choices on what to measure, how, and the threshold for a clinically meaningful difference. Instruments should be reliable, valid, and responsive, developed using robust and reproducible methods [2] and taking account of the patients' perspective [3].

EMA's role in backing these requirements is necessary to assess the therapeutic added value related to a better PRO (which is also important for patients).

However, this may not be enough if investigators do not fully understand how a given PRO could confirm well formulated hypotheses and are not appropriately trained on the use of instruments to collect them. To ensure correct data collection throughout a trial, time and efforts must be invested to make study participants aware of the value of the information they provide with questionnaires on the definition of the overall benefit-harm profile of a new treatment. Clinical sites should be monitored and corrective measures taken to reduce missing or invalid data, which limit the robustness of the results. Even when all these specified measures are adopted, the question of data interpretation remains. To what extent a given difference is meaningful for patients depends on several factors: setting, line of therapy, patients' values and culture. This needs to be defined and agreed by all the stakeholders [4].

PROs can contribute greatly to decision making, but only if investigators and patients' representatives are fully engaged in the discussion about their importance at the same table.

Acknowledgments

The authors thank J. D. Baggott for editing.

Disclosure statement

None of the authors have financial or non-financial personal competing interests to be declared.

Funding

This paper was supported by institutional funds of the Mario Negri Institute.

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LETTER TO THE EDITOR

Acetyl-L-carnitine undervalued in the treatment of chemotherapy-induced peripheral neuropathy?

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ARTICLE HISTORY Received 13 May 2016; revised 20 July 2016; accepted 29 July 2016

To the Editor,

Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most common side effects of anti-cancer therapy with a reported incidence of approximately 40%, occurring mainly in patients treated with platinum compounds, taxanes and vinca alkaloids. CIPN commonly presents with paresthesias and dysesthesias located in the fingers and toes affecting arms and legs symmetrically ('gloves and stockings'). Currently, there is no gold standard for assessment of CIPN severity. However, the consensus is that the gold standard should incorporate assessment of both objective neurological deficits and symptoms from patient perspective, as it is known that clinician-based outcomes tend to underestimate the significance of symptoms [1]. As cancer survival rates are improving, more and more people are living with long-term side effects of chemotherapy (e.g. CIPN), which are reported to have a negative effect on patient's quality of life (QoL) [2,3]. Notwithstanding the high burden of CIPN, available evidence supporting agents used for prevention and treatment of CIPN is limited. Currently, there are no established agents recommended for the prevention of CIPN in patients

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Table 1. Summary of study characteristics and main results.

	Design	Therapy	ALC dose	Goal	Population (n)	Duration	Diagnostic tool for neuropathy used: Summary of main study results
[13]	CS	PAC/CIS	1 g 3x/day	Therapy	25	56 days	NCI-CTC: sensory: 60% improvement; motor 79% improvement TNS: improvement in 92% [74–99%] ($p = 0.0003$)
[14]	CS	PAC/CIS/PAC + CIS	1 g/day Intravenous	Therapy	27	14 days (median)	WHO-TGL: 73% ≥1 grade improvement; All CIS-treated patients ≥1 grade improvement
[15]	RCT	PAC/DOC	3 g/day	Prevention	409	168 days	FACT-NTX-T-score: significantly more neuropathy in ALC-group after 24 weeks
[16]	CCS	BDD	1.5 g 2x/day	Prevention	32	–	CTCAE and FACT-GOG-NTx: non-significant
[17]	RCT	SAG	1 g/3 days	Prevention	150	–	Overall OC + CRPC: effect of ALC is non-significant OC alone: incidence grade 3-4 neuropathy significantly lower in ALC-group
[18]*	RCT	PAC	1 g 3x/day	Prevention	40	56 days	After 2 and 3 cycles significantly less sensory and motor neuropathy in ALC-group
[19]*	RCT	–	3 g/day	Therapy	239	56 days	NCI-CTC: Decrease of neuropathy in 50.5% in ALC, 24.1% in placebo after 8 weeks ($p < 0.001$). Decrease of 51.6% in ALC, 23.1% in placebo after 12 weeks ($p < 0.001$)

ALC: acetyl-L-carnitine; BDD: bortezomib + doxorubicine + dexamethasone; CCS: case control study; CIS: cisplatin; CRPC: castration resistant prostate cancer; CS: case series, CTCAE: Common Toxicity Criteria for Adverse events; DOC: docetaxel; FACT-GOG-NTX: Functional Assessment of Cancer Therapy –Gynecologic Oncology Group – Neurotoxicity; FACT-NTX-T: Functional Assessment of Cancer Therapy Neurotoxicity – taxane; NCI-CTC: National Cancer Institute – Common Toxicity Criteria; OC: ovarian cancer; PAC: paclitaxel; RCT: randomized controlled trial; SAG: sagopilone; TNS: Total Neuropathy Score; WHO-TGL: World Health Organization – Toxicity Grading List.
*: published as (conference)-abstract only.

undergoing chemotherapy, the only agent recommended for treatment of CIPN is duloxetine [4].

An example of a potential neuroprotective agent studied over the past decades is acetyl-l-carnitine (ALC). Carnitine is a natural occurring compound found in all mammalian species which plays an important role in the transport of fatty acids into the mitochondria for subsequent beta-oxidation [5]. Carnitine has been reported to be able to protect various cells against oxidative injury, thus working as an antioxidant [6]. Animal studies, investigating the effect of ALC on CIPN in rats treated with commonly used cytotoxic agents (i.e. paclitaxel, oxaliplatin and cisplatin), showed reductions in both neuropathy and pain in rats treated with ALC [7–9]. Furthermore, less histopathological changes indicative for mitotoxicity have been seen in rats treated with ALC [10,11]. Oxidative stress and mitotoxicity are both recognized as important factors associated with the pathophysiology of CIPN and could be the foundation for more research to assess the potential role of ALC in prevention and treatment of CIPN. This future research should also take in account the effect of ALC on anti-tumor effectivity of chemotherapeutics. Among rats, ALC has not shown any interference with the anti-tumor activity of the used cytostatics [8,9]. However, the use of antioxidants, including ALC, is currently discouraged because of possible negative effects on treatment response in humans [12].

Despite the promising effects of ALC on CIPN in rats, results found in humans are less conclusive. Over the past years, a total of seven studies investigated the potential effect of ALC on prevention and treatment of CIPN, of which only four are published in full text in peer-reviewed journals (Table 1). Of these, two studies showed improvement of CIPN in patients treated with ALC [13,14], whereas one study showed increased neuropathy in patients who were prophylactically treated with ALC [15]. Furthermore, one study showed that ALC had no significant effect on neuropathy among patients treated for multiple myeloma with bortezomib-doxorubicin-dexamethasone [16]. In contrast, the available abstracts generally conclude a therapeutic and preventive effect of ALC on CIPN [17–19]. Two studies reported no interference of ALC with anti-tumor activity of the chemotherapeutics used [13,17]. Currently, the use of carnitine in humans is discouraged by the American Society of Clinical Oncology (ASCO) guidelines, based on only one study. We think the use of ALC needs to be qualified in a different light, at least until further research has been done.

Meta-analysis of these studies is nearly impossible, mainly due to a number of important differences in study design. For example, studies were designed as case series (CS), case control studies (CCS) and randomized controlled trials (RCT), and surprisingly, only one RCT is published in a peer-reviewed journal in full text. Furthermore, methodological quality of the reported studies is diverse. At first, the effect of ALC is investigated as 'therapy' and 'prevention' of CIPN. Second, dose, duration and route of administration vary significantly between studies. Furthermore, CIPN is assessed by a variety of grading scales, of which some are clinical grading scales [National Cancer Institute – Common Toxicity Criteria (NCI-CTC) or Total Neuropathy Score (TNS)] and some are patient-reported outcomes [i.e. Functional Assessment of Cancer Therapy –Gynecologic Oncology Group – Neurotoxicity (FACT-GOG-NTx)]. When the methodological quality of these studies is assessed, several limitations are found. For example, some studies lack a control group, in others patients are not included at the same 'stadium of disease' (i.e. duration of neuropathy varying from 'new-onset neuropathy' to neuropathy existing for years). All these differences complicate meta-analysis.

Despite inconclusive evidence on the effect of carnitine in treatment or prevention of CIPN, we believe carnitine is an agent with high potential. A previous study showed that serum L-carnitine concentrations were significantly lower in cachectic cancer patients when compared to healthy volunteers [20]. Evidence about the course of serum carnitine levels

during chemotherapy is limited to a number of trials performed in children, generally showing a decrease during chemotherapy [21,22]. It is well known that chemotherapy (carboplatin, cisplatin, ifosfamide) increases urinary excretion of different carnitine-esters [23–25]. Therefore, we think that an excessive loss of carnitine due to chemotherapy could lead to a carnitine deficiency, especially in patients with a preexistent deficit in nutritional status (i.e. cachexia). This has not been investigated in previous trials.

Directions for future research

As results from clinical trials reviewed here are difficult to interpret or conflicting, while ASCO guideline discourages the use of ALC, based on one study only, we believe that its final role in prevention and or treatment of CIPN remains to be established. Also, effect of ALC on anti-tumor properties of cytostatics needs to be addressed.

It appears that serum carnitine levels are reduced and urinary excretion increases after platinum-based chemotherapy. Therefore, we assume that one the reasons of conflicting results of the studies reviewed might be explained by differences in baseline serum levels during administration. It might even be hypothesized that, whereas patients are continuously treated with sufficient amounts of ALC throughout the study, its level at the appropriate time is low.

Thus, before we draw final conclusions on the effects of carnitine in CIPN, precise metabolic and pharmacokinetic analyses are required. Then we should redesign a RCT accordingly, after which a more clear answer is likely. In times where we discuss whether the benefits of targeted therapy and immunotherapy outweigh the enormous costs in cancer care, should we not give this simple, cheap and naturally occurring amino acid some more chance to prove its value in often debilitating CIPN?

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