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Review

Nutraceuticals and chemotherapy induced peripheral neuropathy (CIPN): A systematic review

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SUMMARY

Chemotherapy induced peripheral neuropathy [CIPN] is a common significant and debilitating side effect resulting from the administration of neurotoxic chemotherapeutic agents. These pharmaco-chemotherapeutics can include taxanes, vinca alkaloids and others. Moderate to severe CIPN significantly decreases the quality of life and physical abilities of cancer patients and current pharmacotherapy for CIPN e.g. Amifostine and antidepressants have had limited efficacy and may themselves induce adverse side effects. To determine the potential use of nutraceuticals i.e. vitamin E, acetyl-L-carnitine, glutamine, glutathione, vitamin B6, omega-3 fatty acids, magnesium, calcium, alpha lipoic acid and n-acetyl cysteine as adjuvants in cancer treatments a systematic literature review was conducted. Revised clinical studies comprised of randomized clinical trials that investigated the anti-CIPN effect of nutraceuticals as the adjuvant intervention in patients administered chemotherapy. Twenty-four studies were assessed on methodological quality and limitations identified. Studies were mixed in their recommendations for nutraceuticals. Currently no agent has shown solid beneficial evidence to be recommended for the treatment or prophylaxis of CIPN. The standard of care for CIPN includes dose reduction and/or discontinuation of chemotherapy treatment. The management of CIPN remains an important challenge and future studies are warranted before recommendations for the use of supplements can be made.

1. Introduction

Certain neoplastic agents can accumulate in the peripheral nervous system and the neurotoxicity may lead to CIPN. The symptoms of CIPN can be numbness, tingling, burning, decreased touch sensation, decreased strength and movement and sometimes pain in the fingers, toes, hands or feet.[1,2] These neurotoxic chemotherapy agents include the platinum compounds, anti-tubulin agents such as the taxane class and vinca alkaloids, epothilones, thalidomide, proteasome inhibitors and 5-fluorouracil (5FU).[3–8] It is estimated that one third of all patients who undergo chemotherapy experience CIPN and of those, a third can have permanent nerve damage.[3–5] 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] Moreover, CIPN can lead to dose reduction of the chemotherapy agent or possible cessation of treatment which may have an adverse impact on cancer treatment and disease outcomes.[5]

2. The aetiology of CIPN

A differential diagnosis of peripheral neuropathy in patients diagnosed with cancer has been reported (Table 1).[2] Requisites for peripheral nervous system neurotoxicity include chemotherapy agent capacity to cross the blood-nerve barrier and nervous system sensitivity to the drug. People with predisposing conditions such as type II diabetes mellitus (T2DM), HIV/AIDS, alcoholism or a vitamin B12 deficiency may be more prone to the agent's adverse effects on the peripheral nervous system thereby increasing the prevalence of CIPN.[2]

Peripheral nerve fibres are composed of small or large fibres. Small nerve fibres are unmyelinated and are comprised primarily of microtubules. They include nerves that sense pain and temperature. Large nerve fibres are myelinated and are composed mainly of

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Table 1
A Differential diagnosis of peripheral neuropathy in patients with cancer.[2]

Cause	Neurotoxic effect on peripheral nerves
Vitamin B12 deficiency	Large fibre injury, Dorsal root ganglia damage
Cachexia	Diffuse weakness and muscle wastage
Chemotherapy	Small and/or large fibre injury
Charcot–Marie–Tooth Disease	Large fibre injury
Diabetes Mellitus Type 2	Small fibre injury, slow development
Atherosclerotic Ischaemic Disease	Sensory neuropathy in lower extremities
Para–Neoplastic Syndrome	Distal sensory or sensori-motor deficit
Thyroid Dysfunction	Proximal and distal weakness; carpal tunnel syndrome
Alcoholic Neuropathy	Numbness, parasthesias

neurofilaments that act as a framework for the axon. These fibres sense position and vibration as well as motor control.[2] Both fibres are targeted by neurotoxic chemotherapy agents that may explain why patients experience a variety of symptoms.

Although each neurotoxic chemotherapy agent has a different mechanism of action on the nervous system, all induce a glove and stocking distribution. This means the point most distal from the trunk of the body is affected first (e.g. fingers and toes) and progression is then towards the trunk to hands and feet and then limbs.[2] Each agent has been found to affect one nerve fibre more than others e.g. cisplatin targets large fibres while paclitaxel and vincristine target small fibres.[2]

CIPN can be a temporary side effect which can take up to two years for full recovery. In approximately one third of cases it can be a permanent consequence of the drug neurotoxicity. Symptoms may occur within hours, days or weeks after the introduction of the chemotherapy agent, with cumulative doses increasing the severity and length of time the patient experiences this side effect.[2] Cisplatin differs to other neurotoxic agents as it can induce a delayed CIPN several months after the drug has been administered rather than a more immediate response.[4]

3. Mechanism of action of neurotoxic chemotherapy agents

The neurotoxic chemotherapy agents can be divided into four main categories, alkylating and anti-tubulin agents, thalidomide and proteasome inhibitors. A common feature of these drugs is that they are unable to cross the blood-brain barrier thereby protecting the central nervous system. The peripheral nervous system has no protective barrier making it susceptible to neurotoxicity[3] and therefore neurotoxic chemotherapy agents can accumulate and target different regions of the neuron (Fig. 1).[6]

4. Methods

A systematic search of the literature was conducted using PubMed, the Cochrane Library, Science Direct, Scopus, EMBASE, MEDLINE and CINAHL Fig. 2.

4.1. Search terms

Articles were identified using the search terms, “chemotherapy” OR “Cisplatin” OR “Taxanes” OR “Paclitaxel” OR “Docetaxel” OR “Oxaliplatin” OR “Carboplatin” OR “Platinum compounds” OR “Proteasome inhibitors” AND “induced peripheral neuropathy” OR “CIPN” AND “nutrient” OR “vitamin” OR “mineral” OR “Acetyl-L-Carnitine” OR “Glutamine” OR “Vitamin E” OR “Alpha Lipoic acid” OR “Magnesium” OR “Calcium” OR “Vitamin B6” OR “B vitamins” OR “Omega-3 fatty acids”.

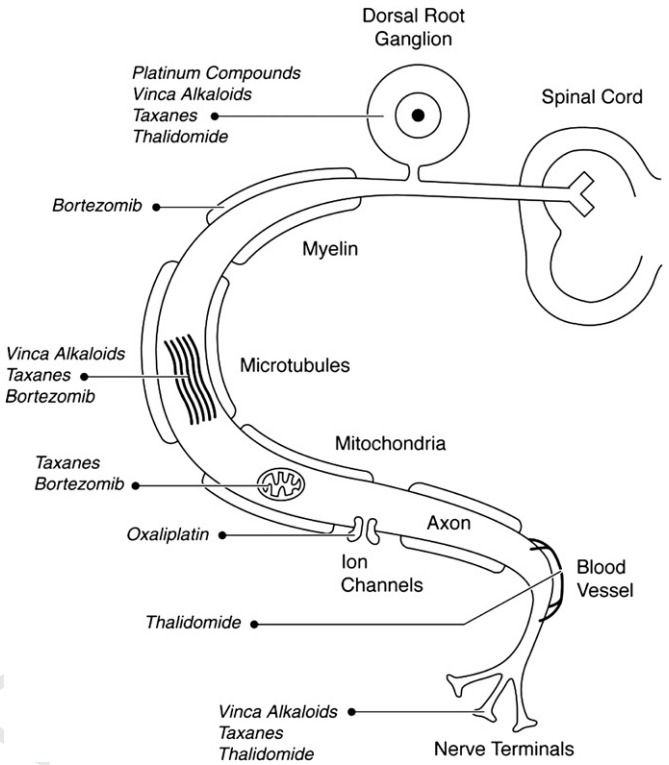

Fig. 1. Site of chemotherapy-induced neurotoxicity.[7]

The inclusion criteria for this review were: 1) An RCT and/or cross-over clinical trial that used either a placebo comparator or current anti-CIPN treatment as a control; 2) Human participants diagnosed with a cancer and administered chemotherapy; 3) The use of a nutraceutical supplement as the main intervention and specifically investigating its effects on reducing the primary

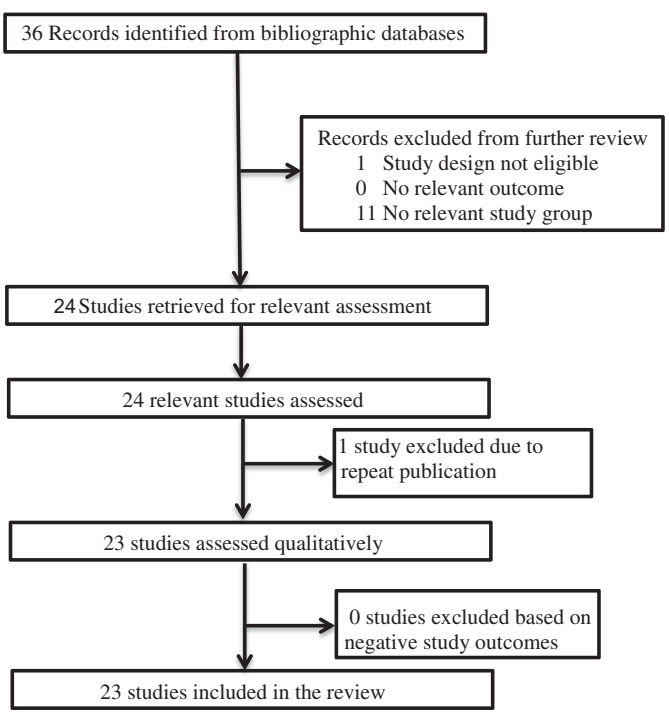

Fig. 2. Flow of information for systematic review.

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outcome i.e., CIPN; and 4) The clinical study was published in English.

The overall body of evidence (based on a summary of the individual studies) (See Supplemental Information: Clinical Studies Investigating the Efficacy of Selected Nutraceuticals for the Prevention of CIPN) evaluated within this review was assessed using a separate tool, the Australian National health and Medical Research Council's (NHMRC) body of clinical evidence assessment matrix. This is an assessment tool that assigns a level/grade (Level I: strongest evidence to level IV: weakest evidence) based on the strength of the published study.[9]

5. Results

5.1. Nutraceuticals and peripheral neuropathy

The search strategy identified twenty-four studies (Supplemental Information) that provided Level II or III evidence and all had a positive quality rating. All studies included in this review were analysed for common scientific characteristics/attributes consistent with rigorous methodologies, randomised group allocation and clear inclusion and/or exclusion criteria, major findings, and potential limitations.

5.2. Study characteristics

The studies selected for this review included randomised controlled trials, open label trials and one retrospective study. The randomised controlled trials identified are divided into eleven double blind placebo controlled trials, five randomised controlled trials including a randomised open label with a blind assessment plus two non-randomised controlled trials. Four open label trials were identified which did not contain a placebo component.

The results of the included studies were mixed. Several nutraceuticals showed initial positive results in reducing CIPN however further studies found that they were either not significant or indicated possible interference with the chemotherapy agents response rate. No nutraceutical currently has been found to significantly show protection or treatment for CIPN.

5.3. Magnesium and calcium

Magnesium and calcium infusions with oxaliplatin also showed initial positive results in a retrospective study.[10] Three clinical trials[11–13] reported that efficacy was not enhanced with one trial ($n = 174$) being terminated due to the treatment group reporting a significant lower response rate compared to placebo.[11]

5.4. Vitamin E

Vitamin E demonstrated positive results in three RCT's showing a significant reduction in the relative risk of cisplatin induced PN, especially ototoxicity.[14–18] However, a phase III multi-centre trial combining vitamin E with taxanes, cisplatin, carboplatin, oxaliplatin or combination concluded that vitamin E did not appear to reduce the incidence of sensory neuropathy.[18] Vitamin E efficacy was limited to those patients administered cisplatin (only 8 from the 207 cohort) during the phase III study. Previous studies have indicated that vitamin E seems to be more protective for cisplatin ototoxicity compared to other neurotoxic agents.[19]

5.5. Lipoic acid

One open label study was conducted with alpha lipoic acid ($n = 15$) co-administered with oxaliplatin.[20] This treatment combination showed a trend toward a reduction in the severity of oxaliplatin induced CIPN in 8 out of 15 patients but the trend was not statistically significant.[20]

5.6. N-Acetyl cysteine

N-acetyl cysteine (NAC) administration to cancer patients has been based on the assumption that NAC can increase glutathione production, an effect that may decrease cytotoxicity.[21] In a further study conducted with NAC no significant changes on electrophysiological testing on both sensory and motor nerves were found between the two groups.[21]

5.7. Glutathione

Glutathione has been reported to show positive results in reducing CIPN.[22] Intravenous glutathione administered before cisplatin administration reported promising outcomes for the prevention of cisplatin induced PN without reducing the anti-tumour activity of the chemotherapeutic agent.[23–25] A positive result was also found in two studies with oxaliplatin.[26,27] Both studies reported a significant reduction in oxaliplatin induced PN, mainly relevant to sural sensory nerve reduction. These results present clinical data that indicates that glutathione administration may aid in the prevention of CIPN. However, additional higher quality studies are required, as these trials were limited due to a high participant dropout rate and without long-term follow-up.

5.8. Glutamine

Two almost identical clinical studies[28,29] that have been published on the administration of glutamine with paclitaxel are the results from the early study[25] that was merged/extended into a second trial.[26] Both studies were conducted at the same institution over the same period of time but with slightly different numbers of participants and authors, presenting similar results. These studies reported that the patients on glutamine tended to have fewer symptoms than those on placebo however the trend in the nerve conduction studies was not statistically significant. There was a drift in the results that indicated that glutamine decreased the severity of dysesthesias in the fingers and toes. An additional study[30] with glutamine and oxaliplatin co-administration reported that glutamine may reduce the incidence and severity of oxaliplatin induced CIPN.[30] No significant differences were found between the two groups.[30]

5.9. Acetyl-L-carnitine

Two open label studies reported that acetyl-L-carnitine (ALC) may be a treatment option for paclitaxel and cisplatin induced CIPN.[31,32] A phase III trial demonstrated that ALC did not provide a positive benefit for the prevention of CIPN.[33] The study concluded that patients should be discouraged from using ALC during treatment with taxane therapy. Notwithstanding this recommendation it may be an option for the treatment of CIPN rather than prevention in patients that already may be experiencing CIPN.

5.10. Vitamin B6

One DBRCT with vitamin B6 found that it significantly reduced CIPN from cisplatin and hexamtheylmelamin administration.[34] Furthermore the results indicated that the high dose vitamin B6 (100 mg) administered may affect response duration and that it requires further investigation.[34]

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5.11. Omega-3 fatty acids

A recent DBRCT investigating the effect of omega-3 fatty acids on paclitaxel induced peripheral neuropathy found that it significantly reduced the incidence of CIPN from paclitaxel by 70%.[35] The sural nerve conduction test was also significant for omega-3 fatty acids compared to placebo. Further testing in larger randomised clinical trials is required but omega-3 fatty acids do show promise for protection against paclitaxel induced peripheral neuropathy.[35]

5.12. Adverse events and adherence

The nutraceuticals trialled were generally well tolerated according to the clinical trials reported. Hence, there were limited adverse events noted from the nutraceuticals trialled for the prevention of CIPN. Adverse events were reported for the use of acetyl-L-carnitine only. These included two patients that reported mild nausea associated with acetyl-L-carnitine administration[29] and one patient reported insomnia following supplementation with acetyl-L-carnitine.[30] One additional study described two participants who stopped their vitamin E supplementation after one month.[18] No interpretation of the result was given as to why the participants had stopped taking the vitamin E.

5.13. Confounding factors

The main confounding factors reported in the clinical studies investigated for this review are presented in Table 2. All studies from the supplemental information table indicated that confounding factors were controlled in the study but were not individually listed in the clinical trials examined. They were itemised under why patients did not complete the trial, why they withdrew their participation or experienced chemotherapy administration toxicity. The confounding factors mentioned may importantly influence the decisions to administer nutraceuticals to cancer patients who are about to undergo chemotherapy treatments. Such decisions may be dependent on those factors that could affect drug absorption, metabolism and or compliance. One study reported the difficulty in reproducing or quantifying peripheral neuropathy as a confounding factor.[25]

5.14. Possible drug interactions with high doses of nutraceuticals

Three studies have reported that there could be possible drug interactions with the administration of high dose nutraceuticals.[11,25,32]

Table 2
Reported confounding factors.

Confounding factors	*n*
Disease progression	5
Grade 3 or 4 nausea and vomiting	4
Metastasis (liver, abdomen, peritoneum, lymph nodes, lung, other)	4
Sudden patient death	4
Grade 3 or 4 diarrhoea	3
Patients refused any further treatment	3
Heamatological toxicity (including transient hepatic failure)	2
Severe neutropenia	2
Stomatitis	2
If the treatment was first, second or third line treatment	2
Lethal toxicity from the chemotherapy agent	2
Cardiac and/or neurocerebellar adverse events	2
Grade 3 or 4 allergic reactions to the chemotherapy drugs	2
Thrombocytopaenia	1
If the patient had resectable or unresectable lesions	1
Wrong diagnosis	1
Change to treatment protocol	1
Use of Alternative treatments	1

The intravenous administration of magnesium and calcium trial with FOLFOX regime was terminated due to the treatment group reporting a significant lower response rate compared to placebo.[11] The study concluded that a possible drug interaction had occurred between the chemotherapy regime and the magnesium and calcium infusions however no further investigations were continued to determine the mechanism of action. A further study with glutamine[25] indicated that there could have been a protective effect on the tumour from the administered glutamine thereby leading to reduced cytotoxicity from the paclitaxel administered. Moreover, no decrease in response rate was reported in the trial and no further testing was undertaken to ascertain the mechanism of action.[25] The third clinical study that administered vitamin B6 showed a significant decrease in the response rate with cisplatin and HMM.[32] The study concluded that this effect was directly due to vitamin B6 supplementation as it occurred in all participants administered the high dose of vitamin B6. However, it also was noted that vitamin B6 reduced response rate. No investigations were undertaken to determine how this occurred or the possible mechanism of action. Further investigations on the vitamin B6 effect are warranted.

5.15. Clinical implications

The current scientific literature demonstrates that there is limited evidence for the concurrent administration of nutraceuticals with neurotoxic agents in the prevention or treatment of CIPN. Nutraceuticals that may be considered include oral vitamin E with cisplatin administration, omega-3 fatty acids with paclitaxel and possibly the intravenous administration of glutathione with oxaliplatin. Although unvaryingly these may not prevent the development of CIPN they may assist in some cases depending on the severity of the diagnosed cancer and the commencement of medical treatment.

Vitamin B6 also warrants further investigation as a potential protective agent of CIPN. A recent *in vitro* experiment with vitamin B6 and oxaliplatin reported that vitamin B6 showed protection against oxaliplatin induced peripheral neuropathy without compromising drug anti-tumour efficacy.[36]

5.16. Review limitations

The exclusion of unpublished literature may significantly affect this review by introducing a publication bias. In addition, several restraints have been identified with this review namely within the selected studies. The low participant numbers in most studies was a significant limitation. The retrospective study[10] was included because it allowed the formulation of a biologically plausible hypothesis for the efficacy of nutraceuticals to prevent CIPN, even though it presented as a low-level evidence study. Furthermore, no objective markers were used in the assessment of the signs and symptoms of CIPN.

Studies reported using a variety of assessment tools to quantify CIPN development and severity. These included the National Cancer Institute-Common Toxicity Criteria (NCI-CTC), total neuropathy score (TNS), nerve conduction studies and/or electrophysiological investigations and quality of life questionnaires. The NCI-CTC is a clinician-based grading scale whereby the assessor may mix impairment, disability and quality of life measures which can lead to different interpretations of results and demonstrates observer objectivity and possible bias.[37] The NCI-CTC is the most commonly used assessment tool in the selected studies. The TNS is stated to be the most comprehensive assessment tool available at this time[37,38] with only two studies using this assessment tool as their main measurement of results.[17,35] The nerve conduction studies and electrophysiological investigations are the other main assessment

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tool used within these studies. These provide information on compound action potential amplitude and conduction velocity but do not provide information regarding ion channel function or resting membrane potential and are still dependent on the skill of the neurologist conducting the assessment.[39] Hence assessment of CIPN was not uniform among the clinical studies examined. This makes comparisons difficult to evaluate when comparing study results. Moreover, it is therefore possible that researchers may have underestimated the nutraceutical efficacy to prevent CIPN, resulting in significant study design bias.

An additional secondary study limitation involves the assessment of the activities of daily living. Activities of daily living is an important factor in CIPN as it may provide a marker of the level of disability experienced from symptoms by interference of daily activity. Hence activities of daily living are generally subjective and signs on a physical examination may not always be predictive of whether activities of daily living is affected or if it is important for the participant entering a CIPN clinical trial.

5.17. Measurement of CIPN

The measurement/grading or assessment of CIPN is critical for accurate clinical and instrumental monitoring. Currently there is no accurate measurement tool that has been used in either clinical trials or in a clinical setting that monitors CIPN.[40] The lack of standardization and reporting mechanisms has resulted in contentious reporting of CIPN data and consequently CIPN has become an under-diagnosed problem.[41]

CIPN is most commonly graded by clinicians by using common toxicity scales such as the National Cancer Institute-Common Toxicity Criteria (NCI-CTC). However, these scales rarely provide a detailed profile on clinical and pathological aspects of peripheral neuropathy that is a requisite for inclusion into clinical trial methodology. However, other measurement tools such as the Total Neuropathy Score [TNS] provide more detailed information pertaining to motor, sensory and autonomic signs and symptoms, determination of vibration perception thresholds and electrophysiological examination.[37,42]

Of the studies evaluated, there were a variety of measurement tools used that makes comparing results difficult. The majority of studies $n = 19$ used the NCI-CTC as their measurement tool.[10–14,21–31,33,34] Of the studies that used the NCI-CTC six also included electrophysiological tests such as nerve conduction tests,[14,23,26,28,29,31] two included a self-reported perception of peripheral neuropathy[18,33] and one included a quality of life questionnaire.[25] Two studies used the TNS as their measurement tool,[17,35] two used modified versions of the Neurologic symptom score (NSS) and the Neurologic Disability Score (NDS) in addition to patient symptom experience[15,16] and one used the World Health Organisation (WHO) toxicity grading list.[32]

Given that the measurement of CIPN remains difficult due to the use of a number of different measurement tools the ideal recommendation is that a variety of standardized tools be used that include a peripheral neuropathy scale i.e. [TNS], quality of life questionnaire, pain scale and patient's perspective questionnaire.[37,42,43] This however, is impractical due to the very time consuming nature of the combined interventions for clinicians, therefore a more realistic recommendation would be the use the NCI-CTC. Hence when patients report experiencing grade 2 or higher neuropathy occurrence during or after chemotherapy they can then be referred to a neurologist for further testing.

6. Discussion

Currently there are no established neuroprotective nutraceuticals for the prevention or treatment of CIPN. Results are inconsistent requiring further clinical investigations to confirm efficacy and safety or obtained from relatively small sample sizes. Several nutraceuticals have shown promise for selective neurotoxic chemotherapy agents such as vitamin E (dose 300–600 mg) with cisplatin, intravenous glutathione (dose 1.5 gm/m^2) for oxaliplatin administration, vitamin B6 (dose 100 mg TID) with HMM and cisplatin although interference with response rate was reported, and omega-3 fatty acids (dose 640 mg TID) for paclitaxel. Acetyl-L-carnitine (dose 3 g) has also demonstrated potential for efficacy as a treatment option for CIPN. Further research with large scale randomised controlled trials are warranted.

7. Conclusion

The overall survival from cancer, free from disease progression has increased in cancer patients, making quality of life an important factor for cancer survivors. CIPN is a major side effect that can interfere with a patient's quality of life, daily activities and also with medical treatments. The disruption of medical therapy for cancer patients that is due to the development of CIPN can affect chemotherapy dose and continuation of treatment that is of clinical importance. Investigating agents that could assist with CIPN prevention and treatment has significant scientific merit. Scientific evidence for nutraceuticals in the prevention and treatment of CIPN is limited. The analysis of the evidence presented according to the NHMRC grading scale of clinical evidence indicates that at the present time there can be no explicit recommendations that can be given for the prevention or treatment of chemotherapy induced peripheral neuropathy. Future clinical studies investigating natural compounds as neuro protective agents should constitute a priority for this clinically relevant side effect.

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Conflict of interest

None other declared.

Appendix A. Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.clnu.2013.04.007.

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