The Effect of Exogenous Nerve Growth Factor "Cerebrolysin" on the Incidence and Severity of Paclitaxel- Induced Peripheral Neuropathy in Cancer Patients

A Thesis submitted for the fulfillment of Master Degree in Pharmaceutical Sciences (Clinical Pharmacy)

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Acknowledgment

In the Name of Allah, the most Gracious the most Merciful

Thanks to God, all praise to Allah for the strength and his blessing in completing this thesis

Special appreciation goes to my supervisor **Dr.Lamia El Wakeel**, Assistant Professor of Clinical Pharmacy, Ain Shams University for her continuous support. Her constructive comments, attention to details and suggestions throughout the practical and thesis work have contributed to the success of this research.

I would like to express my deepest gratitude to **Dr. Mahmoud El Lithy**, Assistant Professor of Clinical Oncology, Faculty of Medicine, Ain Shams University, for his continuous support, technical assistance in the hospital and medical knowledge regarding this topic.

I also would like to express my deepest gratitude to **Dr. Mona Schalaan**, Assistant Professor and head of Clinical Pharmacy and Pharmacy Practice Department, MIU, for her continuous encouragement, creativity, constant support and details oriented suggestions throughout the thesis work.

Sincere thanks and deepest gratitude goes to the world's best parents, husband, brother, sister and daughter for their endless love, prayers, help and continuous encouragement and support.

Sincere thanks to Ain Shams University Hospitals and patients for allowing me to complete my practical part of the thesis within their premises

My deepest love and thanks for my family, friends and colleagues for their kindness and support the past years

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List of Abbreviations

Abbreviation	Full term
AD	Alzheimer's disease
ALC	Acetyl-L-Carnitine
ALT	Alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
BBB	Blood brain barrier
BDNF	Brain Derived Neurotrophic Factor
BRCA	Breast Cancer susceptibility gene
BSA	Body surface area
BSE	Breast self exam
BUN	Blood urea nitrogen
Ca	Calcium
CBC	Complete blood count
CIPN	Chemotherapy induced peripheral neuropathy
CMT	Charcot Marie Tooth
CNS	Central nervous system
CrEL	Cremophor EL
CYP	Cytochrome P
DCIS	Ductal carcinoma in situ
DM	Diabetes mellitus
DNA	Deoxyribonucleic Acid
DRG	Dorsal root ganglia
EDTA	Ethylene- diamine- tetra- acetic acid
EORTC QLQ CIPN20	The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Chemotherapy Induced Peripheral Neuropathy twenty- item scale
ELISA	Enzyme linked immunosorbant assay
EMG	Electromyography
E-site	Exchangeable
FACT- G	Functional Assessment of Cancer Therapy
Fasl	First apoptosis signal ligand
FDA	Food and drug administration
GTP	Guanosine triphosphate
HER2/neu	Human epidermal growth factor receptor 2
HIV	Human immunodeficient virus
HMSN	Hereditary motor and sensory neuropathy

HRP	Horseradish Peroxidase
IDC	Invasive ductal carcinoma
IGF-I	Insulin-like growth factor-I
IL	Interleukin
ILC	Invasive lobularcarcinoma
INCAT	Modified Inflammatory Neuropathy Cause and Treatment
LCIS	Lobular carcinoma in situ
MAOI	Monoamine oxidase inhibitors
mISS	Sensory sumscore
MRI	Magnetic resonance imaging
MTOC	Microtubule organizing centers
Na	Sodium
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute- Common Toxicity Criteria for Adverse Events
NCV	Nerve conduction velocity
NGF	Nerve growth factor
NMDARs	N-methyl-D-aspartate receptors
NRTIs	Nucleoside reverse transcriptase inhibitors
NS	Nervous system
NSAIDs	Non- steroidal anti- inflammatory drugs
N-site	Non-exchangeable
NT	Neurotrophin
NTF	Neurotrophic factor
OTC	Over the counter
P	Phosphrous
P-APS	Paclitaxel acute pain syndrome
PET	Positron emission tomography
PIPN	Paclitacel induced peripheral neuropathy
PNS	Peripheral nervous system
QOL	Quality of life
QST	Quantitative Sensory Testing
RBC	Red blood cell
ROS	Reactive oxygen species
rhNGF	Recombinant human nerve growth factor
SARMs	Selective Androgen Receptor Modulators
SEs	Side effects

SERMs	Selective Estrogen Receptor Modulators
SPSS	Statistical package for social sciences
TNF	Tumor necrosis factor
TNSc	Clinical Total Neuropathy Score
TMB	Tetramethylbenzidine
TrKA	Tyrosine kinase
TRP	Transient receptor potential
US	United States
WHO	World Health Organization

Abstract

Background: Paclitaxel-induced peripheral neuropathy (PIPN) is a common toxicity with no proven agent beneficial for prevention. The potentiality of Nerve Growth Factor (NGF) as a protective agent for PIPN was suggested by several studies.

Aim: The aim of this study is to test the impact of exogenously administered NGF on PIPN and to assess NGF levels in relation to PIPN severity.

Methods: Forty patients were prospectively randomly allocated to Paclitaxel alone (control group) or Paclitaxel + exogenous NGF (test group). Neuropathy occurrence and severity was assessed before enrollment and after each cycle using The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Chemotherapy Induced Peripheral Neuropathy twenty-item scale (EORTC QLQ-CIPN20). Nerve Growth Factor level was assessed in both groups at baseline and at the end of the study. Nerve Growth Factor safety was assessed by laboratory investigations and the occurrence of side effects.

Results: There was significant increase in the EORTC QLQ-CIPN20 score in the control group ($p<0.001$) and a stabilization in the score in the test group. Nerve Growth Factor levels significantly increased in the test group ($p<0.001$) and declined in the control group. A highly significant negative correlation existed between NGF level and the EORTC QLQ-CIPN20 score ($r=-0.781$, $p<0.001$). No significant difference was observed between the two groups in the occurrence of side effects or other toxicities.

Conclusion: Exogenous NGF may have a potential neuroprotective effect against PIPN in breast cancer patients. Higher endogenous NGF level is inversely correlated with the occurrence and severity of PIPN.

Keywords: Nerve Growth Factor, Neuropathy, Paclitaxel, Breast Cancer.