Effect of Acetyl-L-Carnitine on the Incidence and the Severity of Paclitaxel-Induced Peripheral Neuropathy in Cancer Patients

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By

Sara Taher Taeb

Bachelor of Pharmaceutical Sciences

Tripoli University (2007)

Under Supervision of

Dr. Osama Ahmed Badary

Professor of Clinical Pharmacy

Faculty of Pharmacy

Ain Shams University

Dr. Mahmoud Mahmoud Ellithy

Assistant Professor of Clinical Oncology

Faculty of Medicine

Ain Shams University

Dr. Lamia Mohamed El Wakeel

Assistant Professor of Clinical Pharmacy

Faculty of Pharmacy

Ain Shams University

Faculty of Pharmacy

Ain Shams University

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قَالُوا سُبْحَانَكَ لاَ عِلْمَ لَنَا إِلاَّ مَا عَلَّمْتَنَا

إِنَّكَ أَنتَ الْعَلِيمُ الْحَكِيمُ"

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5-HT	5-Hydroxytryptamine receptors
Ach	Acetyl-choline
a-CMAP	Amplitude of Compound Muscle Action Potential
AEs	Adverse Events
ALC	Acetyl-L-Carnitine
ALT	Alanine aminotransferase
a-SAP	Amplitude of Sensory Action Potential
AST	Aspartate aminotransferase
ATP	Adenosine Triphosphate
BBB	Blood Brain Barrier
Bcl-2	B-Cell Lymphoma 2
CIPN	Chemotherapy-Induced Peripheral Neuropathy
CMT	Charcot-Marie Tooth
CNS	Central Nervous System
CrEL	Cremophor EL
DNA	Deoxyribonucleic Acid
DRG	Dorsal Root Ganglion
ECOG	Eastern Cooperative Oncology Group Criteria
EORTCQLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30
FACT/GOG-Ntx	Functional Assessment of Cancer Therapy/Gynaecological Group Neurotoxicity
FDA	Food and Drug Administration
GABA	Gamma-Aminobutyric Acid
GDP	Guanosine Diphosphate
GTP	Guanosine Triphosphate
Hgb	Hemoglobin
HIV	Human Immunodeficient Virus
IENFs	Intraepidermal Nerve Fibers
IFN	Interferon
IL-1	Interleukin-1
IL-6	Interleukin-6

IV	Intra-Venous
LCs	Langerhans Cells
LLN	Lower Limit of Normal
MCV	Motor Conduction Velocity
MDMA	3,4-Methylenedioxy-Methamphetamine
mPTP	Mitochondria Permeability Transition Pore
mRNA	Messenger Ribonucleic Acid
MT	Microtubule
MTs	Microtubules
nab-paclitaxel	Nanometer Albumin-Bound Paclitaxel
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NCV	Nerve Conduction Velocity
NFκB	Nuclear Factor-κB
NGF	Nerve Growth Factor
NGFR	Nerve Growth Factor Receptor
OTC	Over-The-Counter medicines
PIPN	Paclitaxel-Induced Peripheral Neuropathy
PNS	Peripheral Nervous System
QOL	Quality of Life
QST	Quantitative Sensory Testing
ROS	Reactive Oxygen Species
sb-paclitaxel	Solvent-Based Paclitaxel
SCV	Sensory Conduction Velocity
t.i.d	Three times a day
TMB	Tetra Methyl Benzidine
TNF	Tumor Necrosis Factor
TNS	Total Neuropathy Score
WHO	World Health Organization

Abstract

Background: Paclitaxel, the most commonly used chemotherapeutic agent in breast cancer is associated with peripheral neuropathy in about 70- 80% of patients. The neurotoxicity-related symptoms result in severe limitation of patients' daily activity and quality of life. Acetyl-l-carnitine (ALC) has been shown to be useful in the treatment of paclitaxel induced peripheral neuropathy (PIPN). The potential role of ALC in prevention of PIPN is not well investigated.

Objective: This study aimed to evaluate the impact of ALC administration on the frequency and the severity of PIPN.

Patients and Methods: A prospective randomized controlled open-label study. Forty eligible patients with breast cancer were randomized to either; Control group; received paclitaxel + placebo tid for 12 weeks, or Test group; received paclitaxel + 1g oral ALC tid for 12 weeks. The mean dose/cycle was 183.5mg/m^2 and 180.1mg/m^2 for control and test group, respectively cycled every 4 weeks. At baseline and at the end of the study, patients in both groups were assessed by clinical examination, nerve conduction velocity (NCV) and plasma nerve growth factor (NGF) estimation. Frequency and severity of sensory and motor neuropathy were assessed after each cycle using the CTCAE version4.

Results: At baseline, both groups were comparable in age, sex and total dose. In the first cycle, both groups showed no significant difference in frequency of sensory or motor neuropathy or adverse events occurrence. In the 2nd cycle, test group showed a significantly lower frequency of; sensory neuropathy (10 vs 17, p= 0.018) and

motor neuropathy (3 vs 12, p= 0.003) versus control. In the 3rd cycle, test group showed a significantly lower frequency of; sensory neuropathy (6 vs 18, p<0.001) and motor neuropathy (3 vs 17, p<0.001) versus control. The frequency of vomiting was significantly higher in the control group (5 vs 0, p= 0.047) versus test in the 3rd cycle.

Baseline median NGF levels were significantly lower in test group versus control (1.9 vs 9.5, p<0.001). At the end of the study the median NGF levels were significantly lower (2.4, p=0.02) in the control group versus their initial baseline levels. While, the test group median levels were higher than their baseline levels. The delta change in NGF was significantly different between the 2 groups (p<0.001). The NCV was not significantly different between 2 groups at baseline or at the end.

Conclusion: ALC administration decreased the frequency and severity of motor and sensory PIPN, and was accompanied with lesser side effects and an improvement in NGF levels.

Key Words: Acetyl-L-carnitine, Paclitaxel, Paclitaxel-induced peripheral neuropathy, Nerve growth factor, Sensory neuropathy, Motor neuropathy**.**

Introduction

Chemotherapy induced peripheral neuropathy (CIPN) is a common and potentially dose-limiting complication of many effective cytotoxic agents **(Bhatnagar et al., 2014).** The importance of CIPN lies in two factors: it impairs patients 'quality of life (QOL) and it is a dose-limiting factor **(Gutierrez-Gutierrez et al., 2010).**

Among the chemotherapeutic agents that cause CIPN are taxanes (docetaxel, paclitaxel). Paclitaxel functions as a microtubule stabilizing agent and exerts a broad spectrum of cytotoxic effects in cancers of the breast, ovary and lung **(Rowinsky and Donehower, 1995).**

The precise pathogenesis of paclitaxel-induced peripheral neuropathy (PIPN) is unclear; however through its action of disrupting microtubules (MTs) of the mitotic spindle and the subsequent interference in axonal transport, paclitaxel is able to affect the soma of sensory neurons as well as axons. In addition, it has been demonstrated that paclitaxel evokes a “dying back” process starting from distal nerve endings followed by disturbed cytoplasmic flow in the affected neurons **(Argyriou et al., 2012).**

The incidence of PIPN can be variable, but often ranges from 60 to 70% **(Seretny et al., 2014)**. PIPN classically occurs within 24–72 hours following paclitaxel administration and, in most cases is reversible upon prompt discontinuation of the offending agent **(Rowinsky et al., 1993c).**

Symptoms are typically described as numbness and tingling in a "stocking-and-glove" distribution, particularly in the distal lower extremities. Patients may also report intermittent sharp, shooting leg pain **(Argyriou et al., 2008).**

Previously reported risk factors for PIPN include older age, history of alcoholism, diabetes mellitus, inherited neuropathy, and prior therapy with neurotoxic medications **(Tanabe et al., 2013).** In its most severe form, development of PIPN can lead to significant pain syndromes, difficulty with ambulation, and interference with routine daily activities resulting in prompt dose reductions and delays that potentially reduce the efficacy of cancer treatments **(Bhatnagar et al., 2014).**

Currently, there is no universally accepted tool for PIPN evaluation. The diagnosis of PIPN is usually made on clinical grounds. History and examination often suffices. Neurophysiological studies may strengthen diagnosis, but does not always reflect clinical severity **(Farquhar-Smith, 2011).**

The pathophysiology of PIPN is poorly understood, and treatments to prevent PIPN are inadequate. Treatment options for established PIPN are also limited **(Seretny et al., 2014).** At the present time there can be no explicit recommendations that can be given for the prevention or treatment of PIPN **(Schloss et al., 2013).**

Acetyl-L-carnitine (ALC) is an acetylated derivative of L-carnitine, which is intimately involved in the transport of long chain fatty acids across the inner mitochondrial membrane promoting their oxidation **(Ferraresi et al., 2006).** ALC is a compound of great interest for its wide clinical application in various neurological

disorders. Several studies, including double-blinded, placebo controlled, parallel group studies and few open studies showed the effect of ALC in diseases characterized by neuropathies and neuropathic pain. ALC is very well tolerated with no reported significant signs of toxicity **(Onofrj et al., 2013).**

Nerve growth factor (NGF) plays a crucial role in neuronal survival, differentiation and growth **(Colangelo et al., 2008)**. The development of neuropathies induced by antitumor drugs might be the result of impaired synthesis and/or release of endogenous NGF. Chemotherapy treated patients have been shown to have low levels of circulating NGF **(De Santis et al., 2000)**.

As anticancer therapy is often associated with severe adverse events (AEs), there is an increasing demand for effective supportive care strategies preventing or ameliorating drug-induced toxicity. In the last decade, several evidence-based clinical practice guidelines have been developed for supportive care. Still, drug AEs are high among the most feared consequences associated with antineoplastic therapy. The addition of a pharmacist to the health care team may ensure appropriate medication use, maximize adherence, minimizing treatment-related toxicity and, therefore, focus on optimizing supportive care strategies **(Liekweg et al., 2012).** The concordance and communication between patients and pharmacists may improve patients' understanding of pharmacotherapy. Pharmacist intervention has been shown to result in improved patient care. Pharmacist counseling cannot change the physical AEs of adjuvant systemic therapy but may be able to prevent deterioration of QOL by emotionally preparing the patient to tolerate the AEs **(Kawaguchi et al., 2012)**.

1. Peripheral Neuropathy

1.1 Anatomy and physiology of the peripheral nervous system (PNS) The PNS is an extension of the central nervous system (CNS) and connects it to the limbs and the organs and systems. It can be divided into the autonomic and somatic systems, which is normally named the PNS. The PNS includes the cranial nerves, the spinal nerves with their roots and rami, and the peripheral components of the autonomic nervous system. The PNS, unlike the CNS, is not protected by the blood brain barrier (BBB) and this makes it more vulnerable to the toxic effects of drugs **(Catala and Kubis, 2013).**

1.2 Peripheral Neuropathy Definition

Peripheral neuropathy is a general term indicating the malfunction of peripheral nerves due to various causes. Peripheral neuropathies can be categorized by location (distal, proximal), distribution pattern (unilateral, bilateral, symmetrical), underlying cause (toxic, metabolic, vascular, autoimmune, paraneoplastic), impaired neuronal quality (motor, sensory, autonomic), dynamics of manifestation (acute, subacute, chronic) and underlying histopathology (axono-, myelino- and ganglionopathies) **(Mielke et al., 2006).**

Neuropathic pain has been defined by Treede et al. as a pain arising as a direct consequence of a lesion or disease affecting the somatosensory system. **(Treede et al., 2008)**. These injuries arise from diabetic neuropathy, viral infections, major surgeries or trauma (amputation, thoracotomy, entrapment or compression), spinal cord injury, and stroke **(Colleoni and Sacerdote, 2010).**

1.3 Characteristics of peripheral neuropathy

Depending on the type of peripheral neuropathy and the impaired neuronal qualities, sensory, motor and autonomic symptoms may appear. Sensory symptoms may include paraesthesia, numbness, tingling, burning and pain while motor symptoms may range from mild muscular weakness to paralysis. Appearance of orthostatic hypotension, cardiac arrhythmia and paralytic ileus may reflect autonomic involvement **(Hennenfent and Govindan, 2006).**

1.4 Types of peripheral neuropathy

1.4.1 Chemotherapy-induced peripheral neuropathy (CIPN)

CIPN is a toxic neuropathy that results from the direct injury of the PNS by the chemotherapeutic agents **(Walker and Ni, 2007).** CIPN frequently complicates the use of several classes of chemotherapeutic agents as summarized in table (1.1). Because these drugs are frequently used to treat several prevalent cancers (eg, colon, lung, and breast), CIPN is relatively common. CIPN rates available in the literature are highly variable; reports on the incidence range widely among various studies anywhere between 10% and 100% **(Cata et al., 2006)**. Rates may be as high as 60–70% with taxanes agents frequently used as first and second-line treatment for several common malignancies **(Farquhar-Smith, 2011).**

Rapid proliferation of malignant cells is a target characteristic of chemotherapeutic agents, though many agents damage rapidly proliferating normal tissues. Gut lining, hematopoietic, and lymphoid tissue often suffer bystander injury with prominent gastrointestinal adverse events (AEs), anemia, leukopenia, thrombocytopenia, and immune suppression **(Windebank and Grisold, 2008).**