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Symptomatic and neurophysiological responses of paclitaxel- or cisplatin-induced neuropathy to oral acetyl-L-carnitine

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Abstract

Acetyl-L-carnitine (ALC) improves non-oncological neuropathies. We tested oral ALC (1 g tid) for 8 weeks in 25 patients with neuropathy grade ⩾3 (common toxicity criteria – CTC) during paclitaxel or cisplatin therapy, or grade ⩾2 persisting for at least three months after discontinuing the drugs. An independent neurologist assessed patients before and after ALC. All patients except one reported symptomatic relief, and only two described grade 1 nausea. The sensory neuropathy grade improved in 15 of 25 (60%), and motor neuropathy in 11 of 14 patients (79%). Total neuropathy score (TNS) that included neurophysiological measures improved in 23 (92%). Amelioration of sensory amplitude and conduction velocity (sural and peroneal nerves) was measured in 22 and 21 patients, respectively. Symptomatic improvement persisted in 12 of 13 evaluable patients at median 13 months after ALC. In view of its effect in improving established paclitaxel- and cisplatin-neuropathy, we recommend ALC testing in preventing progression or revert symptoms during neurotoxic chemotherapy.

Keywords: Acetyl-L-carnitine; Chemotherapy-neurotoxicity; Sensory-neurotoxicity; Paclitaxel or cisplatin neuropathy

1. Introduction

Active and commonly used drugs such as vinca alkaloids, paclitaxel, platinum-compounds and thalidomide cause cumulative dose-dependent and occasionally persistent neurotoxicity [1]. Although infrequently dose-limiting in a formal sense, drug-induced sensory and motor neuropathy are clinically relevant even if mild in severity, can be disabling, and cause persistent discomfort to patients and negative impact on quality of life. Moreover, high chemotherapy doses and high intensity of administration are often used, and creates an increased risk of neurological symptoms [2]. The taxanes primarily induce a symmetrical peripheral sensory dysfunction which is correlated to both single and cumulative doses of the drug and is characterised by impairment of the sensitivity associated with large fibres (vibration, propioperception), more frequently than disturbances of the sensitivity associated with small fibres (pain, temperature). Deep tendon reflexes are often affected leading to loss or decreased distal ankle reflex. Mild sensory symptoms usually improve with reduction of the drug dose, but more severe neuropathic symptoms may persist for a long period even after discontinuation of therapy. Motor neuropathy is more rarely recognised [3,4]. The neuropathic effect of paclitaxel is most prominent when the drug is administered for short infusion durations, and is very frequent with increased

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intensity of administration, such as with weekly schedules, which are currently viewed as one of the most successful ways of delivering the drug [3,4].

Cisplatin induces peripheral sensory axonal neuropathy affecting large and small diameter sensory fibres. It usually causes clinical signs and symptoms with a typical "glove and stocking" fashion after a cumulative dose of 300 mg/m^2, and neuropathy may persist for years [5,6].

To date, the most effective approach to management of drug-induced neuropathy has been that of limiting the total dose, or reducing individual doses or even discontinuing the neurotoxic drugs at appearance of moderate symptoms [2]. However over the years, several attempts with pharmacological intervention were conducted to deal with prevention or mitigation of chemotherapy-induced neuropathy. Recently, administration of drugs such as ORG 2766, amifostine, reduced glutathione, calcium and magnesium infusions and glutamine were evaluated in large clinical trials [7–11]. Results have been conflicting, calling for further evaluation of those approaches. Of note, large scale trials of that kind have the inherent limitation of delivering the putative neuroprotective agent to all patients at risk, irrespective of individual need to be protected from possible side effect.

Acetyl-L-carnitine (ALC) is a member of the family of carnitines, a group of natural compounds that have an essential role in intermediary metabolism. In detail, ALC is an ester of the trimethylated aminoacid, L-carnitine, and is synthesised in the human brain, liver and kidney by the enzyme acetyl-L-carnitine-transferase. In mitochondria it ensures the availability of acetyl-CoA for the elimination of toxic metabolic by products, and it is involved in the export of acetyl moieties, and acetylation of different proteins including tubulin [12,13]. Of note, acetylation of tubulin plays an important role in neuronal protection [12]. ALC was also demonstrated to enhance the neuronal NGF response via hystone acetylation, a mechanism that is involved in the regulation of gene expression, but could also collaborate in mitigating sensory neuropathy [14–17]. In addition, ALC protected mice and rats afflicted with neuropathy from paclitaxel, cisplatin, oxaliplatin or vincristine [18,19] and improved their sensory nerve conduction velocity [18]. Based on the above evidence, and on indication that ALC did not influence the antitumor activity of paclitaxel and cisplatin [17], we conducted a Phase II study to test whether a short course of ALC could influence the course of established severe neuropathy caused by either drug.

2. Patients and methods

2.1. Study design

This study was designed to evaluate the safety and efficacy of orally given ALC at 1 g tid for 8 consecutive weeks in patients with established drug-induced neuropathy. The assigned dose of ALC is consistent with the dosage used in previous trials aimed to investigate the neuroprotective effects of ALC.

Eligible patients were 18–69 years of age with an Eastern Cooperative Oncology Group (ECOG) performance status $\leqslant 2$. Patients had to have grade $\geqslant 3$ neuropathy (NCI-CTC criteria version 2.0, March 1998) while on paclitaxel or cisplatin treatment, and/or grade $\geqslant 2$ neuropathy persisting for at least 3 months after discontinuation of either drug. Pre-existing diabetes mellitus and/or neuropathy of origin different from that associated with paclitaxel or cisplatin were criteria for exclusion. During the study, the use of steroids, analgesic or neuroprotectant drugs was not permitted. The protocol was approved by the local Ethic Committee, and patients were enrolled after signing written informed consent.

2.2. Safety and efficacy evaluation

All patients underwent physical and neurological examination before and at the end of ALC administration, and were evaluated with neurological and neurophysiological tests by an independent neurologist before and after the planned treatment. An interval visit to rule out negative effects was performed at 4 weeks.

The primary endpoint of the protocol was to demonstrate an improvement of at least 1 grade of the neurotoxicity according to the NCI-CTC scale (neuropathy-motor or neuropathy-sensory) in 40% of the paclitaxel-treated patients and 20% of the cisplatin-treated patients.

Secondary endpoint variables were: (1) an electromyography measure of conduction velocity of sensory and motor fibres of the sural and peroneal nerves, and the corresponding amplitude of the signals. Right sural sensory and peroneal motor nerves were studied with standardised techniques and fixed distances. Skin temperature was maintained at >32 °C with an infrared heat lamp; (2) evaluation of neuropathy according to total neuropathy score (TNS) [20]. The TNS combines information about sensory, motor and autonomic symptoms; pin perception; vibration sensibility; quantitative sensory test vibration; strength; tendon reflexes; and sural and peroneal nerve conduction amplitudes. Alteration of each variable was scored from 0 (none) to 4 (severe) and the sum of the scores of each of the 10 variables was used to define the TNS, which is viewed as a more comprehensive indicator of the subjective and objective neurological status than the CTC score [20]; (3) an evaluation of each of the neurophysiological and clinical variable that constituted the general neurological evaluation such as bulbar symptoms of muscle weakness score (extra-ocular, facial, tongue and throat), limb symptoms of muscle weakness score (shoulder girdle and upper arm, hand, glutei, thigh and legs), sensory

disturbances negative and positive symptoms score (difficulty identifying objects in mouth, hands; unsteadiness in walking; ''numbness'', ''asleep feeling'', ''prickling'' and ''like Novocain'' at any site; pain or burning or deep aching or tenderness at any location) and autonomic symptoms score (postural fainting, impotence in male, loss in urinary control and night diarrhoea). A total score (ranging from 0 to 17) was calculated by summing all the subscale's scores; and (4) neurological examination with motor strength test scores (arm abduction, hip flexion, index-finger abduction and toe extension) performed at both sites; deep reflexes exam scores (patellar and ankle) performed at both sides and vibration sensibility with a quantitative sensory testing (QST) measured at the great toe and at distal phalanx of the index finger of the nondominant hand (both proximal and distal results obtained at both sides).

The *t*-test for paired data was used for within-patient comparison of continuous measures performed before and after ALC. Adverse events were graded according to the NCI-CTC scale.

3. Results

Twenty-five patients were enrolled. All patients were treated according to the protocol. The main patients characteristics are summarised in Table 1. Of note, 20 patients had toxicity attributable to paclitaxel and 5 to cisplatin. Six of the 25 patients were still receiving the taxane at the time of enrolment into the trial, and one was receiving vinorelbine (Table 1). All remaining 18 patients had persisting neurotoxicity after discontinuation of the neurotoxic drug, as per protocol.

ALC sensory neuropathy improved as assessed by NCI-CTC in 15 of 25 patients (by 2 grades in six, and by 1 grade in nine; overall 60%; CI 39–79%), and motor neuropathy in 11 of the 14 cases (by 2 grades in three and by 1 grade in eight) with such dysfunction at baseline (79%; CI 49–95%). As indicated in Table 2, the improvement could already be measured at 4 weeks after starting ALC, but it was much more frequent after 8 weeks of therapy, at the end of the trial's planned period of therapy.

Table 1
Patients charateristics

Number of patients	25
Median age (range)	53 years (32–69)
Sex (m/f)	3/22
Neurotoxic therapy	
Paclitaxel	20
on therapy	6
with G3 NCI-CTC sensory neurotoxicity	9
with G3 NCI-CTC motor neurotoxicity	1
with any grade motor neurotoxicity	11
on vinorelbine after paclitaxel discontinuation	1
Cisplatin	5
on therapy	0
with G3 NCI-CTC sensory neurotoxicity	3
with G3 NCI-CTC motor neurotoxicity	0
with any grade motor neurotoxicity	3
Duration of toxicity prior to study entry	5 months (0–35)

Sensory and motor action potentials (SNAP and CMAP) and conduction velocity (sCV and mCV) were also assessed. The first two measures are correlated to the number of functioning fibres constituting the nerve, while the second two measures are associated with the grade of nerve's myelinisation [20]. SNAP is considered an earlier and more precise indicator of sensory nerve function, while CMAP is a more appropriate parameter for testing the motor nerve damage that usually occurs later. Serial assessments showed a significantly improved SNAP in 21 patients ($P < 0.03$). CMAP improved in 12 patients without reaching statistical significance. In addition, sCV ameliorated in 22 patients ($P = 0.0002$) and mCV in 16 patients (NS), indicating a favourable effect of ALC on the number of fibres and the nerve's myelinisation. When considering the TNS score, that included grading of clinical and neurophysiological parameters, 23 patients (92%; CI 74–99%) had an amelioration of the score ($P = 0.0003$) (Fig. 1). The only patient who had substantial worsening of the TNS (from 6 to 18, see arrow in Fig. 1) was receiving concomitant vinorelbine.

Importantly and in agreement with the pattern of TNS, clinical symptomatic relief occurred in all but one patient. Onset of the relief was rapid and independent of the type of prior neurotoxic chemotherapy, and it also was independent of the duration of the toxicity prior to ALC.

A detailed analysis of the secondary efficacy variables showed that all patients had an improvement of bulbar and limb muscle weakness and of sensory disturbance scores after 8 weeks of ALC treatment. No notable changes of the autonomic symptoms score were observed. In all patients there also was a normalisation of the motor strength test score, the deep reflexes examination score and the QST vibration.

Two patients complained of ALC-induced mild nausea, which was the only reported side effect. Of note is the observation on the duration of the symptomatic relief. At a median follow-up of 13 months after ALC discontinuation as per protocol (range: 3–23 months), 12 of the 13 surviving patients who had symptomatic and neurophysiological improvement of the toxicity maintained the therapeutic benefit.

4. Discussion

The present study showed that ALC is capable of reducing the severity of persistent sensory and motor

Table 2
Modification of the NCI-CTC score for sensory and motor toxicity after 4 and 8 weeks of therapy with ALC

	At 4 weeks		At 8 weeks	
	Sensory ($n = 25$)	Motor ($n = 14$)	Sensory ($n = 25$)	Motor ($n = 14$)
Improvement of 2 grades	2 (8%)	1 (7%)	6 (24%)	3 (21%)
Improvement of 1 grade	7 (28%)	4 (29)	9 (36%)	8 (58%)
Stable	16 (64%)	7 (50%)	9 (36%)	1 (7%)
Worsening of 1 grade	0	2 (14%)	1 (4%)	2 (14%)

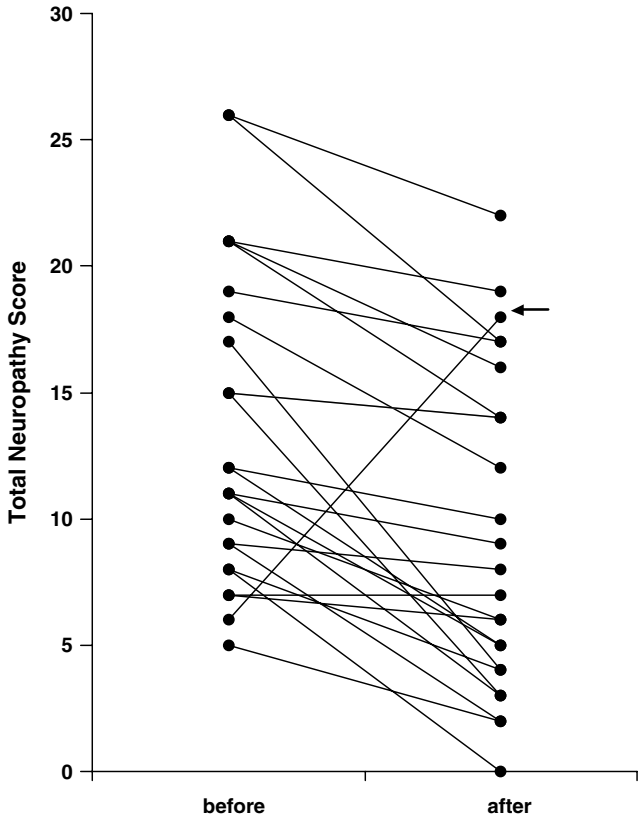

Fig. 1. Total neuropathy score (TNS), that includes scores of clinical and neurophysiological sensory and motor status, was significantly improved after 8 weeks of acetyl-L-carnitine in 23 of 25 patients ($P < 0.0003$ by t-test for paired data). The arrow on the right indicates the case of worsening TNS.

symptoms associated with administration of paclitaxel or cisplatin, and that such an effect is maintained even after discontinuation of the neuroprotectant. Both observations have several clinically relevant implications.

Peripheral neuropathy is a major dose-limiting side effect of many chemotherapeutic regimens, especially those containing paclitaxel or cisplatin [21]. The type and degree of neurotoxicity depends on the drug, the dose intensity and the cumulative dose [21]. Neurological symptoms have a profound impact on the quality of life even when they are of minor intensity, justifying the several investigations conducted over the years with different agents with potential for neuroprotective activity to cope with this problem. None of the tested drugs confirmed its promise so far [7–11]. More recently, the positive protective effect of large doses of vitamin E was documented in a small randomised trial involving 26 patients undergoing cisplatin chemotherapy [22]. The findings on the ability of large doses of vitamin E (600 mg daily) to function as prophylaxis of neuropathy induced by cisplatin or paclitaxel were more recently confirmed by a second small scale randomised trial in 31 patients [23].

Our approach to test the potential effect of ALC on chemotherapy-induced neuropathy was different. We decided to investigate first whether ALC could improve established symptoms of chemotherapy-induced neuropathy instead of testing the drug as a prophylactic measure, an approach that would require the conduct of a large randomised and ideally placebo-controlled trial.

The rationale for testing ALC as a neuroprotective agent was strong. ALC is implicated in different aspects of intermediary metabolism [13]. It is also involved in increasing NGF-induced histone acetylation, thus enhancing the cell response to NGF [12]. The latter may be implicated in neuroprotection in view of the relationship between the onset of neuropathy and the decrease of NGF circulating levels [14–16]. ALC is also involved in the regulation of the cellular levels of acetyl-CoA, and acetylation of tubulin plays an important role in neuronal protection [12,18]. Furthermore, different experimental models suggest a potential neuroprotective role for ALC on chemotherapy-induced neuropathy, without negative effects on the antitumor activity of antineoplastic drugs [17,18]. Finally, exogenous administration of ALC produced relief of symptoms and positive effects on electrophysiological parameters in diabetic neuropathy [19].

In the present study, we adopted the same high dose of oral ALC (1 g tid) that produced positive effects in diabetic neuropathy [19] and administered the drug for 8 consecutive weeks in patients with established neurotoxicity. To avoid the risk of spurious observations, an independent neurologist assessed patients before and after ALC, and a third independent investigator performed the analysis of the electrophysiological tests in a blinded fashion. This modality of performing the study lends weight to the reported observation that ALC successfully relieved persistent neurotoxic symptoms caused by paclitaxel and cisplatin. Both relief of

symptoms and neurophysiological improvement were rapid and persistent. The improvement of the NCI-CTC score was clear-cut both for the sensory and the motor neuropathy. This is especially noteworthy, because motor symptoms are usually more difficult to control [3,4,21]. The good overall effect of ALC was corroborated by the improvement of the TNS score, which compounds in single scale both clinical and neurophysiological evaluations, in almost all patients.

Two additional aspects of the study deserve consideration. The first is that ALC, even at the high dose administered in the present trial, was very well tolerated, causing minimal nausea as the only reported side effect, and in only two patients. The second point of interest is that the beneficial effects associated with ALC therapy were long-lasting. Duration of benefit was not an endpoint of the study, but the observation that 12 of 13 patients still alive at about one year of follow up had maintained the symptomatic and neurophysiological improvement suggests that longer treatment durations may not be needed to control established chemotherapy-induced neuropathy. In addition, the long lasting effect may be relevant in the design of trials in which ALC were used prophylactically.

In summary, the present study provides evidence in support of using ALC in patients with persisting moderate/severe neurotoxicity caused by paclitaxel or cisplatin. The quality and duration of the benefits justifies further examination into whether the use of ALC at first appearance of neurotoxicity can prevent the progression or fully revert the symptoms during chemotherapy using paclitaxel, cisplatin or other neurotoxic drugs.

Conflict of interest statement

In the past two years L.G. has received honoraria from Bristol Myers Squibb for consulting activity and for authorship of Expert Opinion for a total amount of less than USD 10000.

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References

1. Warner E. Neurotoxicity of cisplatin and taxol. *Int J Gynecol Cancer* 1995, **5**, 161–169.
2. Ocean JA, Vahdat LT. Chemotherapy-induced peripheral neuropathy: pathogenesis and emerging therapies. *Support Care Cancer* 2004, **12**, 619–625.
3. Kuroi K, Shimozuma K. Neurotoxicity of taxanes: symptoms and quality of life assessment. *Breast Cancer* 2004, **11**(1), 92–99.
4. Postma TJ, Vermorken JB, Liefting AJM, *et al*. Paclitaxel-induced neuropathy. *Ann Oncol* 1995, **6**, 449–489.
5. Chaudhry V, Chaudry M, Crawford TO, *et al*. Toxic neuropathy in patients with pre-existing neuropathy. *Neurology* 2003, **60**, 337–340.
6. Markman. Toxicities of the platinum antineoplastic agents. *Expert Opin Drug Saf* 2003, **2**(6), 597–607.
7. Roberts JA, Jenison EL, Kim K, *et al*. A randomized, multicenter, double-blind, placebo-controlled, dose-finding study of ORG 2766 in the prevention or delay of cisplatin-induced neuropathies in women with ovarian cancer. *Gynecol Oncol* 1997, **67**(2), 172–177.
8. Openshaw H, Beamon K, Synold TW, *et al*. Neurophysiological study of peripheral neuropathy after high-dose paclitaxel: lack of neuroprotective effect of amifostine. *Clin Cancer Res* 2004, **10**(2), 461–467.
9. Savarese DM, Savy G, Vahdat L, *et al*. Prevention of chemotherapy and radiation toxicity with glutamine. *Cancer Treat Rev* 2003, **29**(6), 501–513.
10. Colombo N, Bini S, Miceli D, *et al*. Weekly cisplatin ± gluthatione in relapsed ovarian carcinoma. *Int J Gynecol Cancer* 1995, **5**, 81–86.
11. Vahdat L, Papadopoulos K, Lange D, *et al*. Reduction of paclitaxel-induced peripheral neuropathy with glutamine. *Clin Cancer Res* 2001, **7**, 1192–1197.
12. Furlong JH. Acetyl-L-carnitine: metabolism and applications in clinical practice. *Altern Med Rev* 1996, **1**, 85–93.
13. Bieber LL. Carnitine. *Annu Rev Biochem* 1988, **57**, 261–283.
14. Cavaletti G, Pezzoni G, Pisano C, *et al*. Cisplatin-induced peripheral neurotoxicity in rats reduces the circulating levels of nerve growth factor. *Neurosci Lett* 2002, **322**(2), 103–106.
15. Tredici G, Braga M, Nicolini G, *et al*. Effect of recombinant human nerve growth factor on cisplatin neurotoxicity in rats. *Exp Neurol* 1999, **159**(2), 551–558.
16. Apfel SC, Lipton RB, Arezzo JC, *et al*. Nerve growth factor prevents toxic neuropathy in mice. *Ann Neurol* 1991, **29**, 87–90.
17. Pisano C, Pratesi G, Laccabue D, *et al*. Paclitaxel and cisplatin-induced neurotoxicity: a protective role of acetyl-L-carnitine. *Clin Cancer Res* 2003, **9**(15), 5756–5767.
18. Onofrj M, Fulgente T, Melchionda D, *et al*. L-Acetylcarnitine as a new therapeutic approach for peripheral neuropathies with pain. *Int J Clin Pharm Res* 1995, **15**(1), 9–15.
19. De Grandis D, Minardi C. Acetyl-L-carnitine in the treatment of diabetic neuropathy. A long-term, randomised, double-blind, placebo controlled study. *Drugs R D* 2002, **3**(4), 223–231.
20. Cornblath DR, Chaudry V, Carter K, *et al*. Total neuropathy score: validation and reliability study. *Neurology* 1999, **53**(8), 1660–1664.
21. Verstappen CC *et al*. Neurotoxic complications of chemotherapy in patients with cancer: clinical signs and optimal management. *Drugs* 2003, **63**(15), 1549–1563.
22. Pace A *et al*. Neuroprotective effect of vitamin E supplementation in patients treated with cisplatin chemotherapy. *J Clin Oncol* 2003, **21**(5), 927–931.
23. Argyriou AA *et al*. Vitamin E for prophylaxis against chemotherapy-induced neuropathy: a randomized controlled trial. *Neurology* 2005, **64**(1), 26–31.