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A PILOT STUDY ON THE EFFECT OF ACETYL-L-CARNITINE IN PACLITAXEL- AND CISPLATIN-INDUCED PERIPHERAL NEUROPATHY

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Aims and background: **In addition to bone marrow suppression and renal toxicity, neurotoxicity is a commonly occurring side effect of widely used chemotherapeutic agents like taxanes, cisplatin and vinca alkaloids. Neurotoxicity can cause antitumor therapy discontinuation or dose regimen modification. The aim of the present exploratory study was to investigate the activity of acetyl-L-carnitine in reversing peripheral neuropathy in patients with chemotherapy-induced peripheral neuropathy.**
Methods and study design: **Twenty-seven patients (16 males and 11 females) with paclitaxel and/or cisplatin-induced neuropathy (according to WHO recommendations for the grading of acute and subacute toxic effects) were enrolled. Patients received at least one cisplatin- (n = 5) or one paclitaxel- (n = 11) based regimen, or a combination of both (n = 11). Patients with chemotherapy-induced peripheral neuropathy were treated with acetyl-L-carnitine 1 g/die iv infusion over 1-2 h for at least 10 days.**
Results: **Twenty-six patients were evaluated for response having completed at least 10 days of acetyl-L-carnitine therapy (median, 14 days; range, 10-20). At least one WHO grade improvement in the peripheral neuropathy severity was shown in 73% of the patients. A case of insomnia related to ALC treatment was reported in one patient. Acetyl-L-carnitine seems to be an effective and well-tolerated agent for the treatment of chemotherapy-induced peripheral neuropathy.**
Conclusions: **Our preliminary results should be confirmed in double-blind, placebo controlled studies.**

Key words: acetyl-L-carnitine, chemotherapy-induced peripheral neuropathy, ciplatin, paclitaxel.

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is often a side effect for patients with cancer who are treated with neurotoxic chemotherapeutic agents, and it is defined as inflammation, injury, or degeneration of the peripheral nerve fiber(s)[1]. Chemotherapeutic agents that can cause or exacerbate CIPN are primarily the vinca alkaloids, cisplatin and paclitaxel.

Although CIPN has received less attention than other symptoms and the actual incidence is unknown, researchers have estimated that severe neuropathy occurs in 3-7% of patients treated with single agents, but this incidence can increase to 38% with polychemotherapy regimens[2-4]. The frequency of CIPN is increasing partly because of the wider use of high-dose chemotherapy, longer survival for many patients with cancer who experience CIPN as a lasting symptom, and new agents and delivery routes that target the nervous system[5].

About 60% of patients treated with paclitaxel develop peripheral sensory neurotoxicity. Paclitaxel-induced neurotoxicity is dose and infusion time dependent, and for weekly doses of 90 mg/m^2, 64% of patients develop grade I-II (WHO) neurotoxicity[6]. With a high single dose (>250 mg/m^2), symptoms may begin after 24-72 hrs from treatment. Symptoms consist of numbness, tingling and burning pain, whereas a neurological examination shows an increased threshold of vibration perception in a distal glove-stocking symmetric pattern. Typically, they are symmetric and length dependent, even though initial symptoms may also be asymmetrical at the onset and progress in a symmetrical pattern. Toxicity is cumulative, with symptoms progressing after each course of therapy, at high and low doses.

Motor neuropathy is rarely observed, probably due to the fact that mild distal weakness rarely affects function. A decrease in the amplitude of distal sensory nerve action potential, indicating axonal damage and nerve fiber loss, is usually the first electro-diagnostic modification of neuropathy. More severe forms of secondary demyelinization lead to a reduction in the nerve conduction velocity. Alterations of nerve conduction velocity and amplitude potential are correlated with the clinical neuropathic symptoms according to WHO criteria[7].

Cisplatin is an alkylating agent that induces peripheral sensory axonal neuropathy affecting large and small diameter sensory fibers. It accumulates in the dorsal root ganglia, inducing axonal changes secondary to neuronal damage[8]. The drug binds tightly and irreversibly to nerve tissue.

Clinical symptoms are represented by the loss of deep tendon reflexes, a decrease in vibratory sensation and paresthesia and numbness of fingers and toes which progress in a glove/stocking fashion. Continuation of therapy may lead to the loss of fine motor coordination and gait disturbance due to proprioceptive sensory loss. Lhermitte's sign is often present. Nerve conduction

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studies have suggested a greater involvement of sensory nerves than motor nerves[9-11].

Cisplatin neurotoxicity generally arises after a total cumulative dose of 300 mg/m^2, and it may progress after cisplatin discontinuation. Such toxicity can even persist for years. In a study of 69 patients with gynecological cancer treated with 50 to 100 mg/m^2 cisplatin at 4-week intervals, 70% of the patients who received a cumulative dose of 600 mg/m^2 of the drug experienced peripheral neuropathy[12].

Acetyl-L-carnitine (ALC) is an ester of the trimethylated amino acid, L-carnitine, and is synthesized in the human brain, liver, and kidney by the enzyme ALC-transferase. Acetyl-L-carnitine's primary biological function is that of facilitating the uptake of acetyl CoA into the mitochondria during fatty acid oxidation. ALC exerts a protective and therapeutic effect in several models of chemotherapy-induced neuropathy without adversely affecting antitumor activity. Even though the ALC mechanism has not yet been fully elucidated, current evidence suggests a pleiotropic action on the metabolism of nerve cells and a protective effect on cytotoxic-induced nerve growth factor (NGF), which is reduced by the enhancement of NGF signaling via NGF-dependent histone hyperacetylation[13].

The clinical safety profile of ALC in other neurological diseases (diabetic peripheral neuropathy, Alzheimer's) has not given cause for serious concern[14,15].

Currently, there is no treatment which has a significant clinical impact leading to an improvement in CIPN symptoms and signs. Thus, ALC, in light of the existing preclinical evidence and its safety profile, appears to be a suitable candidate to be tested for the treatment of patients suffering from CIPN.

Patients and methods

Patients (Table 1) aged between 48 and 75 years, with peripheral neuropathy due to paclitaxel- and/or cisplatin-based chemotherapy, were recruited for the study. Patients with a performance status greater than 2 (ECOG scale) and patients with pre-existing neuropathies different from CIPN were excluded from the study. All patients gave their informed consent.

Time of chemotherapy discontinuation and total cumulative dose of administrated regimens are reported on Table 2.

Cisplatin neurotoxicity was characterized by numbness, tingling sensation, loss of vibratory sensation, and diminished propriocepsis.

Examination of patients with paclitaxel-induced neuropathy revealed an elevated threshold and perception of vibration in a distal, symmetric, glove-and-stocking pattern and an involvement of the motor system as mild weakness of the extensor muscles.

Paclitaxel and cisplatin neuropathy was characterized by paresthesia and loss of proprioception which resulted in functional impairment. Deep tendon reflexes were affected with the distal reflex absent or reduced.

Table 1 - Patient characteristics

No.	27
Median age (yr), range	16/11
ECOG performance status, range	61 (48-75) 0-2
Neurotoxic therapy	
Cisplatin	5
With G3 WHO peripheral neurotoxicity	0
With G2 WHO peripheral neurotoxicity	5
With G1 WHO peripheral neurotoxicity	0
Paclitaxel	12
With G3 WHO peripheral neurotoxicity	0
With G2 WHO peripheral neurotoxicity	11
With G1 WHO peripheral neurotoxicity	1
Paclitaxel/cisplatin	10
With G3 WHO peripheral neurotoxicity	1
With G2 WHO peripheral neurotoxicity	6
With G1 WHO peripheral neurotoxicity	3
Median peripheral neurotoxicity (basal), range	2 (1-3)

Table 2 - Chemotherapy: discontinuation time and total cumulative doses

	Paclitaxel (mg)	Cisplatin (mg)	Combination Paclitaxel (mg)	Combination Cisplatin (mg)
Cumulative dose Mean (range)	2128 (150-6480)	1124 (840-1240)	971 (290-1080)	545 (390-780)
Months from neurotoxic chemotherapy discontinuation Median (range)	4 (1-8)	4,5 (2-14)	 (1-16)	4

Between April 2000 and December 2002, eligible patients were treated with ALC, 1 g/die iv treatment had to last for at least 10 consecutive days (median, 14 days; range, 10-20). CIPN severity was graded according to the World Health Organization (WHO) Toxicity Grading List[16] (Table 3). The treatment was structured over a period of at least 10 days. Clinical neurological assessment was performed at the basal state and at the end of ALC treatment.

Data analysis was conducted using frequency tables and Wilcoxon signed rank test conducted at the 0.05 significance level.

Results

The results are summarized in Tables 4 and 5. Twenty-six patients out of the 27 enrolled were assessable for response, having completed at least 10 days of ALC therapy (median, 14 days; range, 10-20). Overall, 19 of 26 (73%) patients showed at least one grade of improvement in their peripheral neuropathy (S -85.5 Pr ≥S <0.0001, Wilcoxon signed rank test). Detailing the results for neurotoxic therapy, all the cisplatin-treated patients showed at least one grade of neuropathy improvement. In one patient with WHO grade 2 neurotoxicity, signs and symptoms completely disappeared after 11

Table 3 - WHO recommendations for grading of acute and subacute toxic effects

	Neurotoxicity/peripheral			
Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
None	Paresthesia and/or decreased tendon reflexes	Severe paresthesia and/or mild weakness	Intolerable paresthesia and/or marked motor loss	Paralysis

Table 4 - WHO grading: frequency distribution of basal state *vs* final visit

		End ALC treatment		
		0	1	2
Basal	1	1	3	0
	2	1	15	5
	3	0	0	1

Table 5 - WHO grading: frequency distribution at basal state and at the end of ALC treatment

WHO grading	Basal n (%)	Final n (%)
0	0	2 (7.7)
1	4 (15.4)	18 (69.2)
2	21 (80.8)	6 (23.1)
3	1 (3.8)	0
Total	26 (100)	26 (100)

Wilcoxon signed rank test: S -85.5 Pr ≥ |S| <0.0001.

days of treatment. For the patients in the paclitaxel group, 8/12 showed one grade reduction, as did 8/10 in the paclitaxel/cisplatin combination group. All the remaining patients reported stable grading and no worsening of disease. All the improvement symptoms concerned the paresthesia from severe to mild, the post ALC treatment absence of weakness, and the restoration of tendon reflexes from mild to decreased.

No serious adverse event related to ALC iv infusion was reported. Only one patient experienced mild insomnia after the first ALC infusion and withdrew from the study.

Discussion

CIPN is a major clinical problem because it represents the dose-limiting side effect of some widely used antineoplastic drugs, such as taxanes, cisplatin and vinca alkaloids. However, even when CIPN is not a dose-limiting side effect, its onset may severely affect the quality of life of cancer patients and cause chronic discomfort. Several avenues have been explored to protect against CIPN. Recent clinical studies have provided evidence that some agents, including glutamine[17], glutathione[18] and vitamin E[19], can reduce the incidence and the intensity of CIPN. However, no treatment is currently available which can clinically improve neuropathic signs and symptoms when CIPN has already occurred[20].

On this basis, we performed this exploratory study to investigate the possible role of ALC iv infusion in treating moderate or severe persistent peripheral neuropathy induced by cisplatin and/or paclitaxel. Our preliminary results indicated that ALC significantly reduces the intensity and duration of CIPN in more than 70% of the treated patients.

Relief of symptoms was rapid, usually within 14 days of treatment, and occurred irrespective of the type of prior neurotoxic chemotherapy and the duration/severity of the toxicity. The ALC iv infusion treatment was well tolerated: no serious side effects were observed. Only one patient reported ALC-related insomnia.

Vitali *et al.*[21] tested oral administration of ALC in a similar setting of patients. A comparable overall reduction of CIPN intensity was reported, but the clinical improvements were observed after 8 weeks of treatment. In addition, neurophysiological findings indicated an improvement of conduction velocity for sensory and motor fibers and an improvement of amplitude for sensory and motor potential.

Our findings may have important clinical implications. In fact, the ALC iv infusion administration seems to have a faster onset of action. However, our study was not placebo controlled, and significant placebo effects have been described in a variety of studies[22]. Furthermore, the absence of a placebo effect could be important also in terms of spontaneous recovery controlling, mainly for the paclitaxel group.

During paclitaxel therapy, progression of neuropathy as well as amelioration of neuropathic symptoms can be observed. In individual cases, the course of the neuropathy is almost impossible to predict since continued aggravation of neuropathy has been reported even when taxol therapy was stopped several weeks previously[23].

The symptoms of cisplatin neuropathy may start even after cessation of therapy and can persist over the following months[24]. This characteristic phenomenon of cisplatin-induced neuropathy, called coasting, makes it very difficult to grade cisplatin-induced neuropathy since even after discontinuing drug treatment the peak of symptoms might not be reached. The underlying mechanism is not well understood, but it might be related to the ability of the drug to accumulate and persist over a long time in the dorsal root ganglion. Nevertheless, in this our experience, the chronicity of neurological symptoms (lasting meanly 4 months from the neurotoxic chemotherapy discontinuation) and the faster ALC onset of action (14 days) could simplify the interpretation of the data also in absence of a placebo control group.

Additionally, it is also well known that grading chemotherapy-induced neuropathy is difficult as most of the commonly used grading scales are too rough and insensitive to classify and detect neuropathy. In this preliminary experience, we used the WHO scale for grad-

ing CIPN which is, like the NCI-CTC, Ajani, and ECOG scales, less sensitive than a combined neurological score as the Total Neuropathy Scale[25].

No neurological assessments (nerve conduction studies or quantitative sensory testing) were used to support the clinical findings. Electrophysiological studies may have emphasized our findings. However, we would argue that the patient's subjective feelings are potentially more important and have a larger impact on quality of life than quantitative findings. Furthermore, the classical methods of clinical neurophysiology, nerve conduction studies, nerve conduction velocity and electromyography are often insensitive in detecting early signs of neuropathy even when the patients already suffer from sensory or motor symptoms and are not very well tolerated by the patient[2].

We think that, in spite of some flaws in this exploratory study design, the preliminary results could be a valid rationale for further investigation of the role of ALC in CIPN. CIPN is still an unresolved problem as regards its prevention or treatment. Therefore, a new therapeutic approach would be very welcome. In any case, before suggesting that ALC may be helpful in the treatment of peripheral neuropathy induced by paclitaxel and platinum-derived chemotherapy, the effectiveness of ALC needs to be tested in randomized placebo-controlled trials, including electrophysiological and formal neurological and standardized assessments.

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