بسم الله الرحمن الرحيم

MONA MAGHRABY

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

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MONA MAGHRABY

The Use of Vitamin E in Preventing Taxane-Induced Peripheral Neuropathy

Thesis

Submitted for Partial Fulfillment of Medical Doctorate Degree in Clinical Oncology& Nuclear Medicine

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Muhammad Heiba

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List of Abbreviations

Abb.	Full term
ASCO	American Society of Clinical Oncology
ATRA	All-trans retinoic acid
CIPN	Chemotherapy-induced peripheral neuropathy
ECOG	Eastern Cooperative Oncology Group
EMG	Electromyography
EORTC	European Organisation for Research and Treatment of Cancer
IENF	Intraepidermal nerve fiber
IL	Interleukin
mtDNA	Mitochondrial DNA
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NCV	Nerve conduction velocity
NER	Nucleotide excision repair
NYHA	New York Heart Association
PGP	Protein gene product
QST	Quantitative sensory testing
RCTs	Randomized controlled trials
RNS	Reactive nitrogen species
ROC	Receiver operating characteristic
ROS	Reactive oxygen species
TENS	Transcutaneous electrical nerve stimulation
TNF-α	Tumor necrosis factor alpha
TNS	Total Neuropathy Score
WHO	World Health Organization

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INTRODUCTION

Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect of many classes of chemotherapy agents which frequently leads to dose reductions and delays of chemotherapy administration as well as its effect on the quality of life [(1)].

The pathogenesis of CIPN varies among different classes of chemotherapy, depending on several chemical and physical properties. It involves myelin sheath damage, neural ganglia apoptosis, interfering with ion channel activity, microtubule disruption, oxidative stress, and mitochondrial damage among other factors [(2)].

The taxane class of chemotherapy is one of the most widely used chemotherapeutic agents. Among them, paclitaxel and docetaxel are most commonly administered, but newer formulations are being investigated. The anti-neoplastic activity of taxanes is based mainly on the ability of the drugs to disrupt microtubule assembly, leading to mitotic arrest and apoptosis in cancer cells. Peripheral neuropathy is a major side-effect of taxanes, often manifested as painful neuropathy experienced during treatment, and could be irreversible [(3)].

The mechanism of taxane-induced peripheral neuropathy is thought to be related to the microtubule disruption which is the main mechanism of action of taxanes. This leads to impairment of axonal transport which may lead to neuropathy.

Another possible mechanism is the increased production of reactive oxygen species (ROS) induced by mitochondrial damage which creates a state of oxidative stress. These are highly reactive compounds that interact with many cellular components such as DNA and cellular membranes and lead to several oxidation-reduction reactions. This oxidative stress leads to structural and functional changes in normal cells and organ dysfunction. Several classes of chemotherapy lead to the production of free radicals [4,5].

Vitamin E by acting as a free radical scavenger is supposedly helpful in preventing diseases that are associated with oxidative stress, and given the similarity of the peripheral nervous system manifestations of vitamin E deficiency with those of CIPN, it was hypothesized that vitamin E supplementation may lead to decrease the incidence and/or severity of CIPN [6].

To date, many pharmacologic agents have been evaluated for their role in the prevention and treatment of CIPN. There is no substantial evidence available about the efficacy of most agents used [7]**.** The American Society of Clinical Oncology (ASCO) recommendations for prevention and management of CIPN clearly stated that there are no established agents for the prevention of CIPN, and clinicians may offer duloxetine and other antidepressants or gabapentin as a treatment for established CIPN, noting that the available data are limited and very few options are available for this clinical problem [8]**.**

Our literature search has revealed eleven studies with varying methodologies that explored the role of vitamin E in preventing CIPN [6,9,18,10–17]. Seven of those trials have shown a protective effect for vitamin E against CIPN in patients treated with platinum or taxane chemotherapy. They were all small pilot studies with the number of patients analyzed ranging from 27-70 patients. Three of those trials focused exclusively on paclitaxel, three on cisplatin, and one on cisplatin, paclitaxel, or a combination of both. In all of these trials, patients in the vitamin E group had less incidence of CIPN [6,9–13,18].

However, a large multi-centric trial by Kottschade et al failed to confirm those results also. In a randomized double-blind study, 207 patients were randomized to 800 mg of vitamin E daily vs. placebo in patients receiving curative-intent chemotherapy. Of the 189 patients eligible for analysis, there was no significant difference in grade or more sensory neuropathy related to either taxanes or platinum which was 34% in the vitamin E arm vs. 29% in the placebo arm (P = 0.43). The limitation of that study was the use of different classes of chemotherapy which might prevent drawing strong conclusions due to heterogeneity [17].

Three meta-analyses of the randomized controlled trials (RCTs) that used vitamin E to investigate its protective effects for preventing CIPN were conducted to try and clear the contradiction of the individual trials. All of them showed that the incidence of CIPN in the vitamin E group was lower than in

the control group. In two of them, that difference reached statistical significance and in the third one, the difference wasn't statistically significant. However, a solid conclusion couldn't be obtained due to the high degree of heterogeneity and the lack of large-scale studies in both meta-analysis and the RCTs included [19–21].

Interestingly, the three meta-analyses performed a subgroup analysis which showed a significant reduction in the incidence of peripheral neuropathy in the cisplatin group. However, none of them performed a subgroup analysis for paclitaxel probably due to the small number of trials focusing on paclitaxel-induced neuropathy included in those meta-analyses [19–21].

Taken together, these data support that vitamin E may become a promising novel agent in the prevention of CIPN as an inexpensive oral agent, currently available in a generic formulation and has been safely administered to thousands of patients with an excellent tolerance.

AIM OF THE WORK

Primary end point:

To compare the incidence of grade 2+ sensory neuropathy as graded by the National Cancer Institute-Common Toxicity Criteria for adverse events (CTCAE v. 5.0) criteria in patients receiving taxane based chemotherapy with vitamin E prophylaxis to those receiving taxane based chemotherapy only without prophylaxis.

Secondary end points:

To compare the time to onset of grade 2+ sensory neuropathy and the duration of sensory neuropathy in patients receiving taxane based chemotherapy with vitamin E prophylaxis to those receiving taxane based chemotherapy only without prophylaxis.