European Review for Medical and Pharmacological Sciences 2018; 22: 4739-4754

Natural products – alpha-lipoic acid and acetyl-L-carnitine – in the treatment of chemotherapy-induced peripheral neuropathy

S. DINICOLA[1,2], A. FUSO[2,3], A. CUCINA[3,4], M. SANTIAGO-REYES[3,4], R. VERNA[1,2], V. UNFER[5], G. MONASTRA[2], M. BIZZARRI[1,2]

[1]Department of Experimental Medicine, Sapienza University of Rome, Rome, Italy
[2]Systems Biology Group Lab, Sapienza University of Rome, Rome, Italy
[3]Department of Surgery "Pietro Valdoni", Sapienza University of Rome, Rome, Italy
[4]Azienda Policlinico Umberto I, Rome, Italy
[5]Department of Developmental and Social Psychology, Faculty of Medicine and Psychology, Sapienza University of Rome, Rome, Italy

Abstract. – OBJECTIVE: Cancer patients frequently experience Chemotherapy-Induced Peripheral Neuropathy (CIPN), as a typical side effect related to time of administration and dose of anticancer agents. Yet, CIPN pathophysiology is poorly understood, and there is a lack of well-tolerated pharmacological remedies helpful to prevent or treat it. Therefore, new safe and effective compounds are highly warranted, namely if based on an adequate understanding of the pathogenic mechanisms.

MATERIAL AND METHODS: Herein we reviewed and discussed scientific data related to the beneficial role of some non-conventional treatments able to counteract CIPN, focusing our attention on alpha-lipoic acid (ALA) and L-acetyl-carnitine (LAC), two natural products that have been demonstrated to be promising preventive drugs.

RESULTS: Although a growing body of *in vitro* and *in vivo* studies support ALA as a molecule able to counteract CIPN symptoms, mostly due to its antioxidant and anti-inflammatory properties, only two randomized clinical trials evaluated ALA usefulness in preventing chemotherapy-related neuropathy. Unfortunately, these studies were inconclusive and clinical outcomes showed to be highly dependent on the route of administration (oral versus or intravenous injection). LAC has demonstrated beneficial effects on both *in vitro* and in animal studies. Yet, some controversies aroused from randomized clinical trials. Indeed, while CIPN-patients treated with Taxane showed no benefit from LAC treatment, CIPN-patients treated with platinum compounds exhibit significant improvement of CIPN-related symptoms. Therefore, LAC treatment should be used, and thoroughly investigated only in patients treated with chemotherapy protocols Taxanes-free.

CONCLUSIONS: Mechanisms of toxicity triggered by each single drug need to be deeply explored to better identify effective compounds to prevent or treat them. Moreover, additional experiments are mandatory to establish effective doses and length of treatment for each clinical situation in order to perform large and long-term randomized studies.

Key Words:
Alpha-Lipoic acid, Acetyl-L-Carnitine, Chemotherapy, Peripheral Neuropathy.

Introduction

Chemotherapy (CT)-Induced Peripheral Neuropathy (CIPN) is a frequent and potentially debilitating side effect of cancer treatment. Peripheral neuropathy, manifested by neuropathic pain and axonal degeneration, is indeed one of the major sources of disability in patients following antineoplastic therapy after hematological and renal toxicity[1,2]. Availability of efficient anti-emetic drugs and hematopoietic colony stimulating factors has allowed in the last decades high-dosage CT regimens, especially those including 'aggressive' antineoplastic drugs. Consequently, serious side effects including CIPN are currently more frequently observed than in the past and often represent a dose-limiting factor in treatment delivery. Despite its clinical relevance and common occurrence, the epidemiology as well as the pathophysiology of CIPN in the different groups of chemotherapies is still

Corresponding Author: Simona Dinicola, Ph.D; e-mail: simona.dinicola@uniroma1.it

largely unknown and a hypothetical etiological mechanism can be hypothesized only in less than 50% of cases[3].

Several reviews and meta-regression analyses suggest high overall prevalence of CIPN, mostly within the first month after treatment, and falling over time. Usually, the development of CIPN is related to time of administration and to dose and its incidence steadily increases with combination regimens.

Symptoms typically begin several weeks to months after initiation of the therapy and progress while treatment continues; for many compounds, toxicity progressively develops once the cumulative dose has been exceeded[4]. Moreover, according to different reports (for a review, see ref.[5]), approximately from one-third to 50% of patients can expect to have chronic CIPN six months after the completion of specific treatments. Undoubtedly, this has a significant negative impact on long-term quality of life and may impair the possibility to start with new therapeutic protocols, if needed.

Platinum compounds constitute a remarkable exception, as appearance of neurological side effects is often an early symptom.

Pathogenesis of Neuropathy

Despite its clinical relevance and common occurrence, the pathophysiology of CIPN is still insufficiently understood and extensive investigations are warranted. However, it is worth of note that the chemotherapy-related damage is selectively oriented towards the peripheral nervous system[6]. This implies that the peripheral nervous system is vulnerable because of several unique characteristics. Indeed, primary sensory and autonomic neurons are contained in ganglia that lie outside the blood-brain barrier and are supplied by capillaries with fenestrated walls that allow free passage of molecules between the blood circulation and the extracellular fluid in the ganglia. Thus, drugs can easily penetrate in ganglia and diffuse along peripheral nerve axons, where they can induce axonal damage by interfering with cytoskeleton, intracellular transport of metabolites, energy metabolism (hitting mitochondria function), and DNA function. In fact, longer peripheral nerves, such as sensory fibers, are chiefly susceptible to any interference impairing energy metabolism, mitochondrial function, or axonal transport[7].

Yet, the exact pathophysiology of CIPN is still barely understood, and different underlying mechanisms have been proposed. Furthermore, each pharmacological compound may enact several pathogenic mechanisms at the same time.

Schematically, anticancer drugs may hit a discrete number of targets, including microtubules, mitochondria, DNA, and ROS production.

Microtubule disruption. Integrity of axonal microtubules is essential for the development and maintenance of neurons. Microtubule elongation contributes in shaping neurite formation and in promoting its growth. Additionally, microtubule are the mayor elements sustaining axonal anterograde and retrograde transport of neurofilaments, degradative organelles and endosomes containing signaling platforms. Among the antineoplastic drugs, Taxanes (Paclitaxel and Docetaxel) disrupt microtubule structure and coherency, thus impairing the transport along the axons, as demonstrated by *in vitro* studies[8,9].

It is estimated that at standard doses, about 70% of patients have grade 1, very mild peripheral neuropathy, and up to 10% of patients have grade 3 peripheral neuropathy. The prevalence is higher in paclitaxel-treated (57%-83%) than in docetaxel-treated patients (11-64%)[10,11]. New Taxane formulations are being developed to improve antineoplastic properties and minimize toxicities, but CIPN remains an unsolved problem. Indeed, phase III clinical trials comparing standard Paclitaxel with nab-Paclitaxel (second generation of Taxane) showed an even higher incidence of grade 3 neuropathy in nab-paclitaxel than in the standard treatment[12].

Use of Vinca alkaloids is accompanied by severe side effects, including CIPN and chronic neuropathic pain. Vincristine-induced peripheral neuropathy is dose dependent, as up to 60% of patients may develop a clinically significant (grade 1-2) primarily sensory or sensorimotor neuropathy at Vincristine cumulative doses between 30-50 mg[13]. Peripheral neuropathy in Vincristine-treated patients is characterized by disturbances in both sensory and motor functions[13]. Vinca alkaloids disrupt β-tubulin assembly and disassembly, by preventing tubulin polymerization from soluble dimers into microtubules. The resulting perturbation in microtubule-dependent axonal flux leads to axonal swelling in myelinated and unmyelinated fibers and to nervous fiber damage[14,15]. Affinity for tubulin differs among Vinca-alkaloid compounds (decreasing in order Vincristine,

Vinblastine, Vinorelbine), which might explain the distinct neurotoxic profiles of these chemotherapeutic agents[16]. Epothilones – a novel class of microtubule targeting agents – are used in breast cancer treatment and, similarly to Taxanes, they bind to tubulin, hindering their stability and inducing therefore cell apoptosis[17]. Eribulin mesilate, used in breast cancer therapy, is another microtubule disrupting agent, which prevents microtubule growth and sequesters tubulin into non-productive aggregates[18]. Given that sensory neurons within dorsal root ganglion require proper microtubule dynamics for axonal transport, it is not surprising that microtubule-targeting drugs can cause abnormalities in peripheral nerve fibers function and structure.

Mitochondria damage. Chemotherapeutic drugs can induce toxic effect on mitochondria in primary afferent neurons leading to deficit in axonal energy supply and chronic sensory neuropathy[19]. In the rat, paclitaxel neuropathy is associated with significant increase of swollen and vacuolated mitochondria in the axons. Paclitaxel opens the mitochondrial permeability transition pore (mPTP), which is a multi-molecular complex containing the voltage dependent anion channel. Paclitaxel evoked opening of the mPTP causes the calcium release from the mitochondria. This calcium mediated neuronal excitability is suggested to play a role in neurotoxicity. Impairment in mitochondria function may explain the observed changes in neuronal metabolism, as a deficient oxygen consumption in the dorsal root sensory axons from animals treated with paclitaxel, with increased amounts of ATP produced by both respiratory complex I and II[20]. Several evidences suggest that mitochondrial toxicity may be a pivotal feature in many, if not most, chemotherapy-induced peripheral neuropathy. Thereby, drugs that protect mitochondrial function, likewise acetyl-L-carnitine, may be very useful protecting adjuncts[21].

Dorsal root ganglion (DRG) damage. The dorsal root ganglion appears to be the primary site of cisplatin-induced neural damage. Cisplatin accumulates in the cell body of the dorsal root ganglia, reducing their nuclear size, and inhibiting axonal growth and neuronal metabolism in a dose dependent manner[22,23]. Similarly, bortezomib-associated peripheral neuropathy seems to disrupt ganglia neuronal functions, with peripheral nerve degeneration occurring later[24].

Oxidative stress. Deregulated ROS production and increased oxidative stress have been thought as main mechanism supporting CIPN pathogenesis. Indeed, promising results obtained both in pre-clinical models and in clinical practice with antioxidant treatments have provided strong support to this hypothesis. Moreover, since ROS production occurs when mitochondria structure and function are impaired, it has been hypothesized that CT-induced damages on mitochondria might likely raise oxidative stress[25]. However, despite the empirical use of antioxidants in the therapy of CIPN, and some experimental evidence hitherto published, the relationship between ROS generation after CT-treatment and peripheral neurotoxicity is still debatable.

Unknown mechanisms. A group of anticancer drugs, including Thalidomide, Nelarabine, and Cytarabine, induces peripheral neuropathy as main neurotoxic side effect. Mechanisms supporting that effect are still unknown, notwithstanding that deregulation of immune function or direct neurotoxic effect on Schwann cells have been already postulated[26]. Obviously, different drugs may share some common mechanisms. However, critical differences exist among different anticancer agents and, as it will be showed later, they could likely account for the different responsiveness highlighted by clinical trials when using similar protective compounds.

Conventional Treatments

It would seem a truism stating that efficacy of peripheral neuropathy treatment depends, at large, on the cause of the neuropathy. Indeed, suspending the therapy of reducing the dose can usually result in resolution of the symptoms (even if resolution may require different time laps).

Etiology of CIPN is very poorly understood, and consequently treatment options for established drug-based neuropathy are limited. Yet, increasing evidence suggests that different mechanisms are at play when different chemotherapeutics are used[27].

Although several gene-based studies have been promoted to investigate the relationship between single nuclear polymorphisms (SNPs) in genes involved in the pharmacokinetic and pharmacodynamics properties of neurotoxic drugs, during the last decade, no reliable biomarker has thus far been identified. Though some different gene expression patterns have been associated

with different drug regimens[28,29], results were altogether inconclusive. These investigations were biased by several methodological flaws, including small sample size, inaccurate retrospective study design, lack of a pre-study hypothesis based on the known role of the investigated targets and inappropriate outcome measures for neurological impairment[30,31]. Definitely, some studies have identified genetic polymorphisms associated with Taxane-associated CIPN, most of them with inconclusive results[28,32,33], and only few accompanied with replication or validation studies[34,35].

Moreover, clinical trials of antiepileptic or antidepressant agents to treat neuropathic pain have generally been negative[36], besides few exceptions in which minimal benefit has been obtained in duloxetine treated patients[37]. The 2014 American Society of Clinical Oncology CIPN guidelines cautiously designate treatment with duloxetine, even claiming for further research in this area[38]. Conclusively, based on the paucity of high quality, consistent evidence, currently there are no pharmacological agents recommended for the prevention/treatment of CIPN[38]. Thereby, new safe and effective treatments are clearly needed[39].

Non-Conventional Treatments

The lack of effectively curative strategies for CIPN promotes the urgent need to seek help from Complementary and Alternative Medicine (CAM). As a key complement for conventional medical therapy, CAM has been paid attention by the western countries because it is less invasive and more safe, effective, with convenient therapeutic benefits. CAM emphasizes both on disease prevention and treatment and has become an important alternative in treating chronic disease. Recently, several CAM methods including traditional herbal medicines and acupuncture have been described to be beneficial on CIPN, although only a few studies have been properly conducted. The Society of Integrative Oncology Guidelines[40] include within the definition of complementary therapies: dietary, acupuncture, touch therapy, mind-body modalities, and physical activity. These interventions have become significant resources in the field of cancer clinical management, and an increasing number of patients are currently using them. Overall, the prevalence for current use of CAM across the different studies averages 40%. Meta-analysis investigations suggested an increase in CAM use from an estimated 25% in the 1970s and 1980s to more than 32% in the 1990s and to 49% after 2000, with highest trends recorded in the US[41].

Only few comprehensive reviews[42-44] on the mechanisms and the clinical reliability (assessed by means of Randomized Clinical Trials, RTCs) have been so far conducted, especially by focusing on some 'major' players represented by natural compounds like alpha-tocopherol[45,46], magnesium[47], Omega-3 fatty acids[48], herbal remedies[49], vitamin B supplementation[50], glutamate and glutamine[51], Goshajinkigan[52]. Those studies provided mixed and controversial results, and currently no standard regimen can reliably be recommended. Several limitations may explain why no firm conclusion can be drawn based on the published evidence. Objectives across trials were different, with some focusing on CIPN prevention (before any CT delivery), while others are conceived for treating established CIPN. Moreover, lack of long-term follow-up for outcomes, and the use of different evaluation scales and types of chemotherapeutic agents are also major factors preventing useful comparison[53].

The goal of this article is to focus specifically on alpha-lipoic acid (ALA), and L-acetyl-Carnitine (LAC) and their usefulness in counteracting CIPN.

Alpha-Lipoic Acid (ALA)

Discovered in 1937[54] and recognized as an essential factor for potato growth, alpha-lipoic acid (ALA) – 1,2-dithiolane-3-pentanoic acid – has a redox active disulfide group. The carbon atom at C_6 is chiral and the molecule exists as two enantiomers (R)-(+)-lipoic acid (the biologically active enantiomer) and (S)-(-)-lipoic acid (SLA). The reduced form of ALA, the dihydrolipoic acid (DHLA) – a dithiol compound after ALA has been internalized in the cytosol[55] – interacts with reactive oxygen species (ROS), and both ALA and DHLA are considered to be potent anti-oxidants[56], in some cases, at least *in vitro*.

In eukaryotes, ALA is endogenously synthetized from octanoid acid or from a mitochondrial pathway. The octanoid residue is transferred as a thioester of acyl carrier protein to an amide of the lipoyl domain protein by octanoyltransferase. Further, two hydrogens of octanoate are replaced with sulfur groups through S-adenosyl-L-methionine dependent mechanism via a radical SAM mechanism[57]. Lipoic acid is definitively synthe-

sized attached to proteins as no free lipoic acid is produced. Yet, ALA can be removed by lipoamidase, when proteins are committed to degradation[58], or by the ATP-dependent lipoate protein ligase[59].

Under physiologic conditions ALA is prevalently represented as lipoate (the conjugate basis of ALA), acting as cofactor in many enzymatic systems, chiefly within the pyruvate dehydrogenase complex (PDC)[60,61].

Lipoic acid is widely present in several foods (chiefly in kidney, heart, liver, spinach, broccoli, and yeast extract), even if at very low amount[62]. However, ALA provided by from dietary sources is covalently bound to proteins[63] and it has thus poor bioavailability[64-66].

Clinical use of ALA is dating back from the eighties, when ALA was recognized as a powerful, easily water-soluble antioxidant (due to its amphipathic properties)[67]. Not only ALA is able at neutralizing free radicals, but also increases glutathione synthesis[68] and, through DHLA, regenerates other important antioxidants[69], and prevents formation of glycosylated end products (AGE)[70] as well as mitochondria damage from oxidative stress[71]. Later on, ALA was shown to be beneficial in chelating heavy metals[72], and in the adjuvant treatment of a number of diseases, including hypertension[73], hyperglycemia[74], insulin resistance and diabetes[75], liver diseases[76], when the pathological cues should be mostly ascribed to toxic and oxidant factors, like heavy metals, free radicals, venoms and microbe toxins (for a comprehensive review, see ref. [77]).

Moreover, several studies reported that ALA exerts multiple pharmacological actions, overall preventing nervous tissue damage from oxidant species[72], nerve degeneration in experimental *in vitro* models of diabetes mellitus[78], Parkinson[79] and Alzheimer's, diseases[80].

ALA is able in restoring important immunological functional defects in peripheral blood mononuclear cells isolated from cancer patients[81], mostly by counteracting pro-inflammatory factors (including IL-6 and TNFα)[82], or downregulating the expression of genes involved in inflammatory-related pathways[83], thereby reducing the overall inflammatory burden[84]. Indeed, recent comprehensive reviews provide compelling evidence of ALA usefulness as anti-inflammatory ally in several human diseases, including rheumatoid arthritis, chronic pain, neuropathy, ulcerative colitis and splenic inflammatory response[85,86]. Finally, it has been demonstrated that ALA can reduce the expression of IL-1b and IL-6, via epigenetic mechanisms, in *in vitro* models of ovarian and neuronal cancer[87, 88].

It is worth of noting that several reports suggested ALA usefulness in the management of diabetes-induced neuropathy[89-91]. Indeed, in a placebo-controlled trial of symptomatic diabetic polyneuropathy, a significant relief of neuropathic symptoms was observed in patients who received alpha-lipoic acid[92]. Similarly, since the first anecdotal report[93], and despite some controversial results, a growing body of evidence points out that ALA could also be beneficial in CIPN. ALA at pharmacological doses (600 mg daily iv/p.os) quickly ameliorates both pain and neurological deficit[94-96]. Adverse effects have been noticed only for higher doses (1200 mg/day), in a significant percentage of patients (~15-20%)[97]. As a result, ALA is approved in Germany as a drug for the treatment of diabetic neuropathy since 1966[98]. A large, randomized study is currently under way to evaluate usefulness of ALA – alone or in combination with Pregabalin – as analgesic remedy for neuropathic pain[99]. It is noteworthy that ALA treatment presents a very reassuring profile of safety and tolerability[77,100].

Those results prompted in evaluating ALA in antagonizing chemotherapy-induced CIPN, differences in pathophysiological mechanisms between diabetic and CT-related neuropathy notwithstanding[101]. In an *in vitro* model of chemotherapy induced peripheral neuropathy in which primary cultures of dorsal root ganglion (DRG) sensory neurons were exposed to paclitaxel and cisplatin, ALA was highly effective in reducing neuron damage. Both cisplatin and paclitaxel cause early mitochondrial impairment with loss of membrane potential and induction of autophagic vacuoles in neurons. Alpha-lipoic acid exerts neuroprotective effects by rescuing the CT-induced mitochondrial toxicity, and induces the expression of frataxin, an essential mitochondrial protein with anti-oxidant and chaperone properties[102].

In a pilot study involving 14 cancer patients, after a median of eight chemotherapy courses and a median cumulative docetaxel dose of 400 mg/m2, all patients suffered from CIPN grade 2 (10 patients) or 3 (four patients). ALA was administered 600 mg i.v. once a week for 3-5 weeks followed by 1800 mg td p.o. until full recovery from neurological symptoms with an average treatment duration of 2 months. Eight out of 14 patients showed significantly reduction in CIPN

grade, with a median time to response of 4 weeks[103]. Similarly, promising results have been obtained in another pilot study in which ALA, altogether with Boswellia and Bromelain, significantly reduced neuropathic pain in CT-treated patients in a 12 weeks treatment regimen[104].

However, only two randomized study evaluated ALA usefulness in preventing CT-related neuropathy. In the first[105], patients were randomized to receive oral ALA 1.800 mg daily or placebo for 24 weeks (excluding days in which platinum-based chemotherapy was administered). Clinical parameters were assessed according to the 11-item Gynecologic Oncologic Group-Neurotoxicity Component (FACT/GOG-Ntx, Version 4) at week 24. Only 70 patients completed the study due to change of regimens, non-compliance, missing data, or unknown reasons. No between-group statistical differences were found. However, this result could had been biased by the high withdrawal rate from the study, given that only 28% of patients in ALA group were eligible for clinical assessment at the end of the investigation. Moreover, the overall platinum dose delivered in the trial – >750 mg/m^2 – was a huge one, even for the current cisplatin-based CT regimens[106]. These shortcomings prompted the Authors of the paper to outline "the inconclusive nature of our trial", eventually suggesting that "future investigation of ALA as a potential prophylactic against CIPN should not be dismissed if innovative approaches and trial designs can be identified and pursued"[105]. Indeed, results that are more promising have been provided by a recent investigation. In a randomized, multicentric study[107], 126 patients with chemotherapy-induced peripheral neuropathy were randomly divided into two groups (of 63 cases each) to be treated with either ALA (600 mg iv/daily) plus mecobalamin (500 μg iv), or with mecobalamin (500 μg iv, control group) for 2 weeks. The response rate in the treatment group was significantly better than in the control group [80.95% (51/63) *vs*. 47.62% (30/63)]. This second study, besides using a reduced dose in respect to the dosage reported in the previous trial (600 mg *vs*. 1.800), delivered ALA through intravenous injection. It can be surmised that some differences in the resulting pharmacokinetics could account for the observed differences between the two trials. Indeed, it has already been recognized that oral administration of ALA is characterized by pharmacokinetic limitations that reduce its therapeutic efficacy.

Indeed, phenomena such as reduced solubility, lack of gastric stability and hepatic degradation determine a bioavailability of around 30% and a short half-life of ALA (30 minutes), while increased bioavailability has been obtained with intravenous injections of ALA[108]. Recent innovative oral formulation has the potential to overcome these pharmacokinetic limitations as it uses only R-ALA enantiomer as liquid solution, with greater solubility and stability in gastric environment[109].

Acetyl-L-Carnitine (ALC)

Carnitine is a β-amino acid, which plays an important role in the transport of fatty acids into the mitochondria for subsequent beta-oxidation[110], while acetyl-L-carnitine (ALC) is the acetylated form of L-carnitine. Moreover, it has been observed that Carnitine can work as an antioxidant, thus protecting various tissues from oxidative injury[111]. Numerous studies performed in rats exposed to pharmacological doses of neurotoxic chemotherapeutic agents, showed appreciable reduction in neuropathic symptoms in animals treated with ALC[112,113], namely by antagonizing the mechanisms triggering painful symptoms[114]. Additionally, treatment with ALC significantly attenuates mitochondrial and cytological chemotherapy-induced damages in peripheral nerves and tissues[113,115], without affecting CT efficacy[116]. ALC prevents Bortezomib induced impairment in mitochondrial respiration and ATP production in rat models of paclitaxel-induced and oxaliplatin-induced painful peripheral neuropathy[115].

However, despite the promising effects of ALC on CIPN in rats, results found in humans are quite controversial.

A survey of the recent literature allows to retrieve seven studies (published in full text in peer-reviewed journals) investigating the putative usefulness of ALC in preventing/treating of CIPN.

Among these, four studies showed improvement of CIPN occurrence and/or intensity in patients treated with ALC[117-120], in one study ALC had no significant effect on neuropathy in patients treated for multiple myeloma[121], whereas the last two studies performed by the same group, reported a worsening of CIPN among patients prophylactically treated with ALC[122,123].

In the majority of these studies, ALC proven to be beneficial for CIPN bearing patients. However, to date, only three papers reported results from randomized controlled trials (RCT), while

the others have been designed as case series or pilot control studies. In most cases, these investigations lack a control group or have enrolled patients with different anamnestic (age, type of CT) or pathological (neuropathy at its beginnings or already established from years) data. In addition, it is usual not to indicate data about the incidence of diabetes in such groups. Given that diabetes neuropathy may likely superimpose to CT-induced neuropathy, thus leading to 'mixed' clinical pictures, this aspect is of great relevance and should be addressed by future clinical trials.

Moreover, the overall design, the methodological set up and clinical end points greatly differ from each other. Confusion may also arise when considering ALC as 'preventive' or 'treatment' option. Differences in posology, duration and route of administration add further complexity. A main concern is the diversity in grading scales used for assessing CIPN, as some of which are based on patient reported outcome [like Functional Assessment of Cancer Therapy – Gynecologic Oncology Group – Neurotoxicity (FACTGOG-NTx)], while others are clinical grading scales [likewise National Cancer Institute – Common Toxicity Criteria (NCICTC), or Total Neuropathy Score (TNS)].

Differences in eligibility criteria and chemotherapy protocols are probably of utmost relevance in understanding why trials aimed at ascertaining ALC efficacy provided conflicting and even opposite results. Both studies performed by Hershman et al[122] involved only female patients with breast cancer treated with only Taxane based chemotherapy regimens. In those studies, ALC showed to be ineffective after 12 weeks of therapy and to even significantly worsen CIPN symptoms after 24 weeks. Notwithstanding the choice of the grading scale for evaluating CIPN is debatable[124] – given that FACT-NTX scale chiefly relies on 'subjective' patient report – these RTC studies have been rigorously conducted. These results are at odds with those reported by Sun et al[120]. In a clinical trial that meets the criteria of rigorous randomization and proper selection, the therapeutic effect of ALC on neurotoxicity became evident after 8 weeks of treatment, and neuropathy was significantly reduced only in patients treated with ALC. At week 12, a significant difference between ALC and placebo group persists, demonstrating that ALC confers a long-lasting protection. Yet, it is noticeable that patients enrolled in this experimentation have been treated by a mix of anticancer agents, in which a predominantly role was supported by Platinum compounds instead of Taxanes. Although Taxanes and Platinum compounds share some basic neurotoxic mechanisms, critical differences still exist (Table I)[19]. Indeed, Taxanes specifically hinder microtubules organization and impair Aδ and C fibers, thus chiefly affecting sensory fiber function[125]. Regarding the neurons that are affected in most kinds of peripheral neuropathy, it is the length of their axons that best accounts for their selective vulnerability[126]. Moreover, the axonal transport efficiency mostly relies on the integrity of the microtubule system. On the other hand, a global inhibition of ROS trough a mix of anti-oxidant agents significantly reduces CIPN-associated pain in Taxane-treated rats, but without affecting other CIPN clinical features, thus evidencing that Paclitaxel-induced CIPN only partially depends on ROS increase[127].

It is hardly believable that ALC could counteract this kind of damage, given that no significant effects on cytoskeleton can be actually ascribed to ALC.

Acetyl-L-carnitine has been shown to prevent the development of paclitaxel-induced pain[113] and the paclitaxel-induced increase in atypical mitochondria in C-fibers, but not the paclitaxel-induced loss of intraepidermal nerve fibers[128]. Furthermore, ALC is unable to antagonize CIPN in patients treated with other drugs that, as Taxanes, chiefly target cytoskeleton (microtubules) components. In the study from Campone et al[118] patients treated with Sagopilone, a specific microtubule-stabilizing agent acting alike Taxanes, were randomized to receive either ALC or placebo. Even if CIPN events observed in ALC group were low grade respect to the control group, the overall incidence of CIPN did not significantly differ between the two groups. Similar considerations can be made for Bortezomib-induced CIPN. Bortezomib, an inhibitor of the 20S subunit of the proteasome currently used in myeloma therapy, induces peripheral sensory neuropathy. Bortezomib exerts a microtubule stabilizing activity similar to paclitaxel in addition to proteasome inhibition and it is likely that peripheral neurotoxicity could be ascribed to that mechanism[129]. Even in this case, ALC supplementation does not afford any protection nor prevents CIPN onset[121].

These studies further suggest that ALC could be ineffective in counteracting neurotoxic drug-dependent effects on microtubules.

Table I. CIPN mechanisms – Taxanes vs. Platinum compounds.

Taxanes	Platinum	Targets	Mechanisms	References
Paclitaxel	–	Loss of intra-epidermal nerve fibers	• Loss of warm and cool specific Aδ and C fibers leading to heat and cold allodynia	Siau et al[1]
Paclitaxel	–	Calcium	• Increased expression of α2-δ1 subunits in dorsal horn and DRG • Increase in cytosolic calcium from extracellular (by channels) and intracellular stores from mitochondria	Sun and Windebank[2] Siau and Bennett[3] Xiao et al[4] Kaur et al[5]
Paclitaxel	–	Microtubule	• Microtubule disruption	Scripture et al[6]
Paclitaxel	–	Inflammation	• Increase in number of LC cells on skin • Increased release of TNF-alpha and IL-1, IL-6 and NO from glial cells, macrophages and LC cells	Siau et al[1]
–	Cisplatin, Oxaliplatin	Mitogen activated protein kinase	• Activation of p38 and ERK1/2 in DRG neurons along with down regulation of JNK/Sapk • Dual role of ERK1/2 depending on the cellular stimulation	Scuteri et al[7]
–	Oxaliplatin	Nitric oxide	• Dysfunction of the spinal NO/cGMP pathway • Increase in NOS particularly, nNOS in spinal dorsal horn	Kamei et al[8] Mihara et al[9]
–	Oxaliplatin	Protein kinase C	• Increased PKC activity in supra-spinal regions • Up-regulation of gamma/epsilon isoforms of PKC within thalamus and periaqueductal area	Norcini et al[10] Galeotti et al[11]
–	Oxaliplatin	Potassium channels	• Decreased expression of TREK1, TRAAK type of inhibitory channels and increased expression of pro-excitatory channels, HCNs	Descoeur et al[12]

References

1) Siau C, Xiao W, Bennett GJ. Paclitaxel- and vincristine-evoked painful peripheral neuropathies: loss of epidermal innervation and activation of Langerhans cells. Exp Neurol 2006a; 201:507-514.
2) Sun X, Windebank AJ. Calcium in suramin-induced rat sensory neuron toxicity *in vitro*. Brain Res 1996; 742:149-156.
3) Siau C, Bennett GJ. Dysregulation of cellular calcium homeostasis in chemotherapy-evoked painful peripheral neuropathy. Anesth Analg 2006b; 102:1485-1490.
4) Xiao W, Boroujerdi A, Bennett GJ, Luo ZD. Chemotherapy-evoked painful peripheral neuropathy: analgesic effects of gabapentin and effects on expression of the alpha-2-delta type-1 calcium channel subunit. Neuroscience 2007; 144:714-720.
5) Kaur H, Jaggi AS, Singh N. Modulation of neuroprotective effect of ischemic post-conditioning by dichlorobenzamil a Na(+)/Ca(2+) exchanger inhibitor in mice. Biol Pharm Bull 2010; 33:585-591.
6) Scripture CD, Figg WD, Sparreboom A. Peripheral neuropathy induced by paclitaxel: recent insights and future perspectives. Curr Neuropharmacol 2006; 4:165-172.
7) Scuteri A, Galimberti A, Ravasi M, Pasini S, Donzelli E, Cavaletti G, Tredici G. NGF protects dorsal root ganglion neurons from oxaliplatin by modulating JNK/Sapk and ERK1/2. Neurosci Lett 2010; 486:141-145.
8) Kamei J, Tamura N, Saitoh A. Possible involvement of the spinal nitric oxide/cGMP pathway in vincristine-induced painful neuropathy in mice. Pain 2005; 117:112-120.
9) Mihara Y, Egashira N, Sada H, Kawashiri T, Ushio S, Yano T, Ikesue H, Oishi R. Involvement of spinal NR2B-containing NMDA receptors in oxaliplatin induced mechanical allodynia in rats. Mol Pain 2011; 7:8.
10) Norcini M, Vivoli E, Galeotti N, Bianchi E, Bartolini A, Ghelardini C. Supraspinal role of protein kinase C in oxaliplatin-induced neuropathy in rat. Pain 2009; 146:141-147.
11) Galeotti N, Vivoli E, Bilia AR, Vincieri FF, Ghelardini C. St. John's Wort reduces neuropathic pain through a hypericin-mediated inhibition of the protein kinase C gamma and epsilon activity. Biochem Pharmacol 2010; 79:1327-1336.
12) Descoeur J, Pereira V, Pizzoccaro A, Francois A, Ling B, Maffre V, Couette B, Busserolles J, Courteix C, Noel J, Lazdunski M, Eschalier A, Authier N, Bourinet E. Oxaliplatin-induced cold hypersensitivity is due to remodelling of ion channel expression in nociceptors. EMBO Mol Med 2011; 3:266-278.

On the other hand, ALC can conceivably antagonize platinum-based damages by acting on several targets inside the peripheral nervous system[130]. As previously mentioned, ALC displays specific anti-oxidant effects, some of which can neutralize ROS increase within the dorsal horn in Oxaliplatin treated rats[131,132], thus inhibiting neuron damage. Yet, ALC displays several other – usually under-

estimated - neuroprotective effects. ALC provides acetyl groups for acetylcholine synthesis, thus exerting a cholinergic effect and optimizing the balance of energy processes. By acting as a donor of acetyl groups to NF-kb p65, ALC enhances the transcription of the GRM2 gene encoding the mGLU2 receptors, inducing long-term upregulation of the mGluR2[114]. In addition, through its free radical scavenging activity, ALC improves mitochondrial function and ATP production[133], thus restoring mitochondria function, a pivotal target of platinum-based compounds. Indeed, recent data suggest that prophylactic ALCAR treatment against the paclitaxel-evoked pain may be chiefly related to a protective effect on mitochondria within peripheral, sensory c-fibers[128].

ALC also had a strong antinociceptive effect when given once neuropathic pain has been established[134]. In addition, ALC improves the function of peripheral nerves by increasing nerve conduction velocity, by reducing sensory neuronal loss[135] and by promoting nerve regeneration[136], as reported in a number of *in vitro* and *in vivo* studies (for a review see ref. [130]).

Besides the very considerable overlap in the pathophysiological mechanisms, CIPN induced by Taxanes (and other microtubule-disrupting agents) can involve very different mechanisms in respect to those triggered by Platinum compounds[137].

For instance, both Platinum-based compounds and Taxanes produce acute neuropathies that are clinical distinct from each other[45,138].

Thereby, drugs aimed at preventing or controlling the painful peripheral neuropathy produced by one chemotherapeutic agent may not be effective for all anticancer drugs. Indeed, available data seem to suggest that a different treatment strategy should be planned in addressing such issue, chiefly by considering if patients are treated with either Taxane or Platinum compounds. Currently, as far as ALC is concerned, we suggest that valuable evidence does exist only for an ALC-based supplementation of patients in treatment with Platinum compounds. About Taxane and other similar acting drugs (Epothilones, Eribulin mesilate), CIPN is a direct consequence of their specific mechanism of action: interference with microtubule activity. Unless we could identify compounds that selectively protect normal cells from the microtubule-disrupting effect of Taxanes, while preserving the anticancer activity, CIPN prevention/treatment will be difficult if not impossible[124]. A promising option is currently under scrutiny, and is focusing on myo-inositol, a safe natural polyol, which specifically targets several cytoskeleton components, thus promoting microtubules remodeling while displaying at the same time significant anticancer effects[139]. Furthermore, melatonin, already known as anti-oxidant, has recently been shown to promote microtubule remodeling and to inhibit calpain activity[140]. As both microtubule deregulation and calpain activation[141] have been implicated in Taxane-induced CIPN, it is not surprising that a pilot study has evidenced the usefulness of melatonin in antagonizing Taxane-induced neurotoxicity[142].

Conclusions

The need for well-tolerated effective therapy for CIPN is a high priority in oncology because an increasing number of effective anticancer agents results in dose-limiting neurologic toxicity. A preliminary requirement is to explore in depth the mechanisms of toxicities triggered by each single drug to better identify effective means to prevent or treat them.

Second, there is a wide consensus about the need for large trials exploring possible neuroprotective agents. However, the evaluation of compounds intended to prevent/treat chemotherapy-induced neurotoxicity should be pursued by considering separately each neurotoxic anticancer drug, given that each regimen can trigger different pathophysiological mechanisms. As a result, no firm conclusion can be drawn about the efficiency of anti-CIPN agents when patients with different cancers, and consequently treated with promiscuous chemotherapy regimens, are investigated collectively in the same trial[143]. In addition, these studies should rely on adequate measures of assessment including nerve conduction study and validated neurotoxicity scale. Clinical recording of CIPN is still ambiguous, given that scales currently in use do not rely on a formal neurological evaluation and mostly depend on patient's reports and physician's interpretation. Ultimately, large and long-term randomized clinical trials are mandatory. With only few exceptions, clinical data have been mainly provided by pilot or case studies, in which small subsets of patients are involved. Again, no conclusive information can be obtained by such investigations.

In addition, some warnings should be recalled, namely when using ALA formulations. Despite its beneficial properties, oral assumption of ALA is characterized by poor bioavailability (~30% of the dose)[108]. Therefore, it is critical to conduct additional experiments in humans to establish effective doses and length of treatment for each clinical situation studied, along with a definite proof of antagonism/synergism effects when combinatorial approaches are used. Needless to say, that ALA and ALC, in both prevention as well as treatment of CIPN, should be better evaluated at the experimental level in order to set adequately any further randomized clinical trial.

Conflict of Interest

Vittorio Unfer is employee at Lo.Li. Pharma, Rome, Italy. The other authors declare that they have no conflict of interest.

References

1) Windebank AJ, Grisold W. Chemotherapy-induced neuropathy. J Peripher Nerv Syst 2008; 13: 27-46.
2) Di Francia R, De Lucia L, Di Paolo M, Di Martino S, Del Pup L, De Monaco A, Lleshi A, Berretta M. Rational selection of predictive pharmacogenomics test for the Fluoropyrimidine/Oxaliplatin based therapy. Eur Rev Med Pharmacol Sci 2015; 19: 4443-4454.
3) Lema MJ, Foley KM, Hausheer FH. Types and epidemiology of cancer-related neuropathic pain: the intersection of cancer pain and neuropathic pain. Oncologist 2010; 15 Suppl 2: 3-8.
4) Verstappen CC, Koeppen S, Heimans JJ, Huijgens PC, Scheulen ME, Strumberg D, Kiburg B, Postma TJ. Dose-related vincristine-induced peripheral neuropathy with unexpected off-therapy worsening. Neurology 2005; 64: 1076-1077.
5) Quasthoff S, Hartung HP. Chemotherapy-induced peripheral neuropathy. J Neurol 2002; 249: 9-17.
6) Kannarkat G, Lasher EE, Schiff D. Neurologic complications of chemotherapy agents. Curr Opin Neurol 2007; 20: 719-725.
7) Cliffer KD, Siuciak JA, Carson SR, Radley HE, Park JS, Lewis DR, Zlotchenko E, Nguyen T, Garcia K, Tonra JR, Stambler N, Cedarbaum JM, Bodine SC, Lindsay RM, DiStefano PS. Physiological characterization of Taxol-induced large-fiber sensory neuropathy in the rat. Ann Neurol 1998; 43: 46-55.
8) Scripture CD, Figg WD, Sparreboom A. Peripheral neuropathy induced by paclitaxel: recent insights and future perspectives. Curr Neuropharmacol 2006; 4: 165-172.
9) Authier N, Gillet JP, Fialip J, Eschalier A, Coudore F. Description of a short-term Taxol-induced nociceptive neuropathy in rats. Brain Res 2000; 887: 239-249.
10) Rivera E, Cianfrocca M. Overview of neuropathy associated with taxanes for the treatment of metastatic breast cancer. Cancer Chemother Pharmacol 2015; 75: 659-670.
11) Stubblefield MD, Burstein HJ, Burton AW, Custodio CM, Deng GE, Ho M, Junck L, Morris GS, Paice JA, Tummala S, Von Roenn JH. NCCN task force report: management of neuropathy in cancer. J Natl Compr Canc Netw 2009; 7 Suppl 5: S1-S26; quiz S27-28.
12) Gradishar WJ, Tjulandin S, Davidson N, Shaw H, Desai N, Bhar P, Hawkins M, O'Shaughnessy J. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. J Clin Oncol 2005; 23: 7794-7803.
13) Postma TJ, Benard BA, Huijgens PC, Ossenkoppele GJ, Heimans JJ. Long-term effects of vincristine on the peripheral nervous system. J Neurooncol 1993; 15: 23-27.
14) Tanner KD, Levine JD, Topp KS. Microtubule disorientation and axonal swelling in unmyelinated sensory axons during vincristine-induced painful neuropathy in rat. J Comp Neurol 1998; 395: 481-492.
15) Tanner KD, Reichling DB, Levine JD. Nociceptor hyper-responsiveness during vincristine-induced painful peripheral neuropathy in the rat. J Neurosci 1998; 18: 6480-6491.
16) Lobert S, Vulevic B, Correia JJ. Interaction of vinca alkaloids with tubulin: a comparison of vinblastine, vincristine, and vinorelbine. Biochemistry 1996; 35: 6806-6814.
17) Perez EA, Lerzo G, Pivot X, Thomas E, Vahdat L, Bosserman L, Viens P, Cai C, Mullaney B, Peck R, Hortobagyi GN. Efficacy and safety of ixabepilone (BMS-247550) in a phase II study of patients with advanced breast cancer resistant to an anthracycline, a taxane, and capecitabine. J Clin Oncol 2007; 25: 3407-3414.
18) Cortes J, O'Shaughnessy J, Loesch D, Blum JL, Vahdat LT, Petrakova K, Chollet P, Manikas A, Dieras V, Delozier T, Vladimirov V, Cardoso F, Koh H, Bougnoux P, Dutcus CE, Seegobin S, Mir D, Meneses N, Wanders J, Twelves C, investigators E. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Lancet 2011; 377: 914-923.
19) Xiao WH, Zheng H, Bennett GJ. Characterization of oxaliplatin-induced chronic painful peripheral neuropathy in the rat and comparison with the neuropathy induced by paclitaxel. Neuroscience 2012; 203: 194-206.
20) Podratz JL SA, Chen BK, Knight AM, Windebank AJ. Platinum adduct formation in mitochondrial DNA may underlie the phenomenon of coasting. J Peripher Nerv Syst 2007; 12: 69.
21) Zheng H, Xiao WH, Bennett GJ. Mitotoxicity and bortezomib-induced chronic painful peripheral neuropathy. Exp Neurol 2012; 238: 225-234.

22) Gregg RW, Molepo JM, Monpetit VJ, Mikael NZ, Redmond D, Gadia M, Stewart DJ. Cisplatin neurotoxicity: the relationship between dosage, time, and platinum concentration in neurologic tissues, and morphologic evidence of toxicity. J Clin Oncol 1992; 10: 795-803.

23) Weickhardt A, Wells K, Messersmith W. Oxaliplatin-induced neuropathy in colorectal cancer. J Oncol 2011; 2011: 201593.

24) Cavaletti G, Gilardini A, Canta A, Rigamonti L, Rodriguez-Menendez V, Ceresa C, Marmiroli P, Bossi M, Oggioni N, D'Incalci M, De Coster R. Bortezomib-induced peripheral neurotoxicity: a neurophysiological and pathological study in the rat. Exp Neurol 2007; 204: 317-325.

25) Areti A, Yerra VG, Naidu V, Kumar A. Oxidative stress and nerve damage: role in chemotherapy induced peripheral neuropathy. Redox Biol 2014; 2: 289-295.

26) Miltenburg NC, Boogerd W. Chemotherapy-induced neuropathy: a comprehensive survey. Cancer Treat Rev 2014; 40: 872-882.

27) Carozzi VA, Canta A, Chiorazzi A. Chemotherapy-induced peripheral neuropathy: what do we know about mechanisms? Neurosci Lett 2015; 596: 90-107.

28) Sissung TM, Mross K, Steinberg SM, Behringer D, Figg WD, Sparreboom A, Mielke S. Association of ABCB1 genotypes with paclitaxel-mediated peripheral neuropathy and neutropenia. Eur J Cancer 2006; 42: 2893-2896.

29) Cecchin E, D'Andrea M, Lonardi S, Zanusso C, Pella N, Errante D, De Mattia E, Polesel J, Innocenti F, Toffoli G. A prospective validation pharmacogenomic study in the adjuvant setting of colorectal cancer patients treated with the 5-fluorouracil/leucovorin/oxaliplatin (FOLFOX4) regimen. Pharmacogenomics J 2013; 13: 403-409.

30) Cavaletti G, Alberti P, Marmiroli P. Chemotherapy-induced peripheral neurotoxicity in the era of pharmacogenomics. Lancet Oncol 2011; 12: 1151-1161.

31) Sittl R, Lampert A, Huth T, Schuy ET, Link AS, Fleckenstein J, Alzheimer C, Grafe P, Carr RW. Anticancer drug oxaliplatin induces acute cooling-aggravated neuropathy via sodium channel subtype Na(V)1.6-resurgent and persistent current. Proc Natl Acad Sci U S A 2012; 109: 6704-6709.

32) Hertz DL, Motsinger-Reif AA, Drobish A, Winham SJ, McLeod HL, Carey LA, Dees EC. CYP2C8*3 predicts benefit/risk profile in breast cancer patients receiving neoadjuvant paclitaxel. Breast Cancer Res Treat 2012; 134: 401-410.

33) Bergmann TK, Green H, Brasch-Andersen C, Mirza MR, Herrstedt J, Holund B, du Bois A, Damkier P, Vach W, Brosen K, Peterson C. Retrospective study of the impact of pharmacogenetic variants on paclitaxel toxicity and survival in patients with ovarian cancer. Eur J Clin Pharmacol 2011; 67: 693-700.

34) Baldwin RM, Owzar K, Zembutsu H, Chhibber A, Kubo M, Jiang C, Watson D, Eclov RJ, Mefford J, McLeod HL, Friedman PN, Hudis CA, Winer EP, Jorgenson EM, Witte JS, Shulman LN, Nakamura Y, Ratain MJ, Kroetz DL. A genome-wide association study identifies novel loci for paclitaxel-induced sensory peripheral neuropathy in CALGB 40101. Clin Cancer Res 2012; 18: 5099-5109.

35) Abraham JE, Guo Q, Dorling L, Tyrer J, Ingle S, Hardy R, Vallier AL, Hiller L, Burns R, Jones L, Bowden SJ, Dunn JA, Poole CJ, Caldas C, Pharoah PP, Earl HM. Replication of genetic polymorphisms reported to be associated with taxane-related sensory neuropathy in patients with early breast cancer treated with Paclitaxel. Clin Cancer Res 2014; 20: 2466-2475.

36) Chu SH, Lee YJ, Lee ES, Geng Y, Wang XS, Cleeland CS. Current use of drugs affecting the central nervous system for chemotherapy-induced peripheral neuropathy in cancer patients: a systematic review. Support Care Cancer 2015; 23: 513-524.

37) Smith EM, Pang H, Cirrincione C, Fleishman S, Paskett ED, Ahles T, Bressler LR, Fadul CE, Knox C, Le-Lindqwister N, Gilman PB, Shapiro CL, Alliance for Clinical Trials in O. Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. JAMA 2013; 309: 1359-1367.

38) Hershman DL, Lacchetti C, Dworkin RH, Lavoie Smith EM, Bleeker J, Cavaletti G, Chauhan C, Gavin P, Lavino A, Lustberg MB, Paice J, Schneider B, Smith ML, Smith T, Terstriep S, Wagner-Johnston N, Bak K, Loprinzi CL, American Society of Clinical O. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 2014; 32: 1941-1967.

39) Pachman DR, Loprinzi CL, Grothey A, Ta LE. The search for treatments to reduce chemotherapy-induced peripheral neuropathy. J Clin Invest 2014; 124: 72-74.

40) Deng GE, Frenkel M, Cohen L, Cassileth BR, Abrams DI, Capodice JL, Courneya KS, Dryden T, Hanser S, Kumar N, Labriola D, Wardell DW, Sagar S, Society for Integrative O. Evidence-based clinical practice guidelines for integrative oncology: complementary therapies and botanicals. J Soc Integr Oncol 2009; 7: 85-120.

41) Horneber M, Bueschel G, Dennert G, Less D, Ritter E, Zwahlen M. How many cancer patients use complementary and alternative medicine: a systematic review and metaanalysis. Integr Cancer Ther 2012; 11: 187-203.

42) Brami C, Bao T, Deng G. Natural products and complementary therapies for chemotherapy-induced peripheral neuropathy: a systematic review. Crit Rev Oncol Hematol 2016; 98: 325-334.

43) Schloss J, Colosimo M, Vitetta L. New insights into potential prevention and management options for chemotherapy-induced peripheral neuropathy. Asia Pac J Oncol Nurs 2016; 3: 73-85.

44) Schloss J, Colosimo M, Vitetta L. Herbal medicines and chemotherapy induced peripheral neuropathy (CIPN): a critical literature review. Crit Rev Food Sci Nutr 2017; 57: 1107-1118.

45) Argyriou AA, Polychronopoulos P, Iconomou G, Chroni E, Kalofonos HP. A review on oxaliplatin-induced peripheral nerve damage. Cancer Treat Rev 2008; 34: 368-377.

46) Kottschade LA, Sloan JA, Mazurczak MA, Johnson DB, Murphy BP, Rowland KM, Smith DA, Berg AR, Stella PJ, Loprinzi CL. The use of vitamin E for the prevention of chemotherapy-induced peripheral neuropathy: results of a randomized phase III clinical trial. Support Care Cancer 2011; 19: 1769-1777.

47) Ishibashi K, Okada N, Miyazaki T, Sano M, Ishida H. Effect of calcium and magnesium on neurotoxicity and blood platinum concentrations in patients receiving mFOLFOX6 therapy: a prospective randomized study. Int J Clin Oncol 2010; 15: 82-87.

48) Ghoreishi Z, Esfahani A, Djazayeri A, Djalali M, Golestan B, Ayromlou H, Hashemzade S, Asghari Jafarabadi M, Montazeri V, Keshavarz SA, Darabi M. Omega-3 fatty acids are protective against paclitaxel-induced peripheral neuropathy: a randomized double-blind placebo controlled trial. BMC Cancer 2012; 12: 355.

49) Lee G, Kim SK. Therapeutic effects of phytochemicals and medicinal herbs on chemotherapy-induced peripheral neuropathy. Molecules 2016; 21.

50) Schloss JM, Colosimo M, Airey C, Masci P, Linnane AW, Vitetta L. A randomised, placebo-controlled trial assessing the efficacy of an oral B group vitamin in preventing the development of chemotherapy-induced peripheral neuropathy (CIPN). Support Care Cancer 2017; 25: 195-204.

51) Loven D, Levavi H, Sabach G, Zart R, Andras M, Fishman A, Karmon Y, Levi T, Dabby R, Gadoth N. Long-term glutamate supplementation failed to protect against peripheral neurotoxicity of paclitaxel. Eur J Cancer Care (Engl) 2009; 18: 78-83.

52) Kaku H, Kumagai S, Onoue H, Takada A, Shoji T, Miura F, Yoshizaki A, Sato S, Kigawa J, Arai T, Tsunoda S, Tominaga E, Aoki D, Sugiyama T. Objective evaluation of the alleviating effects of Goshajinkigan on peripheral neuropathy induced by paclitaxel/carboplatin therapy: A multicenter collaborative study. Exp Ther Med 2012; 3: 60-65.

53) Frigeni B, Piatti M, Lanzani F, Alberti P, Villa P, Zanna C, Ceracchi M, Ildebrando M, Cavaletti G. Chemotherapy-induced peripheral neurotoxicity can be misdiagnosed by the National Cancer Institute Common Toxicity scale. J Peripher Nerv Syst 2011; 16: 228-236.

54) Snell EE, Strong FM, Peterson WH. Growth factors for bacteria: Fractionation and properties of an accessory factor for lactic acid bacteria. Biochem J 1937; 31: 1789-1799.

55) Packer L, Tritschler HJ, Wessel K. Neuroprotection by the metabolic antioxidant alpha-lipoic acid. Free Radic Biol Med 1997; 22: 359-378.

56) Packer L, Witt EH, Tritschler HJ. alpha-Lipoic acid as a biological antioxidant. Free Radic Biol Med 1995; 19: 227-250.

57) Cicchillo RM, Booker SJ. Mechanistic investigations of lipoic acid biosynthesis in Escherichia coli: both sulfur atoms in lipoic acid are contributed by the same lipoyl synthase polypeptide. J Am Chem Soc 2005; 127: 2860-2861.

58) Jiang Y, Cronan JE. Expression cloning and demonstration of Enterococcus faecalis lipoamidase (pyruvate dehydrogenase inactivase) as a Ser-Ser-Lys triad amidohydrolase. J Biol Chem 2005; 280: 2244-2256.

59) Cronan JE, Zhao X, Jiang Y. Function, attachment and synthesis of lipoic acid in Escherichia coli. Adv Microb Physiol 2005; 50: 103-146.

60) Raddatz G, Bisswanger H. Receptor site and stereospecifity of dihydrolipoamide dehydrogenase for R- and S-lipoamide: a molecular modeling study. J Biotechnol 1997; 58: 89-100.

61) Billgren ES CR, Nesbitt NM, Booker SJ. Lipoic Acid Biosynthesis and Enzymology ed. Comprehensive Natural Products Chemistry II, ed. Mander L LH-W, Begley Vol. Chemistry and Biology, 2nd edn. 2010, Elsevier, Amsterdam, pp. 181-212.

62) Reed LJ. A trail of research from lipoic acid to alpha-keto acid dehydrogenase complexes. J Biol Chem 2001; 276: 38329-38336.

63) Durrani AI SH, Nagl M, Sontag G. Determination of free α-lipoic acid in foodstuffs by HPLC coupled with CEAD and ESI-MS. Food Chem 2010; 120: 1143-1148.

64) Locher M BE, Borbe HO. Metabolism of alpha-lipoic acid in human volunteers. Naunyn-Schmiedeberg's. Arch Pharmacol 1995; 351: R52.

65) Teichert J, Hermann R, Ruus P, Preiss R. Plasma kinetics, metabolism, and urinary excretion of alpha-lipoic acid following oral administration in healthy volunteers. J Clin Pharmacol 2003; 43: 1257-1267.

66) Teichert J, Tuemmers T, Achenbach H, Preiss C, Hermann R, Ruus P, Preiss R. Pharmacokinetics of alpha-lipoic acid in subjects with severe kidney damage and end-stage renal disease. J Clin Pharmacol 2005; 45: 313-328.

67) Barycki JJ AH, Stone JM, Wilson MA, Banerjee R, Becker DF. Antioxidant Molecules and Redox Cofactors ed. Redox Biochemistry ed. Banerjee R BD, Dickman MB, Gladyshev VN, Ragsdale SW, New York: Wiley, 2007.

68) Han D, Handelman G, Marcocci L, Sen CK, Roy S, Kobuchi H, Tritschler HJ, Flohe L, Packer L. Lipoic acid increases de novo synthesis of cellular glutathione by improving cystine utilization. Biofactors 1997; 6: 321-338.

69) Jones W, Li X, Qu ZC, Perriott L, Whitesell RR, May JM. Uptake, recycling, and antioxidant actions of alpha-lipoic acid in endothelial cells. Free Radic Biol Med 2002; 33: 83-93.

70) Jain SK PM, Chen Y. Effects of lipoic acid on glucose utilization, protein glycosylation and viscosity of high glucose-treated red blood cells. Pathophysiology 1998; 008A. PII: S0928-4680(98)80572-5.

71) Hagen TM, Ingersoll RT, Lykkesfeldt J, Liu J, Wehr CM, Vinarsky V, Bartholomew JC, Ames AB. (R)-alpha-lipoic acid-supplemented old rats have improved mitochondrial function, decreased oxidative damage, and increased metabolic rate. FASEB J 1999; 13: 411-418.

72) Lynch MA. Lipoic acid confers protection against oxidative injury in non-neuronal and neuronal tissue. Nutr Neurosci 2001; 4: 419-438.

73) Mazloom Z AH. The effect of alpha-lipoic acid on blood pressure in type 2 diabetics. Iran J Endocrinol Metab 2009; 11: 245-250.

74) Henriksen EJ. Therapeutic effects of lipoic acid on hyperglycemia and insulin resistance. ed. Handbook of Antioxidants, ed. Cadenas E. New York and Basel, Marcel Dekker, 2002.

75) Jacob S, Rett K, Henriksen EJ, Haring HU. Thioctic acid--effects on insulin sensitivity and glucose-metabolism. Biofactors 1999; 10: 169-174.

76) Berkson BM. A conservative triple antioxidant approach to the treatment of hepatitis C. Combination of alpha lipoic acid (thioctic acid), silymarin, and selenium: three case histories. Med Klin (Munich) 1999; 94 Suppl 3: 84-89.

77) Monastra G, De Grazia S, Cilaker Micili S, Goker A, Unfer V. Immunomodulatory activities of alpha lipoic acid with a special focus on its efficacy in preventing miscarriage. Expert Opin Drug Deliv 2016; 13: 1695-1708.

78) Vincent AM, Stevens MJ, Backus C, McLean LL, Feldman EL. Cell culture modeling to test therapies against hyperglycemia-mediated oxidative stress and injury. Antioxid Redox Signal 2005; 7: 1494-1506.

79) Bharat S, Cochran BC, Hsu M, Liu J, Ames BN, Andersen JK. Pre-treatment with R-lipoic acid alleviates the effects of GSH depletion in PC12 cells: implications for Parkinson's disease therapy. Neurotoxicology 2002; 23: 479-486.

80) Abdul HM, Butterfield DA. Involvement of PI3K/PKG/ERK1/2 signaling pathways in cortical neurons to trigger protection by cotreatment of acetyl-L-carnitine and alpha-lipoic acid against HNE-mediated oxidative stress and neurotoxicity: implications for Alzheimer's disease. Free Radic Biol Med 2007; 42: 371-384.

81) Mantovani G, Maccio A, Melis G, Mura L, Massa E, Mudu MC. Restoration of functional defects in peripheral blood mononuclear cells isolated from cancer patients by thiol antioxidants alpha-lipoic acid and N-acetyl cysteine. Int J Cancer 2000; 86: 842-847.

82) Mantovani G, Maccio A, Madeddu C, Mura L, Gramignano G, Lusso MR, Murgia V, Camboni P, Ferreli L, Mocci M, Massa E. The impact of different antioxidant agents alone or in combination on reactive oxygen species, antioxidant enzymes and cytokines in a series of advanced cancer patients at different sites: correlation with disease progression. Free Radic Res 2003; 37: 213-223.

83) Cho YS, Lee J, Lee TH, Lee EY, Lee KU, Park JY, Moon HB. alpha-Lipoic acid inhibits airway inflammation and hyperresponsiveness in a mouse model of asthma. J Allergy Clin Immunol 2004; 114: 429-435.

84) Lin YC, Lai YS, Chou TC. The protective effect of alpha-lipoic Acid in lipopolysaccharide-induced acute lung injury is mediated by heme oxygenase-1. Evid Based Complement Alternat Med 2013; 2013: 590363.

85) Moura FA, de Andrade KQ, dos Santos JC, Goulart MO. Lipoic Acid: its antioxidant and anti-inflammatory role and clinical applications. Curr Top Med Chem 2015; 15: 458-483.

86) Costantino M, Guaraldi C, Costantino D, De Grazia S, Unfer V. Peripheral neuropathy in obstetrics: efficacy and safety of alpha-lipoic acid supplementation. Eur Rev Med Pharmacol Sci 2014; 18: 2766-2771.

87) Dinicola S, Proietti S, Cucina A, Bizzarri M, Fuso A. Alpha-Lipoic Acid Downregulates IL-1beta and IL-6 by DNA Hypermethylation in SK-N-BE Neuroblastoma Cells. Antioxidants (Basel) 2017; 6(4). pii: E74. doi: 10.3390/antiox6040074.

88) Dinicola S S-RM, Canipari R, Cucina A, Bizzarri M, Fuso A. Alpha-lipoic acid represses IL-1B and IL-6 through DNA methylation in ovarian cells Pharma Nutrition 2017; 5: 77-83.

89) Ziegler D. Thioctic acid for patients with symptomatic diabetic polyneuropathy: a critical review. Treat Endocrinol 2004; 3: 173-189.

90) Ziegler D, Ametov A, Barinov A, Dyck PJ, Gurieva I, Low PA, Munzel U, Yakhno N, Raz I, Novosadova M, Maus J, Samigullin R. Oral treatment with alpha-lipoic acid improves symptomatic diabetic polyneuropathy: the SYDNEY 2 trial. Diabetes Care 2006; 29: 2365-2370.

91) Vallianou N, Evangelopoulos A, Koutalas P. Alpha-lipoic Acid and diabetic neuropathy. Rev Diabet Stud 2009; 6: 230-236.

92) Ziegler D, Hanefeld M, Ruhnau KJ, Hasche H, Lobisch M, Schutte K, Kerum G, Malessa R. Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: a 7-month multicenter randomized controlled trial (ALADIN III Study). ALADIN III Study Group. Alpha-Lipoic Acid in Diabetic Neuropathy. Diabetes Care 1999; 22: 1296-1301.

93) Berkson BM, Rubin DM, Berkson AJ. The long-term survival of a patient with pancreatic cancer with metastases to the liver after treatment with the intravenous alpha-lipoic acid/low-dose naltrexone protocol. Integr Cancer Ther 2006; 5: 83-89.

94) Mitsui Y, Schmelzer JD, Zollman PJ, Mitsui M, Tritschler HJ, Low PA. Alpha-lipoic acid provides neuroprotection from ischemia-reperfusion injury of peripheral nerve. J Neurol Sci 1999; 163: 11-16.

95) Ziegler D, Hanefeld M, Ruhnau KJ, Meissner HP, Lobisch M, Schutte K, Gries FA. Treatment of symptomatic diabetic peripheral neuropathy with the anti-oxidant alpha-lipoic acid. A 3-week multicentre randomized controlled trial (ALADIN Study). Diabetologia 1995; 38: 1425-1433.

96) Gries FA. Alternative therapeutic principles in the prevention of microvascular and neuropathic complications. Diabetes Res Clin Pract 1995; 28 Suppl: S201-207.

97) Reljanovic M, Reichel G, Rett K, Lobisch M, Schuette K, Moller W, Tritschler HJ, Mehnert H. Treatment of diabetic polyneuropathy with the antioxidant thioctic acid (alpha-lipoic acid): a two year multicenter randomized double-blind placebo-controlled trial (ALADIN II). Alpha Lipoic Acid in Diabetic Neuropathy. Free Radic Res 1999; 31: 171-179.

98) Ziegler D, Reljanovic M, Mehnert H, Gries FA. Alpha-lipoic acid in the treatment of diabetic polyneuropathy in Germany: current evidence from clinical trials. Exp Clin Endocrinol Diabetes 1999; 107: 421-430.

99) Gilron I, Tu D, Holden R, Jackson AC, Ghasemlou N, Duggan S, Vandenkerkhof E, Milev R. Pain Improvement With Novel Combination Analgesic Regimens (PAIN-CARE): Randomized Controlled Trial Protocol. JMIR Res Protoc 2017; 6: e111.

100) Parente E, Colannino G, Picconi O, Monastra G. Safety of oral alpha-lipoic acid treatment in pregnant women: a retrospective observational study. Eur Rev Med Pharmacol Sci 2017; 21: 4219-4227.

101) Jin HY, Lee NY, Ko HA, Lee KA, Park TS. Comparison of sensory tests and neuronal quantity of peripheral nerves between streptozotocin (STZ)-induced diabetic rats and paclitaxel (PAC)-treated rats. Somatosens Mot Res 2016; 33: 186-195.

102) Melli G, Taiana M, Camozzi F, Triolo D, Podini P, Quattrini A, Taroni F, Lauria G. Alpha-lipoic acid prevents mitochondrial damage and neurotoxicity in experimental chemotherapy neuropathy. Exp Neurol 2008; 214: 276-284.

103) Gedlicka C, Kornek GV, Schmid K, Scheithauer W. Amelioration of docetaxel/cisplatin induced polyneuropathy by alpha-lipoic acid. Ann Oncol 2003; 14: 339-340.

104) Desideri I, Francolini G, Becherini C, Terziani F, Delli Paoli C, Olmetto E, Loi M, Perna M, Meattini I, Scotti V, Greto D, Bonomo P, Sulprizio S, Livi L. Use of an alpha lipoic, methylsulfonylmethane and bromelain dietary supplement (Opera((R))) for chemotherapy-induced peripheral neuropathy management, a prospective study. Med Oncol 2017; 34: 46.

105) Guo Y, Jones D, Palmer JL, Forman A, Dakhil SR, Velasco MR, Weiss M, Gilman P, Mills GM, Noga SJ, Eng C, Overman MJ, Fisch MJ. Oral alpha-lipoic acid to prevent chemotherapy-induced peripheral neuropathy: a randomized, double-blind, placebo-controlled trial. Support Care Cancer 2014; 22: 1223-1231.

106) Extra JM, Marty M, Brienza S, Misset JL. Pharmacokinetics and safety profile of oxaliplatin. Semin Oncol 1998; 25: 13-22.

107) Zheng ZG CY, Hong DH, Lin YB, Zheng WH. Efficacy of α-lipoic acid combined with mecobalamin for chemotherapy-induced peripheral neuropathy Evaluation and Analysis of Drug-Use in Hospitals of China 2015; 15 729-731.

108) McIlduff CE, Rutkove SB. Critical appraisal of the use of alpha lipoic acid (thioctic acid) in the treatment of symptomatic diabetic polyneuropathy. Ther Clin Risk Manag 2011; 7: 377-385.

109) Brufani M, Figliola R. (R)-alpha-lipoic acid oral liquid formulation: pharmacokinetic parameters and therapeutic efficacy. Acta Biomed 2014; 85: 108-115.

110) Reuter SE, Evans AM. Carnitine and acylcarnitines: pharmacokinetic, pharmacological and clinical aspects. Clin Pharmacokinet 2012; 51: 553-572.

111) Ribas GS, Vargas CR, Wajner M. L-carnitine supplementation as a potential antioxidant therapy for inherited neurometabolic disorders. Gene 2014; 533: 469-476.

112) Ghirardi O, Lo Giudice P, Pisano C, Vertechy M, Bellucci A, Vesci L, Cundari S, Miloso M, Rigamonti LM, Nicolini G, Zanna C, Carminati P. Acetyl-L-Carnitine prevents and reverts experimental chronic neurotoxicity induced by oxaliplatin, without altering its antitumor properties. Anticancer Res 2005; 25: 2681-2687.

113) Flatters SJ, Xiao WH, Bennett GJ. Acetyl-L-carnitine prevents and reduces paclitaxel-induced painful peripheral neuropathy. Neurosci Lett 2006; 397: 219-223.

114) Chiechio S, Caricasole A, Barletta E, Storto M, Catania MV, Copani A, Vertechy M, Nicolai R, Calvani M, Melchiorri D, Nicoletti F. L-Acetylcarnitine induces analgesia by selectively up-regulating mGlu2 metabotropic glutamate receptors. Mol Pharmacol 2002; 61: 989-996.

115) Zheng H, Xiao WH, Bennett GJ. Functional deficits in peripheral nerve mitochondria in rats with paclitaxel- and oxaliplatin-evoked painful peripheral neuropathy. Exp Neurol 2011; 232: 154-161.

116) Pisano C, Pratesi G, Laccabue D, Zunino F, Lo Giudice P, Bellucci A, Pacifici L, Camerini B, Vesci L, Castorina M, Cicuzza S, Tredici G, Marmiroli P, Nicolini G, Galbiati S, Calvani M, Carminati P, Cavaletti G. Paclitaxel and Cisplatin-induced neurotoxicity: a protective role of acetyl-L-carnitine. Clin Cancer Res 2003; 9: 5756-5767.

117) Bianchi G, Vitali G, Caraceni A, Ravaglia S, Capri G, Cundari S, Zanna C, Gianni L. Symptomatic and neurophysiological responses of paclitaxel- or cisplatin-induced neuropathy to oral acetyl-L-carnitine. Eur J Cancer 2005; 41: 1746-1750.

118) Campone M, Berton-Rigaud D, Joly-Lobbedez F, Baurain JF, Rolland F, Stenzl A, Fabbro M, van Dijk M,

Pinkert J, Schmelter T, de Bont N, Pautier P. A double-blind, randomized phase II study to evaluate the safety and efficacy of acetyl-L-carnitine in the prevention of sagopilone-induced peripheral neuropathy. Oncologist 2013; 18: 1190-1191.

119) Lin PC, Lee MY, Wang WS, Yen CC, Chao TC, Hsiao LT, Yang MH, Chen PM, Lin KP, Chiou TJ. N-acetylcysteine has neuroprotective effects against oxaliplatin-based adjuvant chemotherapy in colon cancer patients: preliminary data. Support Care Cancer 2006; 14: 484-487.

120) Sun Y LB, Liu P, Wu C, Zheng R, Zhang X, Zhuang Z, Deng Y, Zheng L, Xu Q, Jiang B, Ouyang X, Gao J, Jiang S, Zheng W, Li BX, Shu Y, Yao Y. A prospective study to evaluate the efficacy and safety of oral acetyl-L-carnitine in treatment of chemotherapy-induced peripheral neuropathy. Exp Ther Med 2016; 12: 4017-4024.

121) Callander N, Markovina S, Eickhoff J, Hutson P, Campbell T, Hematti P, Go R, Hegeman R, Longo W, Williams E, Asimakopoulos F, Miyamoto S. Acetyl-L-carnitine (ALCAR) for the prevention of chemotherapy-induced peripheral neuropathy in patients with relapsed or refractory multiple myeloma treated with bortezomib, doxorubicin and low-dose dexamethasone: a study from the Wisconsin Oncology Network. Cancer Chemother Pharmacol 2014; 74: 875-882.

122) Hershman DL, Unger JM, Crew KD, Minasian LM, Awad D, Moinpour CM, Hansen L, Lew DL, Greenlee H, Fehrenbacher L, Wade JL, 3rd, Wong SF, Hortobagyi GN, Meyskens FL, Albain KS. Randomized double-blind placebo-controlled trial of acetyl-L-carnitine for the prevention of taxane-induced neuropathy in women undergoing adjuvant breast cancer therapy. J Clin Oncol 2013; 31: 2627-2633.

123) Hershman DL, Unger JM, Crew KD, Till C, Greenlee H, Minasian LM, Moinpour CM, Lew DL, Fehrenbacher L, Wade JL 3rd, Wong SF, Fisch MJ, Lynn Henry N, Albain KS. Two-year trends of taxane-induced neuropathy in women enrolled in a randomized trial of acetyl-l-carnitine (SWOG S0715). J Natl Cancer Inst 2018.

124) Burotto M, Fojo AT. Acetyl-L-carnitine and prevention of chemotherapy-induced peripheral neuropathy: can anything work? Oncologist 2013; 18: 1151-1152.

125) Dougherty PM, Cata JP, Cordella JV, Burton A, Weng HR. Taxol-induced sensory disturbance is characterized by preferential impairment of myelinated fiber function in cancer patients. Pain 2004; 109: 132-142.

126) Holzbaur EL, Scherer SS. Microtubules, axonal transport, and neuropathy. N Engl J Med 2011; 365: 2330-2332.

127) Fidanboylu M, Griffiths LA, Flatters SJ. Global inhibition of reactive oxygen species (ROS) inhibits paclitaxel-induced painful peripheral neuropathy. PLoS One 2011; 6: e25212.

128) Jin HW, Flatters SJ, Xiao WH, Mulhern HL, Bennett GJ. Prevention of paclitaxel-evoked painful peripheral neuropathy by acetyl-L-carnitine: effects on axonal mitochondria, sensory nerve fiber terminal arbors, and cutaneous Langerhans cells. Exp Neurol 2008; 210: 229-237.

129) Poruchynsky MS, Sackett DL, Robey RW, Ward Y, Annunziata C, Fojo T. Proteasome inhibitors increase tubulin polymerization and stabilization in tissue culture cells: a possible mechanism contributing to peripheral neuropathy and cellular toxicity following proteasome inhibition. Cell Cycle 2008; 7: 940-949.

130) Onofrj M, Ciccocioppo F, Varanese S, di Muzio A, Calvani M, Chiechio S, Osio M, Thomas A. Acetyl-L-carnitine: from a biological curiosity to a drug for the peripheral nervous system and beyond. Expert Rev Neurother 2013; 13: 925-936.

131) Joseph EK, Chen X, Bogen O, Levine JD. Oxaliplatin acts on IB4-positive nociceptors to induce an oxidative stress-dependent acute painful peripheral neuropathy. J Pain 2008; 9: 463-472.

132) Mihara Y, Egashira N, Sada H, Kawashiri T, Ushio S, Yano T, Ikesue H, Oishi R. Involvement of spinal NR2B-containing NMDA receptors in oxaliplatin-induced mechanical allodynia in rats. Mol Pain 2011; 7: 8.

133) Mansour HH. Protective role of carnitine ester against radiation-induced oxidative stress in rats. Pharmacol Res 2006; 54: 165-171.

134) Chiechio S, Copani A, Nicoletti F, Gereau RWt. L-acetylcarnitine: a proposed therapeutic agent for painful peripheral neuropathies. Curr Neuropharmacol 2006; 4: 233-237.

135) Hart AM, Wiberg M, Youle M, Terenghi G. Systemic acetyl-L-carnitine eliminates sensory neuronal loss after peripheral axotomy: a new clinical approach in the management of peripheral nerve trauma. Exp Brain Res 2002; 145: 182-189.

136) De Angelis C, Scarfo C, Falcinelli M, Reda E, Ramacci MT, Angelucci L. Levocarnitine acetyl stimulates peripheral nerve regeneration and neuromuscular junction remodelling following sciatic nerve injury. Int J Clin Pharmacol Res 1992; 12: 269-279.

137) Jaggi AS, Singh N. Mechanisms in cancer-chemotherapeutic drugs-induced peripheral neuropathy. Toxicology 2012; 291: 1-9.

138) Loprinzi CL, Reeves BN, Dakhil SR, Sloan JA, Wolf SL, Burger KN, Kamal A, Le-Lindqwister NA, Soori GS, Jaslowski AJ, Novotny PJ, Lachance DH. Natural history of paclitaxel-associated acute pain syndrome: prospective cohort study NCCTG N08C1. J Clin Oncol 2011; 29: 1472-1478.

139) Dinicola S, Fabrizi G, Masiello MG, Proietti S, Palombo A, Minini M, Harrath AH, Alwasel SH, Ricci G, Catizone A, Cucina A, Bizzarri M. Inositol induces mesenchymal-epithelial reversion in breast cancer cells through cytoskeleton rearrangement. Exp Cell Res 2016; 345: 37-50.

140) Proietti S, Catizone A, Masiello MG, Dinicola S, Fabrizi G, Minini M, Ricci G, Verna R, Reiter RJ, Cucina

A, Bizzarri M. Increase in motility and invasiveness of MCF7 cancer cells induced by nicotine is abolished by melatonin through inhibition of ERK phosphorylation. J Pineal Res 2018; 64: e12467.

141) Wang MS, Davis AA, Culver DG, Wang Q, Powers JC, Glass JD. Calpain inhibition protects against Taxol-induced sensory neuropathy. Brain 2004; 127: 671-679.

142) Nahleh Z, Pruemer J, Lafollette J, Sweany S. Melatonin, a promising role in taxane-related neuropathy. Clin Med Insights Oncol 2010; 4: 35-41.

143) Pace A, Galie E, Koudriavtseva T. Neuroprotective strategies in the prevention of chemotherapy-induced neuropathies. Support Care Cancer 2013; 21: 1-2.