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Review Article

Acetyl-L-carnitine for the prevention of taxane-induced neuropathy in patients with breast cancer: a systematic review and meta-analysis

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Abstract

Background and purpose: Peripheral neuropathy is one of the most prevalent and undesirable side effects of taxane-containing chemotherapy regimens. This study aimed to investigate the effect of acetyl-L-carnitine (ALC) on the prevention of taxane-induced neuropathy (TIN).
Experimental approach: MEDLINE, PubMed, Cochrane Library, Embase, Web of Science, and Google scholar were systemically applied as electronic databases from 2010 to 2019. The current systematic review was carried out based on the main considerations of PRISMA preferential reporting items for systematic review and meta-analyses. Since there was no significant discrepancy, the random-effect model was used for 12-24 weeks' analysis (I^2 = 0%, P = 0.999).
Findings/Results: Twelve related titles and abstracts were found during the search, 6 of them were excluded in the first phase. In the second phase, the full text of the remaining 6 articles was comprehensively evaluated and 3 papers were rejected. Finally, 3 articles complied with the inclusion criteria and pooled analyses. The meta-analysis showed a risk ratio of 0.796 (95% CI between 0.486 and 1.303), so, the effects model was used for 12-24 weeks' analysis (I^2 = 0%, P = 0.999) since no significant discrepancies were observed. There was no evidence of ALC's positive effect on the prevention of TIN during 12 weeks, and it was revealed that ALC significantly increased TIN in 24 weeks.
Conclusion and implications: According to our findings, the hypothesis that ALC had a positive effect on preventing TIN in 12 weeks has not been proved; however, ALC led to an increase in the TIN in 24 weeks.

Keywords: Acetyl-L-carnitine; Breast cancer; Chemotherapy; Neuropathy; Taxane.

INTRODUCTION

Chemotherapy-induced peripheral neuropathy (CIPN) was known as one of the most prevalent and disabling undesirable effects of several common anticancer agents, such as taxanes, vinca alkaloids, and platinum salts. This complication was of utmost vital clinical importance since neurotoxicity would be one of the adverse effects restricting dose and causing early discontinuation of treatment (1). Taxanes are one of the most classes of chemotherapy agents that can cause CIPN, which is somehow attributed to a distal sensory neuropathy realized by pain and paresthesia that causes to decrease in functional capacity (2,3). Up to 80% of patients treated with taxanes reported some extent of neuropathy, and about 25% to 30% reported severe neuropathy (4,5). There are some moderate recommendations for the treatment of painful CIPN. In a randomized double-blind placebo-controlled trial study the unexpected outcomes of acetyl-L-carnitine (ALC) for the prevention of taxane-induced neuropathy (TIN) in women undergoing adjuvant breast cancer therapy have been previously reported (2). Despite many research efforts and successful reports of preclinical studies, there is a paucity of qualified and consistent pieces of evidence of clinical successes (3).

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Experimental designs differ in several parameters and the lack of a standardized CIPN evaluation approach has led to unclear results (5). As a general rule, symptoms that occurred in the middle of chemotherapy could be increased after the completion of therapy (6). If any symptoms were observed, the overall dose would be restricted as well as each dose or the therapy may be discontinued when CIPN appeared, these measures would be possible in each state (7). ALC was a natural compound contributing to intermediary metabolism. In mitochondria, this substance ensured the availability of acetyl-coenzyme A to eliminate toxic by-products. ALC was a considerable role in tubulin acetylation and was known as an important part of neuronal protection (8,9). ALC in CIPN animal models enhanced sensory neuropathy and minimized the severity of neuropathy (10). However, the results of drug treatment in human studies have been generally contradictory due to the small sample size and limitations caused by adverse effects. In none of these prospective studies, these factors have been considered to prevent the long-term effects of CIPN in the adjuvant treatment of breast cancer. However, ALC administration could show neuropathy improvement in patients with non-cancer conditions such as diabetes (11,12). This systematic and meta-analysis study attempted to consolidate available evidence of ALC effects to prevent TIN in women undergoing breast cancer treatment.

MATERIALS AND METHODS

Protocol and registration

The protocol of the current study was registered in the PROSPERO registration platform (CRD42022359330). The Preferred Reporting Items for systematic reviews and meta-analyses (PRISMA) 2020 27-item checklist, was used in methods to identify, select, appraise, and synthesize studies (13).

Eligibility criteria

All of the selected articles were published between Jan 2010 to Dec 2019. The inclusion criteria included all English articles, randomized controlled trials (RCTs), controlled clinical trials, and prospective and retrospective studies, conducted on women over 18 years old under breast cancer therapy while receiving ALC containing ALC dose and duration of administration. *In-vitro* studies, case studies, case reports, review articles, and studies conducted on animals were excluded. The extracted risk estimates from the studies were risk ratio, odds ratio, standardized incidence ratio, rate ratio, hazard ratio, and incidence rate ratio.

Information sources and search

The keywords strategies including “acetyl-L-carnitine” OR “ALC” AND “taxane” AND “neuropathy” AND “breast cancer” AND “chemotherapy” AND (“chemotherapy-induced peripheral neuropathy” OR CIPN) OR (“neurotoxicity OR NTX”) AND “Paclitaxel” AND “Docetaxel” were used by search databases. A total of 110 items were detected by the above-mentioned query in the MEDLINE database from which 72 primary articles were identified. The search of PubMed retrieved a total of 97 items from which 51 primary articles were identified. The search of Embase included a total of 63 items from which 38 primary articles were identified. The Web of Science search was done with a total of 116 items from which 35 primary articles were identified. The advanced search of google scholar resulted in a total of 73 items which 27 primary articles were identified (Table 1). The current systematic review study was carried out based on the main considerations of PRISMA preferential reporting items for systematic review and meta-analyses (14).

Study selection

The two authors (A. Moghaddas and M. Momenzadeh) downloaded all the titles and abstracts retrieved by electronic search to a reference management database, removed the duplicates, and independently examined the remaining references. Studies that did not meet the eligibility criteria were excluded and copies of the full texts of potentially relevant sources were obtained. The eligibility of retrieved articles was assessed independently and disagreements were resolved by discussion between the two authors.

Table1. The search strategy and keywords.

Database	Search strategy and keywords	Time limitation	Total items	Primary articles
MEDLINE	(”acetyl-L-carnitine” OR “ALC”) AND “taxane” AND “neuropathy” AND “breast cancer” AND “chemotherapy” OR AND (“chemotherapy-induced peripheral neuropathy” OR CIPN) OR (“neurotoxicity OR NTX”) AND “Paclitaxel” AND “docetaxel”	2010/01/01-2019/12/30	110	72
PubMed	(”acetyl-L-carnitine” OR “ALC”) AND “taxane” AND “neuropathy” AND “breast cancer” AND “chemotherapy” OR AND (“chemotherapy-induced peripheral neuropathy” OR CIPN) OR (“neurotoxicity OR NTX”) AND “Paclitaxel” AND “docetaxel”	2010/01/01-2019/12/30	289	21
Cochrane Library	(”acetyl-L-carnitine” OR “ALC”) AND “taxane” AND “neuropathy” AND “breast cancer” AND “chemotherapy” OR AND (“chemotherapy-induced peripheral neuropathy” OR CIPN) OR (“neurotoxicity OR NTX”) AND “Paclitaxel” AND “docetaxel”	2010/01/01-2019/12/30	97	51
Embase	(”acetyl-L-carnitine” OR “ALC”) AND “taxane” AND “neuropathy” AND “breast cancer” AND “chemotherapy” OR AND (“chemotherapy-induced peripheral neuropathy” OR CIPN) OR (“neurotoxicity OR NTX”) AND “Paclitaxel” AND “docetaxel”	2010/01/01-2019/12/30	63	38
Web of Science	(”acetyl-L-carnitine” OR “ALC”) AND “taxane” AND “neuropathy” AND “breast cancer” AND “chemotherapy” OR AND (“chemotherapy-induced peripheral neuropathy” OR CIPN) OR (“neurotoxicity OR NTX”) AND “Paclitaxel” AND “docetaxel”	2010/01/01-2019/12/30	116	35
advanced search of google scholar	(”acetyl-L-carnitine” OR “ALC”) AND “taxane” AND “neuropathy” AND “breast cancer” AND “chemotherapy” OR AND (“chemotherapy-induced peripheral neuropathy” OR CIPN) OR (“neurotoxicity OR NTX”) AND “Paclitaxel” AND “docetaxel”	2010/01/01-2019/12/30	73	27

Two independent reviewers conducted the eligibility assessment that evaluated the titles, abstracts, inclusion and exclusion criteria, and full text. Possible disagreements were resolved in a panel discussion; otherwise, the issue was referred to a third reviewer. A modified version of thestrengthening the reporting of observational studies in epidemiology (STROBE) checklist was used for quality assessment (15). STROBE statement is a set of recommendations to improve the reporting of observational studies. STROBE addresses the three main types of observational studies: cohort, case-control, and cross-sectional studies. The statement consists of a checklist of 22 items that relate to the title, abstract, introduction, methods, results, and discussion sections of articles.

In addition, the CONSORT statement was chosen as a tool to evaluate the reporting quality of these RCTs. We assessed each RCT's compliance with 25 items of the CONSORT statement, each item and subsection of the checklist receiving a "yes" or "no" response. According to the above entries, the coincidence rate of each item in the 12 studies was calculated one by one. One point for the item is awarded if all subsections are answered yes, if either subsection is flagged, a score of 0.5 is assigned, then the total score for each study is calculated. It is not necessary to apply items 3b, 6b, and 14b, if applicable, points will be awarded according to the instructions above, and if not applied to this section, no points will be deducted (16).

Data collection process

Data on characteristics of patients including age, paclitaxel administration schedule, inclusion criteria, primary cancer histology, number of patients in each arm, dose and administration routes of pharmacological agents, as well as interventions such as pharmacological or non-pharmacological approaches, follow-up duration, risk of bias and primary outcomes (such as 1-grade improvement in the TIN and significantly less sensory and motor neuropathy in ALC-group after 2 and 3 cycles), were independently extracted for all included studies by the two authors K. Ghadimi and A. Aria.

For the primary outcome, the number of patients in arms of treatment and control who experienced TIN and patients evaluated at the endpoint was extracted to estimate the RR and 95% confidence interval (CI).

A data extraction form was developed including the general information of the studies (*e.g.* article code, article title, reference number, reviewer initials, publication details, first author, journal title and year, volume, first page), study eligibility (*e.g.* total study period, participants, study setting, inclusion criteria, exclusion criteria, total population at the start of the study, age of the study population, type of outcome measures), methods (*e.g.* the aim and design of the study and ethical approval), risk of bias assessment, and risk estimates including relative risks (*e.g.* odds ratio, risk ratio, rate ratio, and hazard ratio).

Assessment of risk of bias

Collaboration's risk of bias tool was used to assess the risk of bias in the studies independently by the two authors regarding the Cochrane domains of allocation sequence generation; allocation concealment; blinding of participants; blinding of outcome assessment; incomplete outcome data, and selective reporting. The authors discussed the differences to resolve them.

Assessment of heterogeneity

Visual inspection of forest plots, chi-square (χ^2) tests, and the I^2 statistic were used to assess heterogeneity among studies. A *P*-value higher than 0.10 for the χ^2 test and an I^2 value lower than 25% was considered as a low level of heterogeneity.

Synthesis of results

The data were enrolled into the STATA software version 14.0 (Stata Corp LLC, Texas, USA). A random-effects model was performed to check the heterogeneity of the studies. The risk of bias was examined using Cochrane Collaboration's risk of bias tool.

RESULTS

Study selection

Generally, 12 related titles and abstracts were found during the electronic and manual search; two articles were excluded due to duplication. In the first phase of the study selection, four articles were excluded based on the title and abstract initial assessment and non-relevancy. In the second phase, the full text of the remaining 6 articles was comprehensively evaluated. In general, 3 papers were rejected at this phase, since they did not match the inclusion criteria. Finally, 3 articles complied with the inclusion criteria of this systematic review (Fig. 1). Table 2 shows the studies included in this meta-analysis.

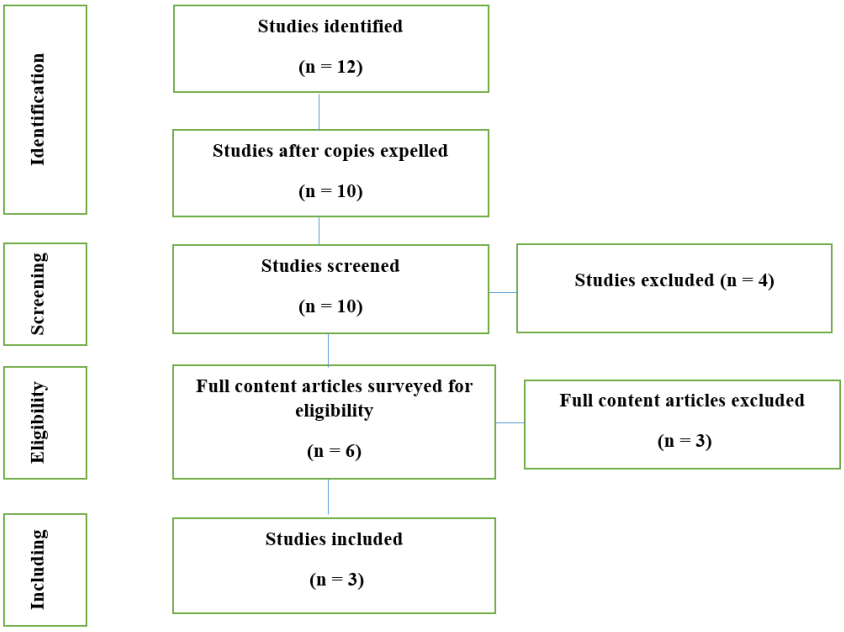

Fig. 1. Flow chart describing the search and selection of studies according to the PRISMA guidelines.

Table 2. Studies selected for systematic review and meta-analysis

Study/year (reference number)	Design	No. of patients	Mean of age (year)	Therapy	Goal	ALC dose (g/day)	Duration of treatment (days)	Primary outcome measures
Hershman *et al.* / 2013 (17)	RCT	409	52	PAC/DOC	Prevention	3	168	All CIS-treated patients 1-grade improvement FACT-NTX-T-score: significantly more neuropathy in the ALC group after 24 weeks
Hershman *et al.* / 2018 (18)	RCT	409	52	PAC/DOC	Prevention	3	168	All CIS-treated patients 1-grade improvement FACT-NTX-T-score: significantly more neuropathy in the ALC group after 24 weeks
Ellithy *et al.* / 2014 (19)	RCT	40	51	PAC	Prevention	3	56	After 2 and 3 cycles significantly less sensory and motor neuropathy in ALC-group

ALC, Acetyl-L-carnitine; FACT-NTX, neurotoxicity component of functional assessment of cancer therapy-taxane scale; NTX, neurotoxicity; PAC/DOC, paclitaxel/docetaxel; CIS, cisplatin; RCT, randomized clinical trial.

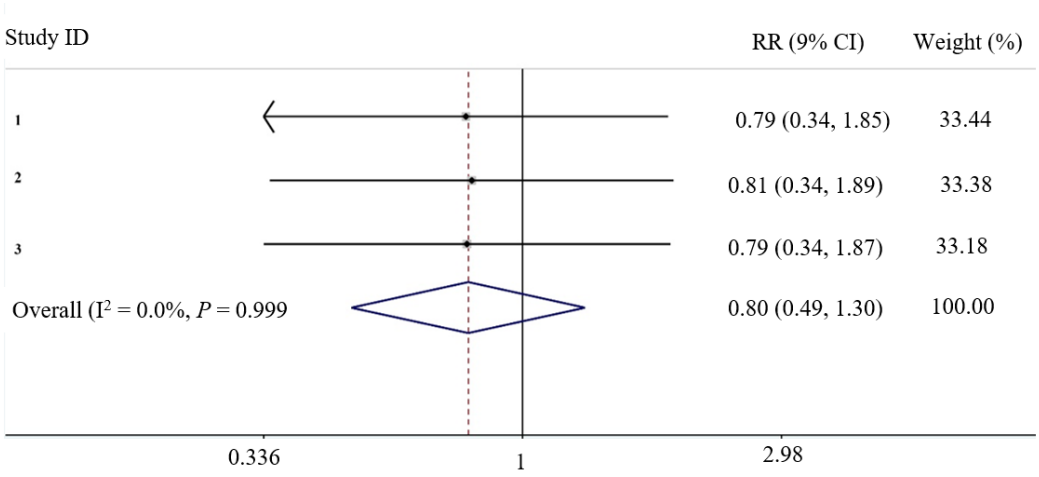

Fig. 2. Forest plot of acetyl-L-carnitine effects on the prevention of taxane-induced neuropathy. Heterogeneity: chi-squared (χ^2) test = 0.00 (degree of freedom = 2), $P = 0.999$, I^2 test (variation in RR attributable to heterogeneity) = 0.0%, test of RR = 1, z = 0.91, $P = 0.363$. RR, Risk ratio.

Study characteristics

Three RCT studies were taken into consideration. The number of patients was 858, the average age was 51.6 years, and they were treated with docetaxel and paclitaxel. The duration of treatment was between 56-168 days (17,18). In one study, after 2 and 3 cycles, it was found that sensory and motor neuropathy was significantly lower in the ALC group. (Table 2).

Risk of bias within studies

Two authors independently assessed the risk of bias included studies using Cochrane Collaboration's risk of bias tool. We used the Cochrane risk of bias tool to assess potential sources of bias in included clinical trials, rating each as low (−), high (+), or unclear risk of bias. Differences were resolved by discussion.

Results of individual studies

After checking for crude and adjusted risk estimates in the primary studies, less than a 10% difference was found between them, indicating no confounding effect. The meta-analysis cleared a risk ratio of 0.796 (95% CI between 0.486 and 1.303), and the effects model was used for 12-24 weeks' analysis since no significant discrepancies were observed ($I^2 = 0\%$, $P = 0.999$) (Fig. 2).

The meta-analysis approved that there was no evidence containing a positive effect of ALC on the prevention of TIN during 12 weeks, and it was revealed that ALC significantly increased TIN in 24 weeks.

Risk of bias across studies

From the twelve selected RCT studies, four were at unclear risk of selection bias due to not reporting their methods for random sequence generation, while five were at unclear risk of selection bias due to not reporting on allocation concealment. Blinding of participants and personnel was not reported in five trials, hence the risk of performance bias was considered unclear. Similarly, seven trials had an unclear risk of detection bias because the blinding of outcome assessors was not reported. Two trials had an unclear risk and three trials had a high risk of attrition bias because more than 30% of study participants were not included in the analysis for various reasons, including missing follow-ups or disease progression.

DISCUSSION

There are great interindividual differences among the breast cancer women treated with taxanes, more than 20-30% of patients are asymptomatic and do not develop neurotoxicity during chemotherapy with these agents (1,2). Among patients who develop neurotoxicity, some spontaneously recover over months after the end of treatment, while others may develop irreversible peripheral axonal damage, and this different individual susceptibility is essentially unexplained.

Many trials have been conducted to find an effective treatment for TIN and many drugs, both natural and synthetic, have been recommended for the prevention of TIN while there is no standard treatment modality officially approved.

Pre-clinical supporting evidence indicated that ALC might be conducive to treating and preventing the symptoms of CIPN caused by taxanes. Supplementation with L-carnitine and its derivatives had been previously addressed for the treatment of chemotherapy-induced adverse events such as cachexia or anorexia and organ failure (19,20).

There was no evidence of a positive effect of ALC on CIPN prevention in women undergoing breast cancer treatment. This issue might be happening due to the paucity of data and the small number of randomized clinical trials included in the meta-analysis causing misleading.

Hershman *et al.* first wondered at the finding whether ALC could lead to an increase in TIN during the 24-week intervention (ALC administration of 1000 mg three times a day) and they were surprised by the finding that 24 weeks of ALC therapy resulted in statistically significantly worse TIN over 2 years. They suggested that the mechanism of this long-term effect may inform prevention and treatment strategies driven by L-carnitine and its derivatives (18).

ALC was an antioxidant that probably had a protective effect against oxidative stress (21).

Most clinical trials reported CIPN symptoms during treatment modalities. However, there are some reports of sustainable symptoms after the completion of chemotherapy which were reported by the patient (22-24). Therefore, the number of articles in which long-term adverse events of CIPN were noted is limited. In the cross-sectional studies carried out on survivors of cancer, the prevalence of CIPN symptoms was estimated between 30%-80% concerning the population (22-24).

These studies reported the used criterion to examine CIPN, the measurement time after treatment, and the prescribed chemotherapy drug. Though, it was somehow difficult to decide whether these symptoms were before chemotherapy or their identification might be under selection and examination without evaluating the basis. Some of these cross-sectional studies reported a relation between a poor score reported by a CIPN patient, a decrease in quality of life, an increased risk of missing data, and an increased dysfunction (25). Also, there is some other dispersity along with the methodology of studies, for instance, some prospective CIPN cohort studies were carried out at different times of chemotherapy administration protocol (5,26). Overall, for making any conclusion, several large and well-designed clinical studies should be conducted with the aim of details on CIPN occurrences and the impact of different modalities.

The concept of ALC administration for the prevention of CIPN extracted from different animal studies indicates the direct neurological benefits of ALC in preventing some chemotherapy agents such as oxaliplatin- or taxane-induced neurotoxicity (27-29). In these studies, the swelling rate and vacuolation of C-fiber mitochondria in peripheral nerve axons were reduced by the administration of ALC, and ALC prevented the minimization of sensory neurons measured by neural conduction.

Another observational study has demonstrated that serum L-carnitine concentrations in cancer patients were less than in healthy volunteers (30), supporting that serum carnitine may also decrease by implementing the chemotherapy protocol in cancer patients (31).

However, the ultimate role of ALC was not yet recognized in the prevention and treatment of CIPN. Regarding finding the possible protective mechanisms, a systematic review and meta-analysis to determine the efficacy of pharmacological and non-pharmacological neuroprotective interventions in preventing TIN carried out by Leen *et al.* (32), evaluated 24 relevant controlled trials and 14 were eligible for meta-analysis. Pooled results from seven non-pharmacological trials were associated with a statistically significant 48% relative reduction of TIN risk with low heterogeneity and the pooled results from six pharmacological trials were associated with a significant 20% relative reduction of TIN risk with moderate heterogeneity. Both pharmacological and non-pharmacological approaches appear effective in reducing TIN incidence in the treatment arm compared to control but they have finally concluded that both interventions may reduce TIN risk, however, it seems that non-pharmacological interventions (especially cryotherapy and compression therapy) are more effective than pharmacological interventions. Off note, among pharmacological agents which were analyzed in this study, only one study with ALC administration was noted (18) and the overall pooled analyses by other pharmacologic agents such as gabapentin, omega-3, vitamin E, minocycline, pregabalin, glutathione, glutamate, amifostine, recombinant human leukemia inhibitory factor, and N-acetylcysteine resulted in positive TIN protective effects.

However, in our study, we just focused on the possible protective effects of ALC on TIN and 4 related studies were included, eventually, as mentioned, we failed to show the positive protective properties when it comes to ALC administration per se.

In general, the quality of evidence in considered studies is overall low, and also the studies suffered from small sample size.

Larger well-designed multicenter trials should examine the effects of these promising agents for more definitive evidence. Future trials may consider a combination of pharmacological and non-pharmacological strategies or a combination of both in the prevention of peripheral neuropathy. Trials should use defined methods of standardized objective assessment and primary and secondary outcomes to ensure the validity of results. Experimental studies are needed to discover the mechanisms of action of these methods. These can be effective in advancing treatment by combining optimal treatment parameters.

Study limitations

While the risk of sampling bias due to the exclusion of gray or non-English literature is reduced through the systematic search, there is still a risk that studies that investigated combinations of antineoplastic drugs (which included paclitaxel) were not included.

Most of the studies reported the incidence of TIN using different cases and assessment tools, this hinders further research on the effect of these interventions on reducing the severity of neuropathy. In addition, methodological heterogeneity among studies and inconsistency of pharmacological interventions were observed in the report, which limited the power of conclusions.

CONCLUSION

The use of taxane-based treatments was increased over time in patients with breast cancer. Presently, there was no cure for CIPN

prevention or treatment despite different prospective randomized trials. This meta-analysis assessed neuroprotectants for preventing TIN and highlights the effects of ALC for the prevention of TIN in patients with breast cancer. Although the evidence from the selected trials demonstrated greater efficacy of non-pharmacological than pharmacological interventions in the reduction of TIN incidence, it was not possible to support the hypothesis that ALC had a positive effect on preventing TIN in 12 weeks, but ALC administration increased TIN in 24 weeks. Regarding the low quality of evidence from the evaluated studies, and the small sample size, meticulous planning of trial design and standardizing CIPN assessment techniques will greatly improve outcome reporting and make it easy to judge the prospective interventions for clinical practice incorporation.

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Conflicts of interest statement

The authors declared no conflict of interest in this study.

Authors' contribution

M. Momenzadeh and A. Aria equally contributed to the study and A. Moghaddas conceptualized the research. Data were analyzed and interpreted by A. Aria and K. Ghadimi drafted the manuscript. A. Moghaddas and M. Momenzadeh reviewed the manuscript totally and provided critical recommendations. All authors contributed to the article and approved the finalized manuscript.

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