6):888–893 Erratum in: Clin Nutr. 2015 Feb:34(1):167
31. Herbert V. (1996) present knowledge in nutrition. 7th Edition ed. Vitamin B12, ed F.L. Ziegler EE. Washington, DC, USA. International Life Sciences Institute Press
32. Kayl AE, Meyers CA (2006) Side-effects of chemotherapy and quality of life in ovarian and breast cancer patients. Curr Opin Obstet Gynecol 18(1):24–28