PREVALENCE AND PREDICTORS OF CISPLATIN INDUCED PERIPHERAL NEUROPATHY AT THE KENYATTA NATIONAL HOSPITAL

A RESEARCH DISSERTATION SUBMITTED IN PART FULFILLMENT OF THE REQUIREMENTS FOR THE FELLOWSHIP IN MEDICAL ONCOLOGY AT THE UNIVERSITY OF NAIROBI

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LIST OF ABBREVIATIONS

AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
cART	Combined Antiretroviral Therapy
CIPN	Chemotherapy Induced Peripheral Neuropathy
CKD	Chronic Kidney Disease
CRF	Chronic Renal Failure
DACH	Diamminocyclohexane
DNA	Deoxyribonucleic Acid
DPN	Diabetic Peripheral Neuropathy
DSP	Distal Sensory Polyneuropathy
ECOG	Eastern Cooperative Oncology Group
HIV	Human Immunodeficiency Virus
IL 6	Interleukin 6
IL 8	Interleukin 8
KNH	Kenyatta National Hospital
MDRD	Modification of Diet in Renal Disease
MGUS	Monoclonal Gammopathy of Undetermined Significance
NCI-CTAE	National Cancer Institute Common Terminology for Adverse Events
NRTI	Nucleoside Reverse Transcriptase Inhibitors
OXAIPN	Oxaliplatin Induced Peripheral Neuropathy
POEMS	Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal Gammopathy and Skin Changes
RIPN	Radiation Induced Peripheral Neuropathy
RNA	Ribonucleic Acid
ROS	Reactive Oxygen Species
SPSS 21.0	Statistical Package for the Social Sciences version 21
TNF α	Tumor Necrosis Factor Alpha

TNS	Total Neuropathy Score
TNSc	Total Neuropathy Score Clinical Version
TRP	Transient Receptor Potential
UoN	University of Nairobi
WHO	World Health Organization

ABSTRACT

Background

Peripheral neuropathy is a common and significant chronic complication of cancer chemotherapeutic drugs especially the platinum compounds like cisplatin. The prevalence of peripheral neuropathy due to cisplatin in not known in our region. We, sought out to determine the prevalence and risk factors in our setup.

Objective

To determine the prevalence, predictors and/or risk factors of chemotherapy induced peripheral neuropathy in patients undergoing chemotherapy with cisplatin at Kenyatta National Hospital.

StudyDesign

Cross-sectional descriptive survey.

Methods

This was a cross-sectional analysis of consecutive sampled cancer patients undergoing chemotherapy with cisplatin for at least two months at the Kenyatta National Hospital oncology units. Consented participants' demographic data and focused medical history and neurological exam was by use of structured pre-tested questionnaires. Data was presented in the form of tables and graphs. Descriptive inferential statistics such as means, medians and proportions were determined where applicable

Results

We recruited 67 patient who were undergoing chemotherapy with cisplatin. Fifty six (83.6%) patients had neuropathy. Forty five (81%) had mild grade (grade 1, and grade 2) of peripheral neuropathy. Two (3.1%) patients had severe or grade 4 neuropathy. None of the risk factors that we evaluated were statistically significant.

Conclusion

In conclusion, we found that peripheral neuropathy due to cisplatin based therapy is quite prevalent (83.6%). Most of our patients had mild peripheral neuropathy.

1.0 INTRODUCTION

Chemotherapy-induced peripheral neuropathies (CIPN) are major adverse effects of various cancer chemotherapeutic drugs. Several commonly used cancer chemotherapeutic drugs cause peripheral neuropathy.

Platinum agents especially cisplatin, are an important group of chemotherapeutic drugs. They are used in the management of various cancers for both curative and/or palliative intent. However, these drugs are associated with numerous adverse effects. Peripheral neuropathy is a major non-hematologic adverse effect associated with the platinum agents.

The prevalence of CIPN is high. Seretny et al reported a prevalence of 68%, one month after chemotherapy. Moreover, the prevalence was still at 30% after 6 months of chemotherapy.

The clinical symptoms of CIPN involve the peripheral nervous system. This is manifested as sensory loss, paresthesia, numbness, tingling sensation and pain in a "stocking and glove" distribution. CIPN and related symptoms severely affects patients' quality of life. Furthermore CIPN, often leads to either to reduction or discontinuation of chemotherapy. CIPN may develop while the patient is on chemotherapy or several months post therapy and symptoms may persist for a period of time even after finishing chemotherapy.

Currently, there is no preventive nor curative treatment for CIPN. Yet most of these neurotoxic chemotherapy drugs are used quite frequently in both the adjuvant and palliative setting. This could have an adverse impact on the patient quality of life. CIPN is also associated with other comorbidities, and a heavy economic cost.

Despite the fact that CIPN is a significant complication of cisplatin chemotherapy, there is no data on its overall impact, prevalence and risk factors in our setting. In this study, we attempted to fill this gap. We evaluated the prevalence and severity of peripheral neuropathy on patients receiving cisplatin based chemotherapy. We, also examined the factors associated with peripheral neuropathy.

2.0 LITERATURE REVIEW

2.1 CAUSES OF PERIPHERAL NEUROPATHY IN CANCER

Peripheral neuropathies are disorders associated with the peripheral nervous system (1). There are multiple causes of peripheral neuropathy in cancer patients. Cancer per se can cause neuropathy. Other causes of peripheral neuropathy in cancer include remote or paraneoplastic effects; infiltration or compression of nerves by tumor or as a side effect secondary to treatment (2).

2.1.1 Cancers associated with Peripheral Neuropathy

The cancers that are most commonly associated with peripheral neuropathy include breast cancer, lung cancer, and Non-Hodgkin's lymphoma and plasma cell dyscrasias.

2.1.1.1 Lymphoma

Lymphoma causes peripheral neuropathy by nerve infiltration, nerve compression or paraneoplastic process (2). Non-Hodgkin's lymphoma causes most of the peripheral neuropathy. The neuropathy manifests mainly as sensorimotor neuropathy. The neuropathy can be acute, progressive or intermittent. Furthermore, it may resolve on treatment of the underlying lymphoma. Hodgkin's disease tends to cause Guillian-Barre syndrome (3)

2.1.1.2 Plasma Cell Dyscrasias

Almost all types of plasma cell dyscrasias are associated with peripheral neuropathy. The plasma cells dyscrasias include monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma, Waldenstrom's macroglobulinemia, amyloidosis, Castleman's disease and Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS Syndrome). Plasma cell dyscrasias causes peripheral neuropathy by malignant infiltration, immune-mediated antibody deposition or local compression of nerve roots (4).

2.1.1.3 Solid Tumors

Case reports and a prospective multicenter study associate breast and lung cancer as the most common solid tumor that is associated with peripheral neuropathy (5)(6).

2.1.2 Paraneoplastic Encephalomyelitis / Sensory Neuronopathy

Paraneoplastic encephalomyelitis / sensory neuronopathy (PEN/SN) is a type of neuropathy that is commonly associated small cell lung cancer. Usually, the immune system produces antibodies

against tumor restricted antigens. However, these antibodies may cross react with normal neuronal cells leading to neuropathy. Patients eventually present with sensory ataxia or loss of proprioception (7).

2.1.3 Vitamin or micronutrient deficiency

Constant supply of adequate and appropriate nutrient is necessary for optimal function of the peripheral nervous system. Vitamin E, vitamin B12, thiamine, niacin, pyridoxine, copper and folic acid are important vitamins and micronutrient required for optimal functioning of the peripheral nervous system (8). Patients with cancer, especially those with advanced disease are often malnourished with multiple nutritional deficiencies.

Vitamin E deficiency usually present as a spinocerebellar syndrome. It causes axonal neuropathy in the peripheral nerves. The role of Vitamin E in chemotherapy induced peripheral neuropathy is controversial. Several randomized trials on the use of Vitamin E for prevention and treatment of peripheral neuropathy have shown mixed results (9)(10).

The neurologic manifestations of Vitamin B12 and folic acid include myeloneuropathy. Myeloneuropathy is peripheral neuropathy with coexistent myelopathy. Vitamin B12 deficiency causes sensorimotor axonopathy. Other neurological manifestations include autonomic dysfunction and neuropsychiatric manifestation (11).

2.1.4 Alcohol

Alcoholic neuropathy is often a consequence of nutritional deficiency, in particularly B vitamins. Persons with alcoholism consume smaller amounts of essential nutrients and/or vitamins. Furthermore, there is reduced absorption of these nutrients from the gastrointestinal tract. Acetaldehyde, metabolite of ethanol oxidation, is in itself a direct neurotoxic agent (12).Patients with alcoholic neuropathy usually present with a sensory motor axonal polyneuropathy.

2.1.5 Human Immunodeficiency Virus / Acquired Immunodeficiency Syndrome (HIV/AIDS)

Distal symmetric polyneuropathy (DSP) is one of the most common neurologic manifestation associated with HIV and its treatment. The prevalence of HIV DSP in the cART era is around 50% (13).This tends to increase in those patients who are on neurotoxic antiretroviral drugs such as stavudine (14). The pathologic hallmark of HIV neuropathy includes distal axonal degeneration, loss of neurons at the dorsal root ganglia and neuronal infiltration by inflammatory

cells (15). Two pathophysiologic processes are responsible for the development of HIV DSP. Firstly, direct neurotoxicity of the virus and its product. Secondly, neurotoxicity of the antiretroviral drugs (16). The nucleoside reverse-transcriptase inhibitors (NRTIs) are shown to be frequently associated with DSP (17). Symptomatic DSP frequently leads to change in HIV treatment regimens (18).

2.1.6 Diabetes Mellitus

The most common complication of diabetes mellitus is diabetic neuropathy. It has a lifetime prevalence of 50% (19). Diabetes causes a variety of neuropathy syndromes. The most common is diabetic peripheral neuropathy (DPN). DPN causes 75% of all diabetic neuropathy (20).

The Toronto Consensus Panel defines DPN as a "symmetrical, length-dependent sensorimotor polyneuropathy attributable to metabolic and micro vessel alterations as a result of chronic hyperglycemia exposure and cardiovascular risk covariates"(22). Sensory symptoms begin at the toes and eventually distribute in a "stocking and glove" pattern. The pathogenesis of DPN is complex. It is associated with both vascular and metabolic factors (23).

2.1.7 Chronic Kidney Disease (Uremic Neuropathy)

The prevalence of chronic kidney disease (CKD) in developing countries is 15%, and 40% among people over the age of 65 years (24). Neurological complication occur in 60% of patients with severe chronic kidney disease (25). The most common neurological manifestation is symmetrical distal sensorimotor polyneuropathy (26). Uremic neuropathy is caused by accumulation of unfiltered medium sized molecules. Hence, the optimal treatment of uremic neuropathy is either hemodialysis or kidney transplant (27).

2.1.8 Hypothyroidism and Hyperthyroidism

Both hypothyroidism and hyperthyroidism cause neuromuscular dysfunction. Hypothyroidism causes mononeuropathy and sensori-axonal polyneuropathy (28). Similarly, hyperthyroidism causes polyneuropathy (29). The prevalence neuropathy especially in hypothyroidism varies between 10% and 70% (30)(31).

2.1.9 Iatrogenic Causes

These are causes of peripheral neuropathy that occur due to the treatment modality used in the management of cancer patients. They include surgery, radiation therapy and chemotherapy.

2.1.9.1 Post-surgical neuropathy

Peripheral nerve damage is a common complication of surgery. It is usually caused by compression, contusion or transection of the nerve during surgery(32).

2.1.9.2 Radiation Induced Peripheral Neuropathy (RIPN)

Radiation-induced peripheral neuropathy is progressive and usually irreversible. It occurs several year after radiotherapy(33). The pathophysiology is not fully elucidated. However, compression of the nerve by radiation induced fibrosis is a major cause of RIPN. Other mechanism of neuronal damage include direct axonal damage and injury to endoneural blood vessels leading to neuronal ischemia(34)(35).

There is varied clinical presentation due to the different anatomic sites irradiated. The most frequent form is radiation induced brachial plexopathy after breast cancer irradiation(36).The risk factors for RIPN are varied. Combined treatment-related factors include surgery and concomitant or previous neurotoxic chemotherapy. Patients risk factor include young or advanced age, obesity, hypertension, diabetes mellitus, dyslipidemia and smoking.

2.1.9.3 Medication Induced Peripheral Neuropathy

Medication induced peripheral neuropathy includes both non cytotoxic and cytotoxic drug (chemotherapy) induced peripheral neuropathy. It is important to identify the non-cytotoxic drugs that could cause or contribute to peripheral neuropathy. Table 1 outlines some of the common non cytotoxic drugs that cause peripheral neuropathy.

Table 1: Non cytotoxic drugs that cause peripheral neuropathy

Antimicrobial Agents	Dapsone Ethambutol Isoniazid Nitrofurantoin Metronidazole
Antiretroviral Agents	Didanosine Zalcitabine Stavudine
Cardiovascular Medications	Amiodarone

	Disopyramide Hydralazine Propranolol
Antirheumatic Medications	Chloroquine Hydroxychloroquine
Anticonvulsants	Phenytoin
Others	Colchicine Indomethacin

2.1.9.3.1 Chemotherapy Induced Peripheral Neuropathy

Chemotherapy-induced peripheral neuropathies (CIPN) are major dose limiting adverse effects of various cancer chemotherapeutic drugs(37). Platinum anticancer drugs (cisplatin, oxaliplatin, carboplatin), taxanes (paclitaxel, docetaxel), vinca alkaloids (vincristine, vinorelbine), proteasome inhibitors (bortezomib) and angiogenesis inhibitors (thalidomide) are mostly associated with CIPN(38).

The prevalence of CIPN is high. Seretny et al reported a prevalence of 68%, one month after chemotherapy. Moreover, the prevalence was still at 30% after 6 months of chemotherapy(39).

The clinical symptoms of CIPN involve the peripheral nervous system. This is manifested as sensory loss, paresthesia, numbness, tingling sensation and pain in a “stocking and glove” distribution(37).CIPN and related symptoms severely affects patients’ quality of life. Furthermore CIPN, often leads to either to reduction or discontinuation of chemotherapy. CIPN may develop several months post therapy and symptoms may persist for a considerable period of time after finishing chemotherapy(40).

Currently, there is no preventive nor curative treatment for CIPN(41). Yet most of these neurotoxic chemotherapy drugs are used quite frequently in both the adjuvant and palliative setting. This could have an adverse impact on the patient quality of life. CIPN is also associated with other comorbidities(42), and a heavy economic cost(43).

3.0 PLATINUM COMPOUNDS

Many platinum compounds have been developed. However, very few have been registered for treatment of different cancers. The most commonly used are cisplatin, oxaliplatin and carboplatin (44)(45)(46). The platinum analogs are very effective cancer chemotherapy drugs. However, serious side effects like peripheral neuropathy usually limit administration of total effective doses. In addition, it also adversely affects the patient's quality of life (40)(47).

3.1 CISPLATIN

Cisplatin is a potent chemotherapy drugs. It is used for a wide spectrum of malignancies (48). The chemical structure of cisplatin is cis-Diamminedichloroplatinum (49). Cisplatin is a heavy metal platinum complex. It irreversibly binds to DNA, and disrupts its function (50).

3.1.1 Mechanism of Action

Cisplatin reacts by forming a variety of monofunctional and bifunctional DNA adducts (51). These adducts form DNA intrastrand and interstrand crosslinks. The formation of adducts and crosslinks has been associated with therapeutic efficacy (52). They cause cell death by apoptosis, necrosis, or autophagy.

3.1.1 Medical Use

Cisplatin is usually given as a short term intravenous infusion. It is used for the treatment of sarcomas, lung cancers, head and neck cancers, ovarian cancers, lymphomas, genitourinary cancers, esophageal cancers, gastric cancers and germ cell tumors.

3.1.2 Adverse Effects

Cisplatin use is associated with severe dose limiting toxicities or side effects. These include both general and specific side effects. The general side effects include nausea and vomiting and myelosuppression. The specific side effects include nephrotoxicity, neurotoxicity and ototoxicity (53).

3.2 EPIDEMIOLOGY

The prevalence of chemotherapy induced peripheral neuropathy is high. A meta-analysis done by Seretny et al in 2014 found a prevalence of 48.1%. 68% of the patients analyzed had CIPN in the first month after chemotherapy. This prevalence dropped to 60% to 30% in the subsequent three months and six months respectively. Furthermore, different chemotherapy drugs are associated with differences in CIPN prevalence (39).

The overall incidence of cisplatin neurotoxicity is about 47% as determined by Vanderhoop et al. Most of the patients had grade 1 and grade 2 neuropathy about 21%. However the incidence of severe neurotoxicity was 4% (54). However, the onset of cisplatin induced neuropathy is variable. Some patients develop it after the first dose of chemotherapy while others develop after 12 cycles of chemotherapy (55).

3.3 PATHOPHYSIOLOGY

Peripheral neuropathy caused by platinum drugs involves multi- factorial processes. It involves oxidative stress, apoptosis, dysregulated calcium homeostasis, axonal degeneration and membrane remodeling. Neuro-inflammation is also associated with peripheral neuropathy (56).

Several mechanism contribute to cisplatin induced neurotoxicity. They include sensory neuron loss, cell signaling alterations and mitochondrial dysfunction due to DNA plantination (57).

The figure 1 below illustrates the putative mechanism involved in the development of cisplatin induced peripheral neuropathy.

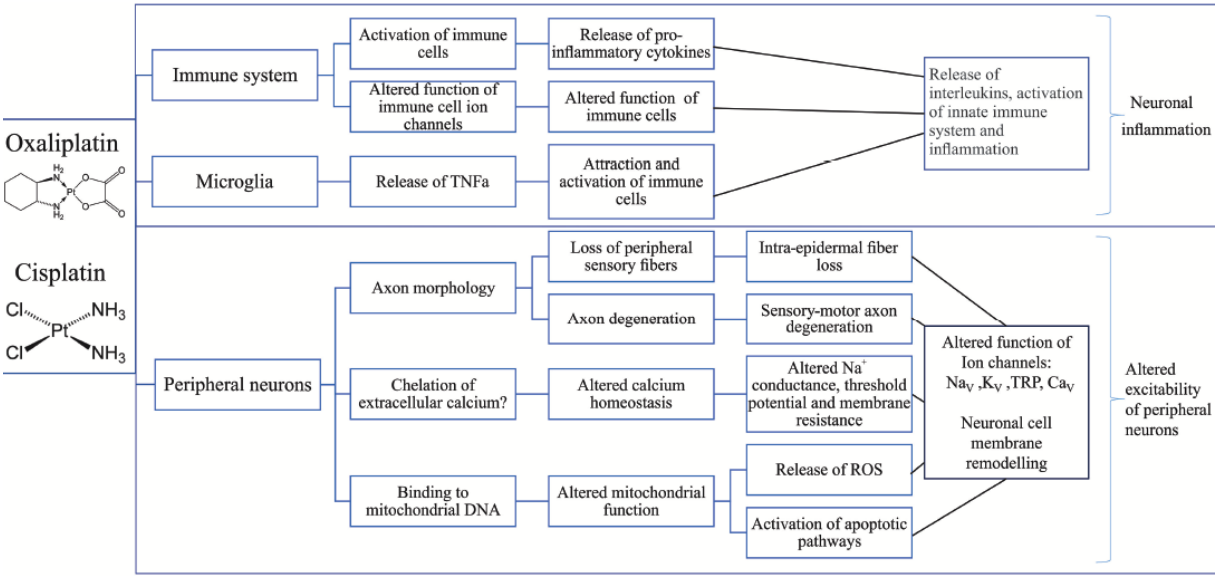


Figure 1: Mechanism involved in the development of cisplatin induced peripheral neuropathy (56)

3.3.1 Oxidative Stress

Cisplatin binds to mitochondrial DNA. It forms mitochondrial DNA adducts that cannot be repaired like chromosomal DNA as the mitochondria does not have DNA repair systems. The mitochondrial DNA adducts impair mitochondrial function(58), with production of reactive oxygen species (ROS) and increased oxidative stress(59). This in turn damages intracellular biomolecules leading to demyelination and disruption of peripheral nerves(60).

3.3.2 Calcium Homeostasis

Calcium is a very important regulatory ion in neuronal homeostasis. Calcium homeostatic dysregulation alters membrane excitability and neurotransmitter release(61).

3.3.3 Axon Degeneration

Cisplatin causes axon degeneration and loss of intraepidermal nerve fibers(62).However the molecular mechanism leading to axonal degeneration remains unclear.

3.3.4 Changes in Neuronal Excitability

The changes in neuronal excitability are caused by disruption of both expression and function of various ion channels such as the voltage gated sodium channels, voltage gated potassium channels and transient receptor potential (TRP) channels(63).There is reduced expression of voltage gated potassium channels(64) and altered expression of several thermos and mechano-sensitive TRP channels(65).

3.4 PREDICTORS OR RISK FACTORS

There are several risk factors or clinical predictors that could predict the development of peripheral neuropathy. The most important risk factor is the cumulative dose(66). The cumulative dose is generally the total amount drug given to a patient over time. Cisplatin neurotoxicity generally occurs after a total cumulative dose of 300 mg/m^2(67). 70% of patients developed peripheral neuropathy when they received a cumulative dose of 600mg/m^2(68). The neuropathy progresses after discontinuation of therapy and even persists for years (69).

There is conflicting evidence regarding association of age and gender with increased risk of developing peripheral neuropathy. Some studies suggest a positive association while others suggest otherwise(70)(71). In a retrospective study done by Vincenzi et al showed no association with development of peripheral neuropathy and age and sex. About half of the patients in both the old group and group developed peripheral neuropathy. Similarly 50% of male and 54% of female developed peripheral neuropathy(72).

A couple of studies have evaluated other clinical risk factors that could predict development of peripheral neuropathy in being treated with a platinum based agent. The first study done by Vincenzi et al is a retrospective study. It enrolled 169 patients and evaluated for chronic renal failure, diabetes, anemia, hypocalcaemia, hypomagnesaemia, hypoalbuminemia, vitamin B12 deficiency, folate deficiency, number of cycles received and alcohol consumption. He concluded that the incidence of neuropathy was significantly higher in patients with anemia, hypoalbuminemia, hypomagnesemia and those with heavy alcohol intake. There was no correlation with hypocalcemia, diabetes and chronic renal failure(72). A similar but prospective study done by Ali Shariari-Ahmadi found the same clinical parameters that significantly affect the incidence of peripheral neuropathy in patients undergoing treatment with a platinum based agent. He also noted that patients with higher body mass index were more predisposed to neuropathy(73).

3.5 ASSESSMENT OF CIPN

Currently, there is no universal accepted standard for assessing CIPN. Various combination of laboratory tests, physical evaluation and grading systems are used so as to get an accurate and reliable diagnosis. However, this poses a major challenge(74).

3.5.1 Clinical Assessment

The patient is initially screened for any pre-existing neuropathies, comorbidities and any past chemotherapy treatment. This is followed by a comprehensive physical exam focusing on sensory, motor and autonomic functions(75).

3.5.2 Sensory Symptoms

Initially sensory symptoms such as dysesthesias, paresthesia generally predominate(76). The disease usually begins with paresthesia at the feet, which usually progresses proximally and symmetrically towards the trunk. When the symptoms advance towards the knee level, the finger tips become involved and similarly progresses proximally in the upper limbs(77).

Neuropathic pain is a serious problem. It usually presents as an intense burning sensation, intermittent pulses or a dull aching sensation. In some patients, neuropathy and neuropathic pain occurs late in the course of treatment and may persist for months after completion of treatment. This phenomenon is called coasting(78).

3.5.3 Motor symptoms

The motor symptoms in CIPN are less common and usually milder than the sensory symptoms. However, they may become severe and progress to paralysis. Motor neurotoxicity follows the same stocking and glove distribution as sensory neuropathy. Clinical symptoms may range from mild reduction of distal muscle group strengths that is detectable on clinical examination to weakness of feet dorsiflexion with subsequent foot drop. Reduced or loss of the ankle reflex is an early sign of motor neuropathy(79). Patients may notice that they stumble while walking, or need to hold onto a rail when going up and down the stairs. They may have difficulty with fine motor tasks of the hands like difficulty in writing, typing or buttoning their shirt.

3.5.4 Autonomic symptoms

The autonomic neuropathy due to chemotherapeutic agent is infrequent(80). Autonomic system dysfunction include orthostatic hypotension, anhidrosis, cardiac arrhythmias, xerostomia, gastrointestinal dysmotility, urinary dysfunction and erectile dysfunction. Gastrointestinal dysmotility manifests as alternating diarrhea and constipation and early satiety due to gastroparesis(81). Urinary dysfunction is caused by an atonic or neuropathic bladder leading to urinary retention with intermittent overflow incontinence(82). Erectile dysfunction represents a very early symptom of autonomic neuropathy(80).

3.5.5 Neurophysiological assessment:

This provides a practical and convenient method for confirming a diagnosis of CIPN. They are useful to elicit functional and pathological nerve damage(83). The neurophysiological assessments include motor and sensory nerve conduction testing, electromyography and evoked potentials.

Electromyoneurography involves nerve conduction studies and electromyography. Most patients with CIPN show an axonal pathology with reduction of sensory and/or common motor action potential. In a study done by Karup-Hansen et al in patients treated with cisplatin, showed a 60% reduction in sensory neural action potential at doses of 300mg/m^2(84).

3.5.6 Vibration perception threshold

Vibration perception threshold has been used to differentiate patients with a lower risk of developing CIPN and those at risk of developing higher grades(85). It has also shown promising results in diabetic neuropathy(86).

3.5.7 Nerve and skin biopsy

Sural nerve biopsies have been done in patients with suspected inflammatory and inherited causes of peripheral neuropathy. It is used to investigate large sensory and motor nerve fiber disorders(87). Skin biopsies are done for assessment of small fiber neuropathy. The skin biopsy allows evaluation of intraepidermal nerve fibers(88).

3.6 GRADING OF CIPN

The findings from clinical examination and patient's report regarding the symptoms and severity of CIPN is usually compared against one or more grading scales to establish the degree of peripheral neuropathy. There are various toxicity scales in common use. These include the World Health (WHO) scale, the National Cancer Institute Common Terminology for Adverse Events (NCI-CTAE) scale, the Ajani Score, the Eastern Cooperative Oncology Group (ECOG) score and the Total Neuropathy Score.

The standard method for assessing CIPN is the NCI-CTCAE scale. The NCI-CTAE grades CIPN severity from Grade 1 to Grade 5 (see Table 2). The grading is based on the severity of sensory and motor symptoms in relation to patient's function.

Table 2: Grading of CIPN as per the NCI-CTAE scale.

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	5
Peripheral motor neuropathy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; assistive device indicated	Life threatening consequences; urgent intervention indicated	Death
Peripheral sensory neuropathy	Asymptomatic; loss of deep tendon reflexes or paresthesia	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	Life threatening consequences; urgent intervention indicated	Death
Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.					

However, clinical experience with the tool seems to underestimate the prevalence and severity of CIPN(89). The CI-PeriNoms group in 2013 did a validity and reliability study for the various grading scales. They concluded that the Total Neuropathy Score clinical version (TNSc©) is superior to NCI – CTAE(90).

3.6.1 Total Neuropathy Score

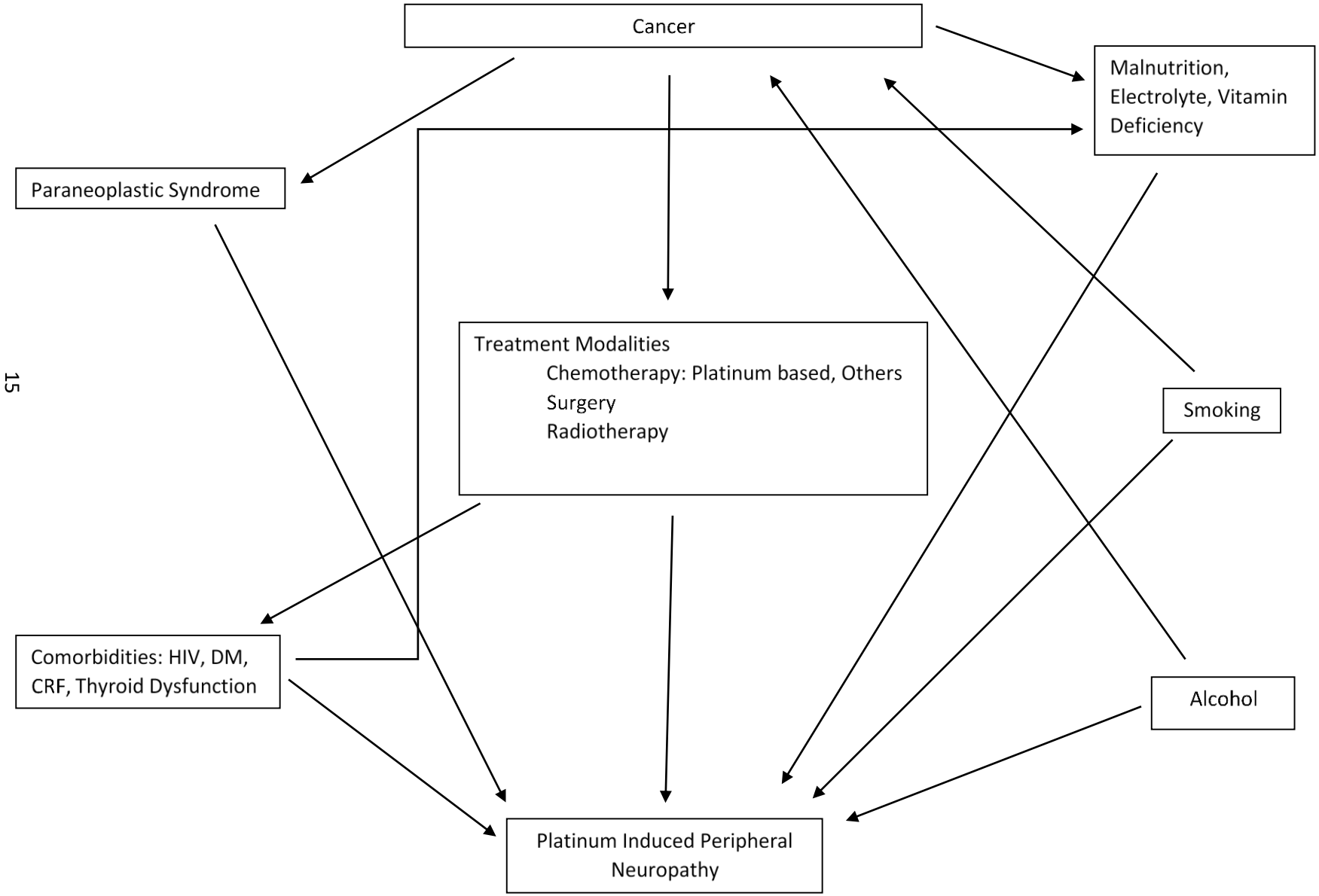
The Total Neuropathy Score (TNS) was developed by Johns Hopkins University(91). It has been validated in a multicenter setting. It correlates well with other measures of sensory dysfunction.(92). The TNS clinical version (TNSc) uses only clinical measures(93). The TNS versions have also been validated(94).

The TNSn© consists of five components namely sensory symptoms, motor symptoms, autonomic symptoms, pin sensibility and vibration sensibility. The strengths of the tool are numerous and include:

i. Assessment of both symptoms and deficits.
ii. Separate measures of sensory, motor and autonomic function.
iii. Use of standardized instruments: Neuropen, Rydel-Seiffer calibrated tuning fork.
iv. Quantitative measure of sensation bilaterally for both upper and lower limbs.
v. Sensitivity to change along a distal-to-proximal gradient, as most neuropathies begin in the hands and feet and progress to include more proximal sites.
vi. Assessment of both large (vibration) and small (pin) fiber sensory function, as these differ in their receptors, pathways, and vulnerabilities to injury.

A TNS score of >2 suggests presence of neuropathy. Furthermore, TNS score can further be graded according to severity from Grade 1 to Grade 4. This grading corresponds to NCI-CTAE grade(40) (90).

3.7 Conceptual Framework


Cancer
Malnutrition, Electrolyte, Vitamin Deficiency
Paraneoplastic Syndrome
Treatment Modalities
Chemotherapy: Platinum based, Others
Surgery
Radiotherapy
Smoking
Comorbidities: HIV, DM, CRF, Thyroid Dysfunction
Alcohol
Platinum Induced Peripheral Neuropathy

4.0 STUDY JUSTIFICATION

Platinum agents especially cisplatin, are an important group of chemotherapeutic drugs. They are used in the management of various cancers for both curative and/or palliative intent. However, these drugs are associated with numerous adverse effects. Peripheral neuropathy is a major non-hematologic adverse effect associated with the platinum agents.

Peripheral neuropathy due to cisplatin may require dose reduction or, in most severe cases, treatment cessation. This can increase both morbidity and mortality.

Despite the fact that CIPN is a significant complication of chemotherapy especially with platinum compounds like cisplatin, there is no data on its overall impact, prevalence and risk factors in our setting. Understanding the impact of CIPN in our setting would help in coming up with protocols for both preventive and therapeutic management. It was anticipated that information generated from this study may form a basis for further studies.

4.1 Research Question

What was the magnitude of CIPN in patient on cisplatin based chemotherapy regimen and its determinants?

4.2 Aims and Objectives

To determine the prevalence and determinants of CIPN in patients undergoing chemotherapy with cisplatin at Kenyatta National Hospital.

4.3 Primary Objectives

1. To determine the prevalence of CIPN using the TNSn grading tool
2. To determine the severity of CIPN using the TNSn grading tool

5.0 RESEARCH METHODOLOGY

5.1 Study Design

This was a cross sectional study, that was conducted at the Kenyatta National Hospital (KNH). KNH is a national teaching and referral hospital in Nairobi, Kenya. The study was specifically conducted in the Haemato – Oncology Outpatient Clinics (Clinic 23, Gyne – Oncology Clinic), Outpatient Chemotherapy Infusional Center (GFC) and the adult medical oncology wards (8C, GFD, 1B).

The patients were selected by consecutive sampling, until the desired sample size was achieved. The sample population comprised of 66 patients undergoing chemotherapy containing cisplatin, either as a single drug or in combination with other chemotherapeutic drugs. The patients were thirteen years and above and had chemotherapy for at least two months. Those patients who had prior neuropathy before commencement of chemotherapy or refused consent for the study were excluded from the study.

The dependent variable was the prevalence of CIPN, while the independent variables were the predictors or risk factors for CIPN.

5.2 Sample size Determination

5.2.1 Assumptions:

Approximately 20 eligible patients are seen monthly. This study was done over a period of 4 months hence a total of 80 patients were accessible for sampling. The sample was drawn from this finite population. The sample size was calculated using the formula for finite populations (less than 10,000). The calculation done was as be as follows:

$$n' = \frac{NZ^2P(1-P)}{d^2(N-1)+Z^2P(1-P)}$$

Where

n' = sample size with finite population correction,

N = size of the target population = 80

Z = Z statistic for 95% level of confidence = 1.96

P = Estimated prevalence of CIPN = 47% (54)

d = margin of error = 5%

$$= \frac{80 \times 1.96^2 \times 0.47 \times 0.53}{0.05^2 (80-1) + 1.96^2 \times 0.47 \times 0.53}$$

n = **66**

A minimum of 66 patients were sampled to estimate prevalence of CIPN within 5% level of precision.

5.3 Recruitment, Consenting and Data Collection Procedure

The patients were recruited from the Haemato – Oncology Outpatient Clinic (Clinic 23), Gyne – Oncology Clinic (Clinic 18), Outpatient Chemotherapy Infusional Center (GFC) and the adult medical oncology wards (8C, GFD, 1B) in KNH. I initially perused through the files to identify patients who are on a cisplatin based chemotherapy regimen for at least two months. For each eligible identified sample patient, the following was done on the same day:

1) Explanation of the study to the patient and obtaining consent
2) Demographic, medical history and clinical examination.
3) Evaluating for laboratory based risk factor

5.4 Obtaining Informed Consent

I, explained the purpose of the study to the patient and consent for the study was obtained. The participants were given time to read through the participant information sheet and the consent form. Their concerns and questions were addressed before signing of the consent. Thereafter, the study participant signed the consent forms if they agreed to participate in the study. Those participants who had difficulty understanding English, the consent form was translated into Kiswahili. If a patient was unable to sign the consent form, his thumb print was appended. An independent or impartial witness also attested that the consent had been given freely.

5.5 Data Collection Procedure

The demographic and clinical data was collected using questionnaire that contained both closed and open ended question (see appendix). A focused neurological exam was carried out as per the Total Neuropathy Score requirements (see appendix). The presence of neuropathy was graded accordingly.

Baseline laboratory blood values (blood result parameters before initiation of chemotherapy) were ascertained from the patient's file. This blood tests results included Urea, Electrolyte and Creatinine, Full Haemogram and Liver function Tests. All patients had these test results in the file as they are a prerequisite before starting chemotherapy.

The following clinical parameters were looked for: age, sex, type and stage of cancer, cumulative dose, concurrent other neurotoxic chemotherapy drugs or radiotherapy, hypoalbuminemia, anemia, diabetes mellitus, chronic renal failure (CRF), HIV, habit of alcohol consumption and smoking status.

5.5.1 Definition of Terms

This was defined as following:

1) Cumulative dose (mg/m^2): Total amount of a drug given to a patient over time divided by the patients' body surface area
2) Anemia: Hemoglobin levels of <12.0g/dL in women and <13.0g/dL in men
3) Hypoalbuminemia: Serum albumin levels <35g/L
4) Renal Dysfunction: GFR <60ml/min/1.73m^2 (calculated through MDRD formula)
5) Alcohol Use: ≥5 glasses in a single occasion for men and ≥4 glasses in a single occasion for women, usually within 2 hours
6) Smoking:
    i) Current Smoker: >100 cigarettes in lifetime and has smoked in the last 28 days
    ii) Former Smoker: >100 cigarettes in lifetime but has not smoked in the last 28 days
    iii) Never Smoker: Never smoked a cigarette or has smoked <100 cigarettes in lifetime

5.6 Data Management

At the end of each interview, the data collection tools were cross checked for completeness and any inconsistencies rectified. Data was entered and managed in Microsoft Excel 2013 spreadsheet. Statistical analysis was done using the SPSS 21.0 version. Study population was described by summarizing demographic and clinical characteristics into percentages and means or medians for categorical and continuous variables respectively. Prevalence of CIPN was presented as a percentage with 95% confidence interval. Presence of CIPN was associated with selected demographic and clinical characteristics to determine the risk factors of developing CIPN. Test of associations were done using Chi square test while comparison of means was done using independent t test. Multiple logistic regression analysis was done to determine independent

factors associated with CIPN. Odds ratio was calculated and presented as relative risk associated with CIPN. Findings were presented in the form of texts, graph and tables as illustrated below. All data was stored under lock and key. The data was coded for confidentiality.

5.7 Ethical Consideration

The research was only conducted after approval from the Kenyatta National Hospital / University of Nairobi Ethics and Research Committee. Participants gave voluntary consent to the study. They were also notified of their right to withdraw or refuse participation. They were not penalized for doing so. Questionnaires was only administered after consent had been given. Measures were put in place so as to ensure patients' confidentiality, such as: privacy and concealing their identity. The participants did not incur any extra financial cost and there was no monetary gain by the primary investigator. Those participants who suffered from neuropathy were referred to the appropriate medical practitioner for further specialized care.

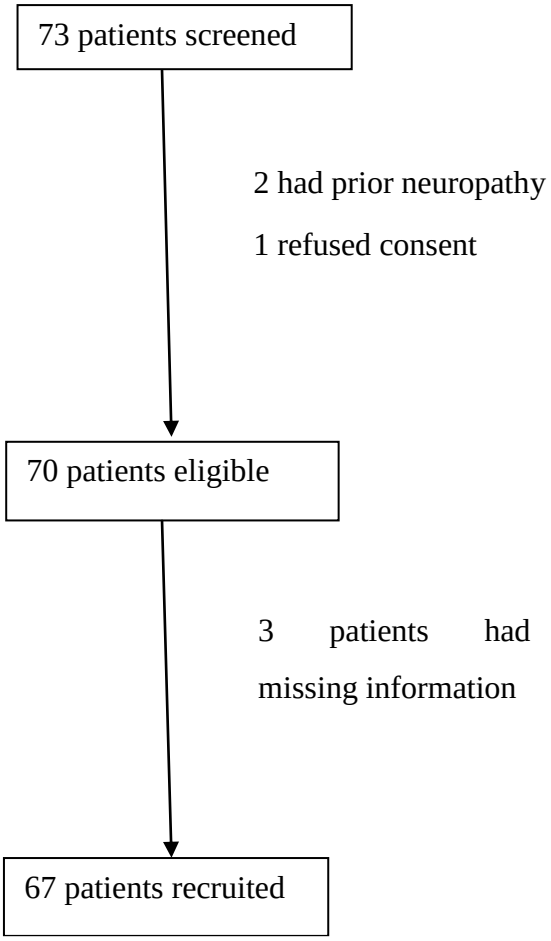
5.8 Dissemination and Application of the results

The results of this study will be submitted to the University of Nairobi, in form of a thesis, required for completion of the Fellowship. The findings will also be shared with various stakeholders through various scientific fora. The study will also be published in peer reviewed journals.

6.0 RESULTS

Sixty seven patients were recruited for the study. Forty four patients (66%) were receiving treatment as inpatient, while 23 patients (34%) were receiving treatment as outpatients.

Figure 2:Flow-chart illustrating Screening, Eligibility and Recruitment of Patients

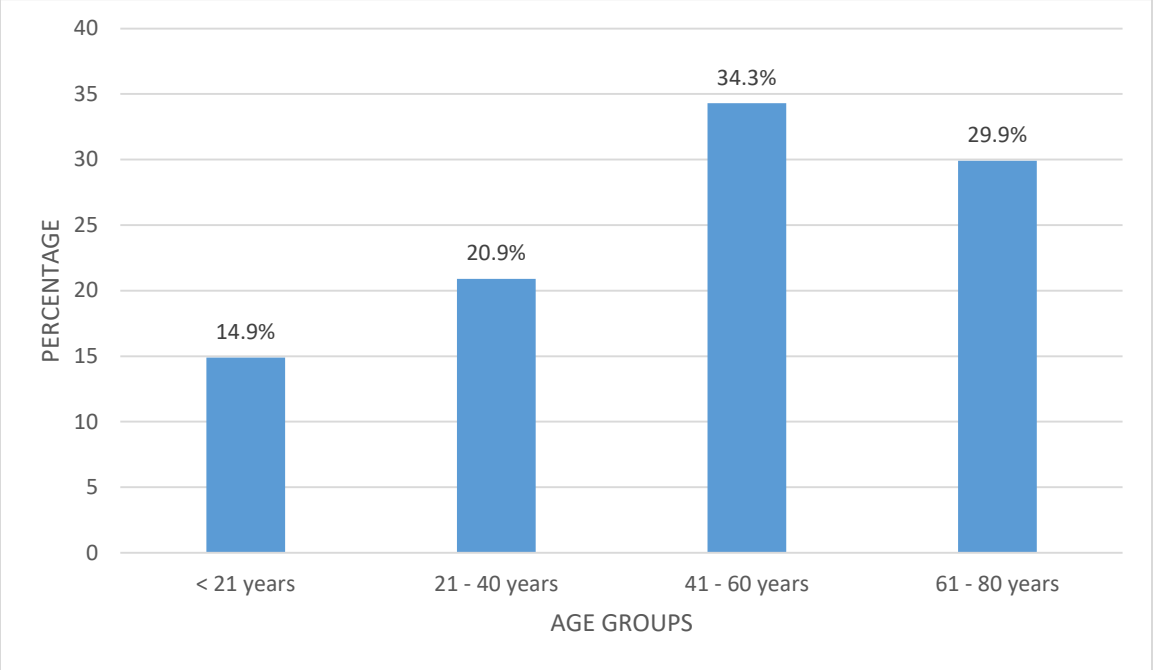


6.1 DEMOGRAPHIC CHARACTERISTICS

6.1.1 Age Distribution

The median age of the patients recruited for this study was 51 years old, ranging from the youngest of 14 years old to the oldest of 80 years old. The most frequent age group was 41 – 60 years, which had 23 (34.3%) patients while the least frequent age group was less than 21 years, which had 10 (14.9%) patients.

Figure 3: Age Distribution of Patients Who Were Undergoing Chemotherapy With Cisplatin.



6.1.2 Sex Distribution

There proportion of the female patients recruited was higher at 62.7% (n=42) than that of the male patients of 37.3% (n=25) with a male to female ratio of 1: 1.7

6.1.3 Distribution of Tumors by Primary Site and Stage

The commonest tumor primary site in these patients was the genito-urinary site (40%) which consisted tumors from the ovary, cervix, uterus, testes and the urinary bladder. Majority of the patients recruited had stage 3 (41.8%) and stage 4 (44.8%) disease

Figure 5: Primary Sites of Cancer in Patients Who Were Undergoing Chemotherapy with Cisplatin

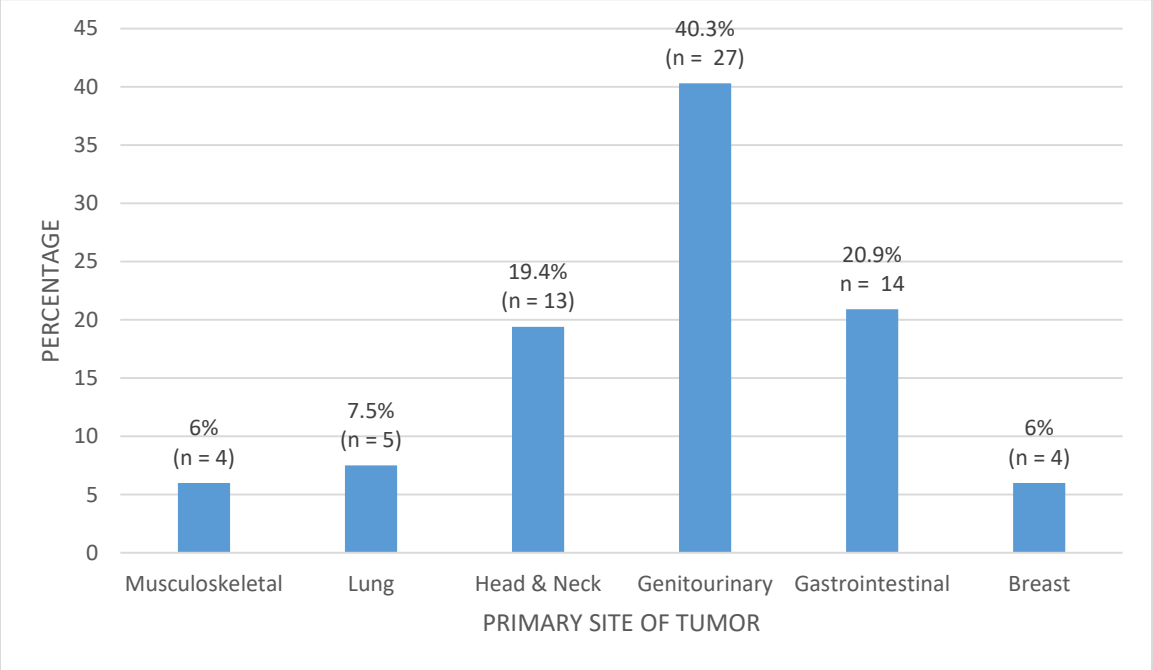
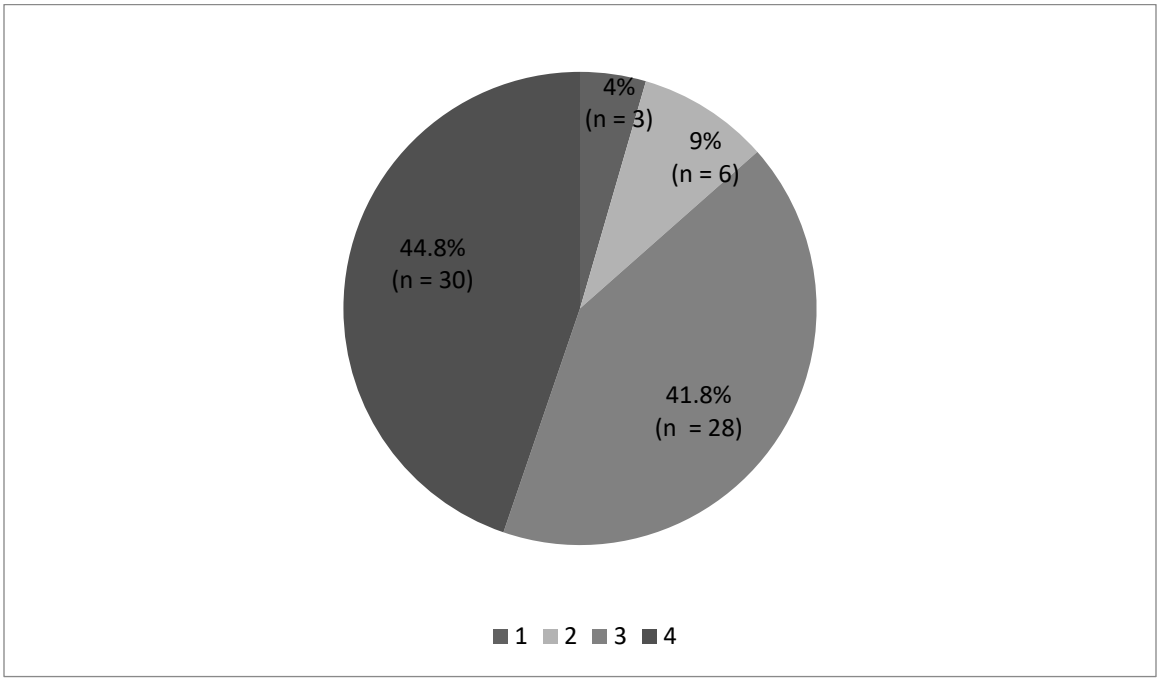


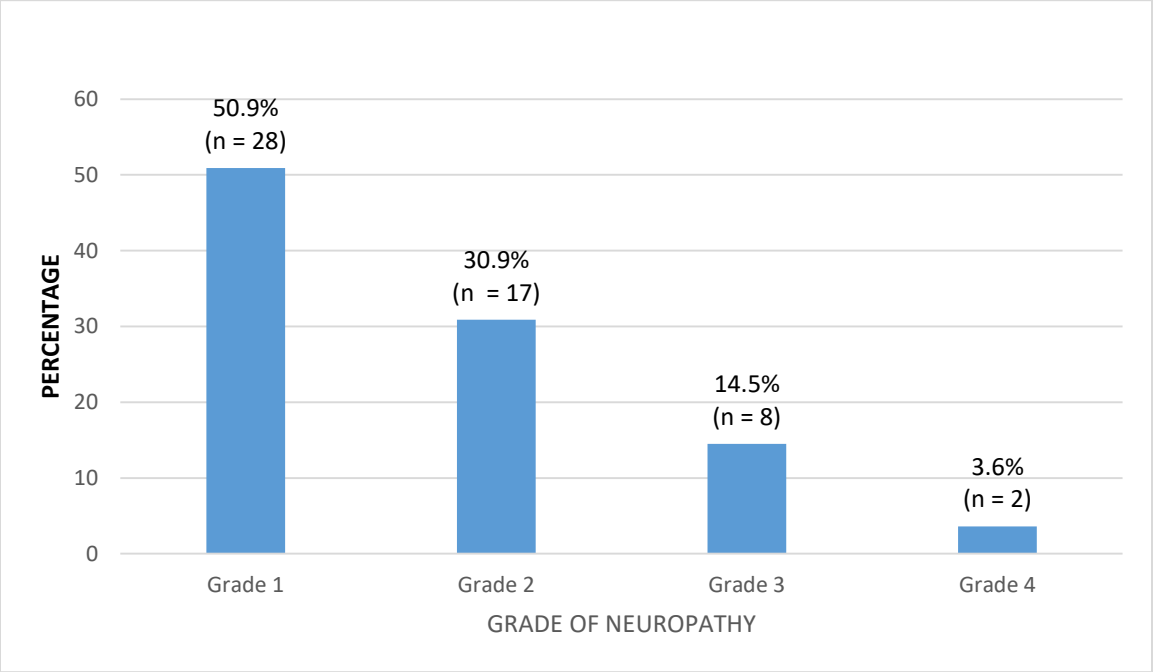
Figure 4: Stages of Cancer in Patients Who Were Undergoing Chemotherapy with Cisplatin



6.2 PREVALENCE OF NEUROPATHY

Fifty six (83.6%) patients had neuropathy as per the Total Neuropathy Scoring System. Forty five (81%) patients had mild neuropathy (Grade 1 and Grade 2). Two (3.6%) patients had grade 4 or severe neuropathy.

Figure 5: Grades of Peripheral Neuropathy in Patients Undergoing Chemotherapy with Cisplatin



6.3 RISK FACTOR FOR NEUROPATHY

6.3.1 Demographic characteristics

There was no significant association between age, sex and the development of neuropathy.

Table 3: Demographic Characteristics and Neuropathy

Variable	**Neuropathy**		**OR (95% CI)**	**P value**
	Yes	**No**		
Median age (IQR)	53 (34-65)	39 (35-55)	-	0.206
Sex				
Male	20 (80.0)	5 (20.0)	0.7 (0.2-2.5)	0.734
Female	36 (85.7)	6 (14.3)	1.0	

6.3.2 Cumulative Dose

The median cumulative dose of cisplatin given was 300mg/m2, with a range from 180mg/m2 to 675mg/m2. There was no significant association between the median cumulative dose and the development of neuropathy.

Table 4: Association between Cumulative Dose and Neuropathy

Variable	**Neuropathy**		**OR (95% CI)**	**P value**
	Yes	**No**		
Median cumulative dose (IQR)	300 (260-400)	300 (225-400)	-	0.948

6.3.2 Body Mass Index

Thirty seven (55%) patients had a normal Body Mass Index (BMI) as calculated by the DuBois method. Seven (10%) patients were obese (BMI >30). Almost all patients who were overweight and obese developed peripheral neuropathy but this was not significant.

Figure 6: Distribution of BMI in patients who underwent chemotherapy with Cisplatin

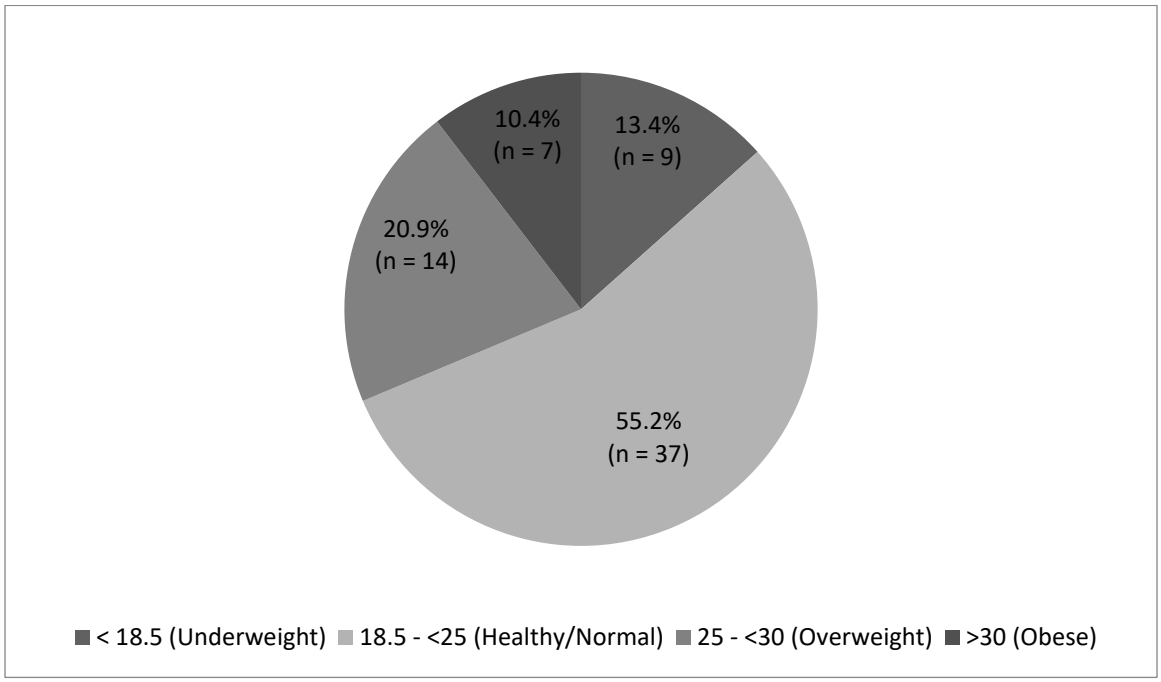


Table 5: Association between Body Mass Index and Neuropathy

Variable	Neuropathy		OR (95% CI)	P value
	Yes	No		
Body Mass Index				
< 18.5 (Underweight	10 (71.4)	4 (28.6)	0.5 (0.1-2.1)	0.327
18.5 - <25 (Healthy/Normal)	31 (83.8)	6 (16.2)	1.0	
25 - <30 (Overweight)	7 (100.0)	0	-	0.999
>30 (Obese)	8 (88.9)	1 (11.1)	1.6 (0.2-14.8)	0.704

6.3.3 Stage and Site of Tumor

There was no significant association between the site, stage of tumor and development of neuropathy.

Table 6: Association between Stage and Site of Cancer and Neuropathy

Variable	Neuropathy		OR (95% CI)	P value
	Yes	No		
Tumor site				
Breast	1 (25.0)	3 (75.0)	1.8 (0.2-18.7)	0.633
Gastrointestinal	2 (14.3)	12 (85.7)	0.8 (0.2-4.3)	0.809
Genitourinary	3 (11.1)	24 (88.9)	0.5 (0.1-2.1)	0.335
Head and neck	3 (23.1)	10 (76.9)	1.7 (0.4-7.7)	0.470
Lung	0	5 (100.0)	-	0.582
Musculoskeletal	2 (50.0)	2 (50.0)	6.0 (0.7-48.2)	0.062
Tumor stage				
1	0	3 (100.0)	-	0.500
2	2 (33.3)	4 (66.7)	1.0	
3	6 (21.4)	22 (78.6)	0.5 (0.1-3.7)	0.609
4	3 (10.0)	27 (90.0)	0.2 (0.0-1.8)	0.186

6.3.4 Diabetes mellitus

Three (4.5%) patients had diabetes mellitus and they were on treatment for the same.

Table 7: Association between Diabetes Mellitus and Neuropathy

Variable	**Neuropathy**		**OR (95% CI)**	**P value**
	Yes	**No**		
Diabetes Mellitus				
Yes	2 (66.7)	1 (33.3)	0.4 (0-4.5)	0.421
No	54 (84.4)	10 (15.6)	1.0	

6.3.5 Human Immunodeficiency Virus (HIV) Infection

Three (4.5%) patients had HIV infection, and all of them were on treatment for the same.

Table 8: Association between HIV and Neuropathy

Variable	**Neuropathy**		**OR (95% CI)**	**P value**
	Yes	**No**		
HIV				
Yes	3 (100.0)	0	-	1.000
No	53 (82.8)	11 (17.2)		

6.3.5 Renal Dysfunction

Eleven (16.4%) patients had renal dysfunction prior to beginning chemotherapy with cisplatin. There was no significant association between renal dysfunction and development of neuropathy.

Table 9: Association between Renal Dysfunction and Neuropathy

Variable	Neuropathy		OR (95% CI)	P value
	Yes	No		
Renal Dysfunction				
Yes	10 (90.9)	1 (9.1)	2.2 (0.3-19.0)	0.676
No	46 (82.1)	10 (17.9)	1.0	

6.3.6 Concurrent Neurotoxic Drugs

Fifty (74.6%) patients were using cisplatin combined with another neurotoxic chemotherapeutic agent. The most frequently combined neurotoxic chemotherapeutic drugs were taxanes. Forty four (88%) patients were using cisplatin combined with a taxane. Forty one (82%) of the patients who had concurrent neurotoxic chemotherapeutic agent developed peripheral neuropathy, however, this was not significant. Patients who had combined cisplatin and taxane had a higher median TNS score of 5 (range 0 – 17), than those without taxane combination (median = 3, range 0 – 14)

Table 10: Association between Concurrent Neurotoxic Drug and Neuropathy

Variable	Neuropathy		OR (95% CI)	P value
	Yes	No		
Concurrent Neurotoxic Drug				
Yes	41 (82.0)	9 (18.0)	0.6 (0.1-3.1)	0.716
No	15 (88.2)	2 (11.8)	1.0	

6.3.7 Previous Radiotherapy

Forty four (65.7%) patients had previously undergone radiotherapy. There was no significant association between prior radiotherapy and development of neuropathy.

Table 11: Association between Previous Radiotherapy and Neuropathy

Variable	Neuropathy		OR (95% CI)	P value
	Yes	No		
Radiotherapy				
Yes	38 (86.4)	6 (13.6)	1.8 (0.5-6.5)	0.492
No	18 (78.3)	5 (21.7)	1.0	

6.3.8 Alcohol intake and Cigarette Smoking

A high percentage of the sample population had neither drunk alcohol (59 patients) nor had ever smoked cigarette (61 patients), 88% and 91% respectively.

Table 12: Association between Alcohol Intake and Neuropathy

Variable	Neuropathy		OR (95% CI)	P value
	Yes	No		
Habit to Alcohol Use				
Yes	5 (62.5)	3 (37.5)	0.3 (0.1-1.3)	0.117
No	51 (86.4)	8 (13.6)	1.0	

Table 13: Association between Cigarette Smoking and Neuropathy

Variable	Neuropathy		OR (95% CI)	P value
	Yes	No		
Smoking Status				
Never	51 (83.6)	10 (16.4)	1.0	
Former	3 (75.0)	1 (25.0)	0.6 (0.1-6.2)	0.660
Current	2 (100.0)	0	-	0.999

6.3.9 Anemia and Hypoalbuminemia

In this study 30 (44.8%) patients had anemia, whereas 19 (28.4%) had hypoalbuminemia. However, these patients did not show any significant p – value to presence or absence of neuropathy.

Table 14: Association between Presence of Anemia and Neuropathy

Variable	Neuropathy		OR (95% CI)	P value
	Yes	No		
Anemia				
Yes	25 (83.3)	5 (16.7)	1.0 (0.3-3.5)	0.961
No	31 (83.8)	6 (16.2)	1.0	

Table 15: Association between Hypoalbuminemia and Neuropathy

Variable	Neuropathy		OR (95% CI)	P value
	Yes	No		
Hypoalbuminemia				
Yes	17 (89.5)	2 (10.5)	2.0 (0.4-10.1)	0.715
No	39 (81.3)	9 (18.8)	1.0	

7.0 DISCUSSION

This is the first cross sectional study on prevalence of chemotherapy induced peripheral neuropathy in our region. It has provided a profile of CIPN in patients treated with cisplatin. The study population had a median age of 51 years, which is a relatively young population. Most of the patients had advanced disease. This is comparable with the local cancer registry that states that 60% of Kenyans affected with cancer are younger than 70 years old and 70 – 80% of cancer stages are diagnosed at late stages (https://kenyacancernetwork.wordpress.com/kenya-cancer-facts/).

The rate of CIPN ranges from 20% to 90% (95)(96)(97)(98)(9)(99)(100)(78). A meta-analysis by Seretny et al found the overall prevalence of CIPN to be 48%. He also states that 68% had peripheral neuropathy one month after chemotherapy(39). Our study assessed peripheral neuropathy in patients receiving cisplatin and found the prevalence was 83.6%. Most of these patients had mild to moderate peripheral neuropathy. Only 3.6% of our patients had severe neuropathy. Seretny further comments that three large studies in his meta-analysis did not include mildest grades of neuropathy and this could have lowered the prevalence of CIPN. Two out of the three studies mentioned was evaluating neurotoxicity caused by cisplatin. This wide range may be influenced by several factors such as, study population, length of follow up, chemotherapy regimen and the assessment tools used(101)(102)(89). The TNSr© is a sensitive tool for screening CIPN, as it detected mild levels of neuropathy.

In a cross sectional study of 29 patients done by Vasquez et al in 2014, found that all of the patients had clinical evidence of neuropathy. The patients developed peripheral neuropathy while on the 4^{th} cycle of chemotherapy with no mention of the cumulative dose(103).

A cross sectional cohort study, by Glendenning et al, found a prevalence of 21% for grade 3 neuropathy. He recruited patients with testicular cancer who had finished chemotherapy for at least 5 years. The median time since initial treatment was 11 years. He only assessed for ≥ grade 3 peripheral neuropathy using the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire C30 with testicular model (EORTC QLQ-C30). 28% of his patients had been exposed to chemotherapeutic regimen containing both cisplatin and a vinca alkaloid. On multivariate analysis, the significant predictors were cisplatin dose and age. The median cumulative dose of cisplatin given was 400mg/m^2 (100mg/m^2 – 960mg/m^2) while for

ours was 300mg/m^2. In addition the median age in his study was 41 years old, while ours was 51 years old(104).

The rest of the studies that evaluated cisplatin induced peripheral neuropathy are mostly prospective cohort studies and controlled trials. Argyriou et al reported an incidence of 50%, of which 30% had moderate to severe neuropathy. This is in contrast to our study which had a prevalence of 18% with moderate to severe peripheral neuropathy (Grade 3 and 4). He had recruited 35 patients with lung cancer and prospectively followed them up at baseline, at the third, the sixth course of chemotherapy and up to three months after completion of chemotherapy. He had used a modified Peripheral Neuropathy (PNP) score. His primary aim was to determine whether patients who are older than 65 years at a higher risk of CIPN than those who are younger than 65 years. 45% of his patients were on cisplatin while the rest were on paclitaxel. None of his patients received combined cisplatin and paclitaxel. Those who were on cisplatin had received a mean cumulative dose of 720mg/m^2(105).

A prospective cohort study by Von Schlippe, reported a peripheral neuropathy incidence of 11% at the end of chemotherapy. The incidence rose to 65% three months after chemotherapy. A year after chemotherapy the incidence was 17%. He had recruited 29 patients, ranging from 14 years to 50 years (median 30 years), who had metastatic testicular cancer and followed them from initiation of chemotherapy to 4 years post chemotherapy. He initially followed up his patients every six weeks for six months and then every two monthly. Most of his patients had received 300mg/m^2 to 400mg/m^2 of cisplatin. He had assessed for neuropathy using neuro-physiological examination(78).

A randomized clinical trial conducted by Cascinu et al reported an incidence of 66% at 9 weeks post exposure and 88% at 15 weeks post exposure. He had recruited 50 patients with advanced gastric cancer who were given weekly cisplatin at a dose of 40mg/m^2 combined with epidoxorubicin and fluorouracil. He followed them up at baseline, after nine weeks (360mg/m^2) and later after fifteen weeks (600mg/m^2). He used the National Cancer Institute Common Terminology Criteria (NCI-CTC) in combination with electrophysiological testing to evaluate for peripheral neuropathy(96).

Another randomized clinical trial conducted by Pace et al, evaluating the neuro-protective effect of vitamin E supplementation found the incidence of peripheral neuropathy by cisplatin without vitamin E supplementation to be 85% (12 out of 14 patients), while those who were given

Vitamin E supplementation had an incidence of 30% (4 out of 13 patients). He had recruited 47 patients. However 20 patients dropped out of the study and only 27 patients were assessable. These 27 patients had received a cumulative dose of cisplatin higher than 300mg/m^2 (median cumulative dose of 420mg/m^2). The median age was 57 years. The study had patients with mixed tumor pathology with 50% of his patients having lung cancer. The rest had ovarian, gastric and nasopharyngeal cancer. He evaluated for peripheral neuropathy by using the modified Neurological Symptom Score(98).

The median cumulative dose in our study was 300mg/m^2. The earliest signs of cisplatin induced peripheral neuropathy occurs at a cumulative dose of 250mg/m^2 – 350mg/m^2(104). This could explain why majority of patients in our study had mild grade of peripheral neuropathy.

Not much information is available on the demographic and clinical characteristics that increases the risk for CIPN development. In most registry studies, the risk factors for CIPN were neither evaluated(106)(107), nor demonstrated to influence the prevalence and severity of cisplatin induced peripheral neuropathy(108). However a study by the Southwest Oncology Group identified older age, prior or concurrent treatment with a neurotoxic drug and decreased creatinine clearance as risk factors for the development of CIPN(109). None of the risk factors that we evaluated were statistically significant. This is because that our study is underpowered, because of the small sample size.

This study has several limitations. The cross sectional design assesses clinical features of peripheral neuropathy at one point in time. It cannot assess or determine the progression and evolution of the clinical features. Furthermore, we were not able to assess the impact of CIPN on quality of life and therapies used to mitigate peripheral neuropathy. The associations identified between demographic and clinical characteristics warrant confirmation as determinants of CIPN in a prospective study, as these associations were not adequately powered for in this study due to the small sample size. This should be evaluated before commencement of chemotherapy, during chemotherapy and following completion of chemotherapy. Furthermore, a prospective study over the course of chemotherapy and beyond would enable to look at the changes in neuropathy score.

In addition the data obtained was from a single tertiary hospital, hence introducing a potential for selection bias. The study only collected data from patients who had received or were receiving cisplatin based chemotherapy, hence the finding of this study cannot be generalized to patients receiving other neurotoxic chemotherapy drugs.

In conclusion, we found that peripheral neuropathy due to cisplatin based therapy is quite prevalent (83.6%). Most of our patients had mild peripheral neuropathy. The TNSr© can be used to clinically screen for CIPN. Long term prospective studies are needed to determine the natural course, associated risk factors and attenuating factors for CIPN. Furthermore, patients should be screened for peripheral neuropathy when being treated with neurotoxic chemotherapeutic drugs.

Currently, the screening for CIPN, relies on the subjective description by the patients. Most patients with mild peripheral neuropathy may be asymptomatic or hesitant in reporting any symptoms in fear that their treatment will be interrupted. However, the neuropathy may increase in severity as treatment progresses. This is detrimental to the patient as their treatment could be interrupted leading to a suboptimal response. Furthermore, it may also affect their quality of life as they might be restricted in their activity of daily living. Health care workers should be trained to screen, evaluate and manage peripheral neuropathy in the initial stages. Further studies are needed to focus on etiology, evolution, risk factors, complications and psychological distress associated with neuropathy caused by cisplatin and other neurotoxic chemotherapeutic drugs.

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APPENDIX I

PARTICIPANT INFORMATION AND ADULT CONSENT FORMFOR ENROLLMENT IN THE STUDY

Title of Study: PREVALENCE AND PREDICTORS OF PLATINUM INDUCED PERIPHERAL NEUROPATHY AT THE KENYATTA NATIONAL HOSPITAL

Principal Investigator\and institutional affiliation: DR. MOHAMMED EZZI (UNIVERSITY OF NAIROBI)

Co-Investigators and institutional affiliation: _____

Introduction:

I would like to tell you about a study being conducted by the above listed researchers. The purpose of this consent form is to give you the information you will need to help you decide whether or not to be a participant in the study. Feel free to ask any questions about the purpose of the research, what happens if you participate in the study, the possible risks and benefits, your rights as a volunteer, and anything else about the research or this form that is not clear. When we have answered all your questions to your satisfaction, you may decide to be in the study or not. This process is called 'informed consent'. Once you understand and agree to be in the study, I will request you to sign your name on this form. You should understand the general principles which apply to all participants in a medical research: i) Your decision to participate is entirely voluntary ii) You may withdraw from the study at any time without necessarily giving a reason for your withdrawal and ii) Refusal to participate in the research will not affect the services you are entitled to in this health facility or other facilities. We will give you a copy of this form for your records.

May I continue? YES / NO

This study has approval by The Kenyatta National Hospital-University of Nairobi Ethics and Research Committee protocol No. _____

WHAT IS THIS STUDY ABOUT?

The researchers listed above are interviewing individuals who are on chemotherapy with a platinum based agent. The purpose of the interview is to find out how many will develop peripheral neuropathy with this drugs and what risk factors predispose one to develop peripheral neuropathy. Participants in this research study will be asked questions about numbness in the limbs and undergo a neurological examination.

There will be approximately 385 participants in this study randomly chosen. We are asking for your consent to consider participating in this study.

WHAT WILL HAPPEN IF YOU DECIDE TO BE IN THIS RESEARCH STUDY?

If you agree to participate in this study, the following things will happen: You will be interviewed by a trained interviewer in a private area where you feel comfortable answering questions. The interview will last approximately 10 minutes. The interview will cover topics such as type of cancer, the chemotherapy drugs used, and about numbness in the limbs. After the

interview has finished, you will undergo a neurological examination of your limbs. The neurological exam will include being pricked by a sharp object but this will not cause you injury or harm.

We will ask for a telephone number where we can contact you if necessary. If you agree to provide your contact information, it will be used only by people working for this study and will never be shared with others. The reasons why we may need to contact you is to clarify any doubts and to inform you that if you suffer from peripheral neuropathy, what further steps are to be taken.

ARE THERE ANY RISKS, HARMS DISCOMFORTS ASSOCIATED WITH THIS STUDY?

Medical research has the potential to introduce psychological, social, emotional and physical risks. Effort should always be put in place to minimize the risks. One potential risk of being in the study is loss of privacy. We will keep everything you tell us as confidential as possible. We will use a code number to identify you in a password-protected computer database and will keep all of our paper records in a locked file cabinet. However, no system of protecting your confidentiality can be absolutely secure, so it is still possible that someone could find out you were in this study and could find out information about you.

Also, answering questions in the interview may be uncomfortable for you. If there are any questions you do not want to answer, you can skip them. You have the right to refuse the interview or any questions asked during the interview. It may be embarrassing for you to have a neurological examination. We will do everything we can to ensure that this is done in private. Furthermore, all study staff and interviewers are professionals with special training in these examinations.

ARE THERE ANY BENEFITS BEING IN THIS STUDY?

You may benefit by receiving health information about your illness. We will refer you to a hospital for care and support where necessary. Also, the information you provide will help us better understand and improve management of patients who develop this condition.

WILL BEING IN THIS STUDY COST YOU ANYTHING?

You, being in the study will not cost you anything financially. You will be recruited in the study at your usual appointment date. The only indirect cost that you may incur is you will spend extra time at the clinic answering the questionnaire.

WILL YOU GET REFUND FOR ANY MONEY SPENT AS PART OF THIS STUDY?

As you will be interviewed and examined on the same day, hence no issue of refund will be anticipated

WHAT IF YOU HAVE QUESTIONS IN FUTURE?

If you have further questions or concerns about participating in this study, please call or send a text message to the study staff at the number provided at the bottom of this page. For more information about your rights as a research participant you may contact the Secretary/Chairperson, Kenyatta National Hospital-University of Nairobi Ethics and Research Committee Telephone No. 2726300 Ext. 44102 email uonknh_erc@uonbi.ac.ke.The study staff

will pay you back for your charges to these numbers if the call is for study-related communication.

WHAT ARE YOUR OTHER CHOICES?

Your decision to participate in research is voluntary. You are free to decline participation in the study and you can withdraw from the study at any time without injustice or loss of any benefits.

CONSENT FORM (STATEMENT OF CONSENT)

Participant's statement

I have read this consent form or had the information read to me. I have had the chance to discuss this research study with a study counselor. I have had my questions answered in a language that I understand. The risks and benefits have been explained to me. I understand that my participation in this study is voluntary and that I may choose to withdraw any time. I freely agree to participate in this research study. I understand that all efforts will be made to keep information regarding my personal identity confidential. By signing this consent form, I have not given up any of the legal rights that I have as a participant in a research study.

I AGREE TO PARTICIPATE IN THE STUDY	**O YES O NO**

Participant's name: _____

Participant signature / Thumb stamp _____

Date _____

Researcher's statement

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has willingly and freely given his/her consent.

Researcher's Name: _____

Date: _____

Signature: _____

Role in the study: _____

In case you have any concerns about the study, you may contact myself – Dr. Mohammed Ezzi on 0721211807, my supervisor or the Ethics (KNH/UoN ERC) Secretariat whose names and contacts are as follows:

Prof N. A. Othieno-Abinya (Lead Supervisor): +254 2 726300-9

KNH/UoN ERC Secretariat +254 2 726300-9 / Ext 44102

PARTICIPANT INFORMATION AND CHILD (PARENTAL CONSENT) ENROLLMENT IN THE STUDY

Title of Study: PREVALENCE AND PREDICTORS OF PLATINUM INDUCED PERIPHERAL NEUROPATHY AT THE KENYATTA NATIONAL HOSPITAL

Principal Investigator \ and institutional affiliation: DR. MOHAMMED EZZI (UNIVERSITY OF NAIROBI)

Introduction:

I would like to tell you about a study being conducted by the above listed researchers. The purpose of this consent form is to give you the information you will need to help you decide whether or not your child should participate in the study. Feel free to ask any questions about the purpose of the research, what happens if your child participates in the study, the possible risks and benefits, the rights of your child as a volunteer, and anything else about the research or this form that is not clear. When we have answered all your questions to your satisfaction, you may decide if you want your child to be in the study or not. This process is called 'informed consent'. Once you understand and agree for your child to be in the study, I will request you to sign your name on this form. You should understand the general principles which apply to all participants in a medical research: i) Your child decision to participate is entirely voluntary ii) You child may withdraw from the study at any time without necessarily giving a reason for his/her withdrawal and iii) Refusal to participate in the research will not affect the services your child is entitled to in this health facility or other facilities.

May I continue? YES / NO

For children below 18 years of age we give information about the study to parents or guardians. We will go over this information with you and you need to give permission in order for your child to participate in this study. We will give you a copy of this form for your records. If the child is at an age that he/she can appreciate what is being done the he/she will also be required to agree to participate in the study after being fully informed.

WHAT IS THE PURPOSE OF THE STUDY?

The researchers listed above are interviewing individuals who are on chemotherapy with a platinum based agent. The purpose of the interview is to find out how many will develop peripheral neuropathy with this drugs and what risk factors predispose one to develop peripheral neuropathy. Participants in this research study will be asked questions about numbness in the limbs and undergo a neurological examination. There will be approximately 385 participants in this study randomly chosen. We are asking for your consent to consider your child to participate in this study.

WHAT WILL HAPPEN IF YOU DECIDE YOU WANT YOUR CHILD TO BE IN THIS RESEARCH STUDY?

If you agree to participate in this study, the following things will happen: Your child will be interviewed by a trained interviewer in a private area where he/she will feel comfortable answering questions. The interview will last approximately 10 minutes. The interview will cover topics such as type of cancer, the chemotherapy drugs used, and about numbness in the limbs. After the interview has finished, he/she will undergo a neurological examination of your limbs.

The neurological exam will include being pricked by a sharp object but this will not cause you injury or harm.
We will ask for a telephone number where we can contact you if necessary. If you agree to provide your contact information, it will be used only by people working for this study and will never be shared with others. The reasons why we may need to contact you is to clarify any doubts and to inform you that if you suffer from peripheral neuropathy, what further steps are to be taken.

ARE THERE ANY RISKS, HARMS, DISCOMFORTS ASSOCIATED WITH THIS STUDY

Medical research has the potential to introduce psychological, social, emotional and physical risks. Effort should always be put in place to minimize the risks. One potential risk of being in the study is loss of privacy. We will keep everything you tell us as confidential as possible. We will use a code number to identify your child in a password-protected computer database and will keep all of our paper records in a locked file cabinet. However, no system of protecting confidentiality can be absolutely secure so it is still possible that someone could find out your child was in this study and could find out information about your child. Also, answering questions in the interview may be uncomfortable for you or your child. If there are any questions you or your child does not want to answer, you can skip them. You and your child have the right to refuse the interview or any questions asked during the interview. It may be embarrassing for you or your child to have a neurological examination. We will do everything we can to ensure that this is done in private. Furthermore, all study staff and interviewers are professionals with special training in these examinations.

ARE THERE ANY BENEFITS BEING IN THIS STUDY?

Your child may benefit by receiving health information about his/her illness. We will refer your child to a hospital for care and support where necessary. Also, the information you provide will help us better understand and improve management of patients who develop this condition.

WILL BEING IN THIS STUDY COST YOU ANYTHING?

You, being in the study will not cost you anything financially. Your child will be recruited in the study at his/her usual appointment date. The only indirect cost that you may incur is that you and your child will spend extra time at the clinic answering the questionnaire.

IS THERE REIMBURSEMENT FOR PARTICIPATING IN THIS STUDY?

As you and your child will be interviewed and examined on the same day, hence no issue of refund will be anticipated.

WHAT IF YOU HAVE QUESTIONS IN FUTURE?

If you have further questions or concerns about your child participating in this study, please call or send a text message to the study staff at the number provided at the bottom of this page. For more information about your child's rights as a research participant you may contact the Secretary/Chairperson, Kenyatta National Hospital-University of Nairobi Ethics and Research Committee Telephone No. 2726300 Ext. 44102 email uonknh_erc@uonbi.ac.ke.The study staff will pay you back for your charges to these numbers if the call is for study-related communication.

WHAT ARE YOUR OTHER CHOICES?

Your decision to have your child participate in this research is voluntary. You are free to decline or withdraw participation of your child in the study at any time without injustice or loss of benefits. Just inform the study staff and the participation of your child in the study will be stopped. You do not have to give reasons for withdrawing your child if you do not wish to do so. Withdrawal of your child from the study will not affect the services your child is otherwise entitled to in this health facility or other health facilities.

CONSENT FORM (STATEMENT OF CONSENT) FOR MINORS

The person being considered for this study is unable to consent for him/herself because he or she is a minor (a person less than 18 years of age). You are being asked to give your permission to include your child in this study.

Parent/guardian statement

I have read this consent form or had the information read to me. I have had the chance to discuss this research study with a study counselor. I have had my questions answered by him or her in a language that I understand. The risks and benefits have been explained to me. I understand that I will be given a copy of this consent form after signing it. I understand that my participation and that of my child in this study is voluntary and that I may choose to withdraw it any time. I understand that all efforts will be made to keep information regarding me and my child's personal identity confidential. By signing this consent form, I have not given up my child's legal rights as a participant in this research study.

I voluntarily agree to my child's participation in this research study: O YES O NO

Parent/Guardian printed name: _____

Signature_____

Researcher's statement

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has knowingly given his/her consent.

Printed Name: _____ **Date**: _____

Signature: _____

Role in the study: _____

In case you have any concerns about the study, you may contact myself – Dr. Mohammed Ezzi on 0721211807, my supervisor or the Ethics (KNH/UoN ERC) Secretariat whose names and contacts are as follows:

Prof N. A. Othieno-Abinya (Lead Supervisor):	+254 2 726300-9
KNH/UoN ERC Secretariat	+254 2 726300-9 / Ext 44102

CHILD ASSENT FORM

PROJECT TITLE: PREVALENCE AND PREDICTORS OF PLATINUM PERIPHERAL NEUROPATHY AT THE KENYATTA NATIONAL HOSPITAL

INVESTIGATOR(S): DR. MOHAMMED EZZI

We are doing a research study about numbness in the limbs in people undergoing cancer treatment. Permission has been granted to undertake this study by the Kenyatta National Hospital-University of Nairobi Ethics and Research Committee (KNH-UoN ERC Protocol No. _____. This research study is a way to learn more about people. There would be a few children participating in this research with you. If you decide that you want to be part of this study, you will be asked to answer questions about the type of cancer, the type of treatment given, the chemotherapy drugs used, and about numbness in the limbs. This will done in a private area where you will feel comfortable. The interview will last approximately 10 minutes. After the interview has finished, you will undergo a neurological examination of your limbs. The neurological exam will include being pricked by a sharp object but this will not cause you injury or harm. Not everyone who takes part in this study will benefit. A benefit means that something good happens to you. We think these benefits might be that you will better understand your illness. When we are finished with this study we will write a report about what was learned. This report will not include your name or that you were in the study. You do not have to be in this study if you do not want to be. If you decide to stop after we begin, that's okay too. Your parents know about the study too. If you decide you want to be in this study, please sign your name.

I, _____, want to be in this research study.

_____ _____

(Signature/Thumb stamp) (Date)

FOMU YA MAELEZO YA KUHUSU UTAFITI

Nambari ya Utafiti: _____

Kiini cha Utafiti:KUTHATMINI NI IDADI GANI YA WAGONJWA WALIO KATIKA MATIBABU YA SARATANI WANAATHIRIWA NA UDHAIFU WA MISHIPA NA NI KIPI KINACHOSABABISHA UDHAIFU HUU.

Mtafiti mkuu: DKT MOHAMMED EZZI. (CHUO KIKUU CHA NAIROBI)

Msimamizi: PROF NICHOLAS OTHIENO-ABINYA

MAELEZO ZAIDI KUHUSU UTAFITI

Kushiriki kwa utafiti huu ni wa hiari yako. Lengo la utafiti huu ni kuthatmini ni idadi gani ya wagonjwa walio katika matibabu ya saratani wanaathiriwa na udhaifu wa mishipa na ni kipi kinachosababisha udhaifu huu

Je huu udhaifu wa mishipa ni upi?

Udhaifu wa mishipa ni aina moja ya magonjwa yanayosababisha na madhara ya madawa yanayotumika kutibu saratani. Ugonjwa huu husababisha kudhoofika kwa maisha ya walioadhiriwa. Utafiti uliofanywa hapa kwetu kuhusu ugonjwa huu hautoshi, kwa hivyo tungetaka kuongeza ujuzi wetu kuhusu ugonjwa huu ili tuweze kuwasaidia wagonjwa wengine siku za usoni

Unapokubali kushiriki kwa utafiti huu, utaulizwa maswali mbalimbali kuhusu ugonjwa ulionao na jinsi matibabu unayopata yanakuathiri mishipa. Baadaye tutakagua mguu na mkono.

Madhara:

Hakuna madhara au gharama yoyote yatakayotokana na kushiriki kwako au mtoto wako katika utafiti huu.Kushiriki ni kwa hiari yako na hautashrutishwa kwa njia yoyote. Una haki ya kukataa kushiriki au kutamatisha ushirikiano wako wakati wowote bila kuhujumiwa.

Hakuna malipo yoyote utakayopata ila shukrani kwa kukubali kushiriki katika utafiti huu. Ujuzi tutakaopata kwa utafiti huu utaweza saidia wagonjwa wengine siku za usoni.

Habari yote utakayotoa kukuhusu itawekwa kwa siri. Jina lako au la mtoto wakohalitachapishwa popote bila idhini yako. Hata hivyo, majibu tutakayopata tutayajadili bila kutoa kitambulisho chako au cha mtoto wako kwa mtu yeyote.

KIBALI CHA UTAFITI CHA WATU WAZIMA

Kushirika kwako katika utafiti huu ni kwa hiari yako.

Mimi_____ kutoka _____, nambari ya utafiti _____, nimekubali kuhushiswa katika utafiti huu unaoangalia ugonjwa wa udhaifu wa mishipa kwa walio katika matibabu ya saratani. Nimekubali baada ya kusoma na kufahamishwa na Dkt _____.

Sahihi _____

Tarehe _____

Mimi Dkt _____ nadhibitisha kuwa nimemwelezea mgonjwa yote yanayohusika na utafiti huu

Sahihi _____

Tarehe _____

KIBALI CHA UTAFITI CHA WATOTO

Kushiriki kwa mtoto wako katika utafiti huu ni kwa hiari yako na wa mtoto wako.

Mimi _____ mzazi / msimamizi wa _____ kutoka _____, nambari ya utafiti _____ nimekubali mtoto wangu kuhushiswa katika utafiti huu unaoangalia ugonjwa wa udhaifu wa mishipa kwa walio katika matibabu ya saratani. Nimekubali baada yo kusoma na kufahamishwa na Dkt _____.

Sahihi _____ (mzazi / msimamizi)

Tarehe _____

Mimi Dkt _____ nadhibitisha kuwa nimemwelezea mgonjwa yote yanayohusika na utafiti huu.

Sahihi _____

Tarehe _____

Ikiwa unaswali na ungetaka kupata maelezo zaidi kuhusu utafiti huu, wasiliana na:

Dkt. Mohammed Ezzi (Mtafiti mkuu): 0721211807

Prof N. A. Othieno-Abinya (Msimamizi): +254 2 726300-9

KNH/UoN ERC Secretariat +254 2 726300-9 / Ext 44102

APPENDIX II

TNSn Supplementary Instruction Manual

SENSORY SYMPTOMS:

READ THE FOLLOWING TO THE SUBJECT: I want to ask about your sensory symptoms. I want to concentrate on any change in the past week and any change that is present on multiple occasions or for days at a time. I do not want to ask about sensory symptoms that are longstanding or due to a known disease.

Have you had tingling in your limbs over the past week? Yes or No?

If no, stop.

If yes, is it on multiple occasions or for days at a time?

If no, stop.

If yes, is it in your lower limbs?

If no, continue to upper limbs questions.

If yes, is it on both the right and left sides or just one side?

Is it in your toes, and if so, how high does it go? SCORE form.

If yes, is it in your upper limbs?

If no, stop.

If yes, is it on both the right and left sides or just one side?

Is it in your fingers, and if so, how high does it go? SCORE form.

Are there other reasons for these symptoms? This might include pain due to osteoarthritis, pain due to an injury, pain due to another medical condition, etc.

If the subject has symptoms that are not distal predominant or occur in other distributions or proximally, do not score, but capture as Sensory AE.

MOTOR SYMPTOMS:

READ THE FOLLOWING TO THE SUBJECT: I want to ask about your strength and how well you function. I want to concentrate on any change in the past week and any change that is on multiple occasions or for days at a time. I do not want to ask about difficulties that are longstanding or due to known disease such as osteoarthritis pain, low back pain, or prior injuries.

Do you have any new or worsening symptoms in the feet such as difficulty walking on tiptoes or heels, difficulty clearing your foot over a curb or a step, or operating pedals in the car?

If no, stop.

If yes, are these in the right foot, the left foot, or both feet? If yes, are these new in the last week and have they occurred on multiple occasions or for days at a time? If yes, for each

foot, rate the level of difficulty as slight, moderate, requiring help or assistive device, or unable to do at all.

Do you have any new or worsening symptoms in the legs such as difficulty climbing steps or difficulty standing from a sitting position?

If no, stop.

If yes, are these in the right leg, left leg or both legs? If yes, are these new in the last week and have they occurred on multiple occasions or for days at a time? If yes, for each leg, rate the level of difficulty as slight, moderate, requiring help or assistive device, or unable to do at all.

Do you have any new or worsening symptoms in the hands such as difficulty with buttoning, writing, tying shoe laces, opening jars or turning a key in a lock?

If no, stop.

If yes, are these in the right hand, left hand or both hands? If yes, are these new in the last week and have they occurred on multiple occasions or for days at a time? If yes, for each hand, rate the level of difficulty as slight, moderate, requiring help or assistive device, or unable to do at all.

Do you have any new or worsening symptoms in the arms such as difficulty combing hair, using a hair dryer or reaching to a high shelf?

If nuo, stop.

If yes, all are these in the right arm, left arm or both arms? If yes, are these new in the last week and have they occurred on multiple occasions or for days at a time? If yes, for each arm, rate the level of difficulty as slight, moderate, requiring help or assistive device, or unable to do at all.

AUTONOMIC SYMPTOMS:

READ THE FOLLOWING TO THE SUBJECT: I want to ask about the following symptoms. I want to concentrate on any change in the past week and on any change that has occurred on multiple occasions or for days at a time. I do not want to ask about symptoms that are longstanding or due to another medical condition.

1. Do you have lightheadedness or dizziness when getting up from a lying position? If yes, is this new in the last week and has this occurred on multiple occasions or for days at a time? If yes, SCORE.

2. Do you have difficulty eating a meal because you get full too quickly or get bloated? If yes, is this new in the last week and has this occurred on multiple occasions or for days at a time? If yes, SCORE.

3. Do you have diarrhea that awakens you at night? If yes, is this new in the last week and has this occurred on multiple occasions or for days at a time? If yes, SCORE.

4. Do you have constipation that cannot be attributed to your medications? If yes, is this new in the last week and has this occurred on multiple occasions or for days at a time? If yes, SCORE.

5. Do you have problems controlling your bladder such as needing to go urgently or wetting yourself? If yes, is this new in the last week and has this occurred on multiple occasions or for days at a time? If yes, SCORE.

6. For men only, do you have difficulty with erections that cannot be due to another illness or medication? If yes, is this new in the last week and has this occurred on multiple occasions or for days at a time? If yes, SCORE.

PIN SENSIBILITY

INSTRUCTIONS TO TESTER: Prior to testing, please gain familiarity with the Neuropen (see Manual). This instrument has a sharp point on one end and a cap on the other end. You will show the subject how the testing is done by testing a site with the subject's eyes open. This is most easily done by testing on the face.

READ THE FOLLOWING TO THE SUBJECT: I am going to test how well you can tell a sharp point from a dull point. This is similar to tests a doctor would do in the office. We will start with a practice test on the face so you can learn about the test and then we will test your legs and arms. We will do the practice test with your eyes open so that you can see the difference between the sharp and the dull sensation. During the actual test, your eyes will be closed, and I will touch you 10 times. Each time I touch you, I will ask you whether the touch is sharp or dull. We will start by testing the face with the eyes open.

INSTRUCTIONS TO TESTER: Test the sharp side three times and then test the dull side three times. If the subject gets those correct and seems to understand the test, ask the subject to close their eyes. Test 6 more times: three sharp and three dull in random order. If the subject gets those correct, begin the real testing. If the subject does not get this correct, repeat until they do the test correctly.

READ THE FOLLOWING TO THE SUBJECT: We are now going to begin the actual testing. We are going to start by testing the toe. During testing, I will touch you at a site with one of the stimuli and ask you whether the touch feels sharp or dull. I will present 10 stimuli with a random order of five sharp and five dull. You must get 8 correct to pass. If you do not get 8 correct, we will test another site. Even if you do not feel the touch, please say sharp or dull.

INSTRUCTIONS TO TESTER: Hold the Neuropen perpendicular to the site of stimulation and press until the gauge reaches the 40 g marker for the sharp stimuli. For the dull stimuli, you should also press until the gauge reaches the 40 g marker. Hold each stimulus for 1 to 2 seconds. If the subject correctly identifies eight or more of the stimuli of 10, check the normal box and stop testing that limb. If the subject makes more than two errors in the 10 presentations, check the abnormal box and test the next most proximal location.

Each side is tested separately.

Once you have finished with the lower limbs, repeat starting at the fingertips testing each side.

Locations:

great toe: top surface of the great toe immediately proximal to the nail bed

ankle: top surface of the ankle, midway between the lateral and medial malleolus

knee: overlying the medial epicondyle of the femur

mid-thigh: anterior surface of quadriceps muscle midway between the knee and hip

Finger: top surface of the index finger immediately proximal to the nail bed

Wrist: top surface of the wrist at the midline, approximately 1 cm proximal to the wrist crease

Elbow: overlying the medial epicondyle

Mid-upper arm: anterior surface over biceps muscle

VIBRATION TESTING

INSTRUCTIONS TO TESTER: Prior to testing, please gain familiarity with the Rydel-Seiffer graduated tuning fork. This device will measure vibration sensation and give a number. You will show the subject how the testing is done by testing a site with the subject's eyes open. This is most easily done by testing on the head.

The test is started by strongly pinching the top of the tuning fork using two fingers. Never bang the tuning fork against a hard object. Place the metal bulb at the base of the stem of the tuning fork against the skin at the test site and hold the fork with moderate pressure perpendicular to the test surface. Throughout testing, maintain an unobstructed view of the triangles on each prong. As the vibration intensity diminishes, an optical illusion will cause the appearance of two merging triangles on each prong, with the point of their intersection gradually ascending. Record the vibration intensity on the 0-8 scale at the time the subject reports that he/she can no longer feel the vibration, and enter the intensity to the nearest 0.5 units. If the subject reports that he/she does not feel the vibration at the initial contact, enter a score of 0.

READ THE FOLLOWING TO THE SUBJECT: I am going to test how well you can feel vibration. This is similar to tests a doctor would do in the office. We will start with a practice test on your head, so you can learn about the test, and then we will test your legs and arms. We will do the practice test with your eyes open. During the actual test, your eyes will be closed. Each time I put the tuning fork on you, I will ask you whether you feel it at all and then if you feel it, when you stop feeling the vibration. I know you will still feel the tuning fork itself, a pressure sensation, but I am interested in the vibration feeling. We will start by testing on your head with the eyes open.

INSTRUCTIONS TO TESTER: Start the test as above by placing the vibrating tuning fork on the subject's head. Ask if they can feel the vibration and when it ends. Almost all subjects should score 8. If the subject scores 7 or above and seems to understand the test, ask the subject to close their eyes. Test again. If the subject scores 7 or above, you can begin the real testing. If the subject does not get this correct, repeat until they do the test correctly.

READ THE FOLLOWING TO THE SUBJECT: We are now going to begin the actual testing. We are going to start by testing the toe. During testing, the vibrating tuning fork will be placed on you like we did with your head. Please let me know if you feel the vibration and then when it ends.

INSTRUCTIONS TO TESTER: Start the test as above by placing the vibrating tuning fork on the subject's toe. Ask if they can feel the vibration and when it ends. Record the vibration intensity on the 0-8 scale at the time the subject reports that he/she can no longer feel the

vibration and enter the intensity to the nearest 0.5 units. If the subject reports that he/she does not feel the vibration at the initial contact, enter a score of 0.

If the subject scores normally (see normal values below), do stop testing in that limb and go to the opposite side. If the subject scores in the abnormal range, move proximally.

Locations:

Great Toe: top surface of great toe, immediately proximal to the nail bed

Ankle: top surface of the medial malleolus

Knee: overlying the medial epicondyle of the femur

Hip: overlying the iliac crest

Finger: top surface of index finger, immediately proximal to the nail bed

Wrist: surface of the ulnar styloid

Elbow: overlying the medial epicondyle

Shoulder: overlying the acromion

MWONGOZO WA MAFUNDISHO

Mfumo wa Hisia

Je, umekuwa na upungufu katika miguu yako juu ya wiki iliyopita? Ndio au Hapana?

Ikiwa hapana, acheni

Ikiwa ndio, ni kwa mara nyingi au kwa siku kwa wakati?

Ikiwa hapana, acheni.

Ikiwa ndio, ni katika miguu yako ya chini?

Ikiwa hapana, endelea maswali ya miguu ya juu.

Ikiwa ndio, je, ni miguu miwili, ama moja?

Je, ni katika vidole vyako, na ikiwa ni hivyo, ni juu gani? Fomu fomu .

Ikiwa ndio, ni katika mikono yako?

Ikiwa hapana, acheni.

Ikiwa ndio, je, ni mikono miwili ama moja?

Je, ni katika vidole vyako, na ikiwa ni hivyo, ni juu gani? Fomu fomu.

Mfumo wa musuli

Soma kwa mgonjwa

Je, umekuwa na shida ya kutembea kwa vidole au kuinua juu ya vikwazo kwa wiki iliyopita?

Ikiwa hapana, acheni

Ikiwa ndio, ni mguu moja (kushoto au kulia) au miguu miwili

Je, umekuwa na shida ya kupanda ngazi kwa wiki iliyopita?

Ikiwa hapana, acheni

Ikiwa ndio, ni mguu moja (kushoto au kulia) au miguu miwili?

Je, umekuwa na shida ya kufunga shati, kuandika, kuunganisha lace ya viatu, ama kugeuka kifunguo kwa lock?

Ikiwa hapana, acheni

Ikiwa ndio, ni mkono moja (kushoto au kulia) au mikono miwili?

Je, umekuwa na shida ya kuchanganya nywele ama kufikia rafu ya juu

Ikiwa hapana, acheni

Ikiwa ndio, ni mkono moja (kushoto au kulia) au mikono miwili?

Mfumo wa neva wa kujitegemea

Je, umekuwa na shida ya kizunguzungu kwa wiki iliyopita?

Je, umekuwa na shida ya kusikia kama umeshiba kwa haraka kwa wiki iliyopita?

Je, umekuwa na shida ya kuhara ambao inamfanya uamke usiku kwa wiki iliyopita?

Je, umekuwa na shida ya kuvimbiwa kwa wiki iliyopita?

Je, umekuwa na shida ya kumshikilia mkojo kwa wiki iliyopita?

Kwa mwanamume pekee yake: Je, umekuwa na shida ya kupata nguvu wa mume kwa wiki iliyopita ambao haijasababisha na ugonjwa ama madawa mengine?

Uchunguzi wa neva

Tutaanza kwa kupima vidole. Wakati wa kupima, nitakugusa kwenye tovuti na moja ya msisitizo na kukuuliza kama kugusa kunahisi mkali au wepesi. Nitawasilisha vizuizi mara kumi Lazima ufikie sahihi mara nane. Ikiwa hupata sahihi 8, tutajaribu tovuti nyingine. Hata kama huhisi hisia, tafadhali sema mkali au wepesi. Tutapima kwa kidole kikubwa cha mguu, mguu, goti, katikati ya mguu, kidole cha mkono, mkono, kijiko na kati ya mkono wa juu

Tutaanza kwa kupima vidole. Wakati wa kupima, fikra ya kuunganisha ya vibrating itawekwa kwako. Tafadhali napenda kujua kama unasikia vibration na kisha inakapomalizika. Tutapima kwa kidole kikubwa cha mguu, mguu, goti, pua, kidole cha mkono, mkono, kijiko na bega.

APPENDIX III

CIPN Screening / Eligibility Questionnaire

Date: ___/___/_____

Inpatient or Outpatient Number:		
Clinic or Ward Number:		
Name:		
Sex:	O Female	O Male
Physical Address:		
Contact Number:		
Date of Birth:		
Age:		
Did you have peripheral neuropathy before starting treatment?	O Yes	O No

If the above is yes, excluded from the study.

Clinical Questionnaire

Anthropometric Measures

Height (cm):	Weight (kg):
Body Surface Area (m^2):	
Body Mass Index (kg/m^2):	

Tumor Characteristic

Site of Primary Tumor:	
Tumor Type:	
Stage:	O 1 O 2 O 3 O 4

Treatment Details

Treatment Modality Given (check all that applies):		
☐ Radiotherapy	☐ Surgery	☐ Chemotherapy

Chemotherapy Details:

Type of Drug Given (check all that applies):

☐ Cisplatin	☐ Paclitaxel	☐ Vincristine
☐ Oxaliplatin	☐ Docetaxel	☐ Vinblastine
☐ Carboplatin		

Platinum Drugs Details:

Dose (mg/m^2) per session:
Frequency drug given:
Cumulative dose (mg/m^2):

Risk Factor Analysis

Do you have HIV?	O Yes	O No	O I don't know
Do you have Diabetes Mellitus?	O Yes	O No	O I don't know
Do you drink alcohol?	O Yes	O No	
If Yes, do you drink ≥5 glasses (men) or ≥4 glasses (women) in a single occasion, usually within 2 hours?	O Yes	O No	
Do you or have you ever smoked cigarettes?	O Yes	O No	
If Yes, Did you smoke in the last month?	O Yes	O No	
How many cigarettes have you smoked in your lifetime?	O<100	O>100	

Laboratory Results

Hemoglobin (g/dL):	Sodium Levels (mmol/L):
Potassium Levels (mmol/L):	Creatinine (µmol/mL):
eGFR (ml/min):	Total protein (g/L):
Albumin (g/L):	Aspartate Transaminase (U/L):
Alanine Transaminase (U/L):	Alkaline Phosphatase (U/L):
Bilirubin (mg/L):	Gamma Glutamyltransferase (U/L):

Interpretation Form

Tumor Characteristics

Tumor Site:	
Tumor Type:	
Tumor Stage:	O 1 O 2 O 3 O 4

Neuropathy Profiling

Is there Neuropathy?	O Yes O No
If Yes, What is the grade?	O 1 O 2 O 3 O 4
Grade 1 (TNS Score 2 – 5) Grade 3 (TNS Score 10 – 14)	Grade 2 (TNS Score 6 – 9) Grade 4 (TNS Score >14)

Risk Factor Analysis

Age (years):	O<21 O 21 - 40 O 41 - 60 O 61 – 80 O>81
Sex	O Male O Female
Body Mass Index	O< 18.5 (Underweight) O 18.5 - <25 (Normal) O 25 - <30 O>30 (Obese)
Cumulative Dose (mg/m^2):	
Diabetes Mellitus	O Yes O No
HIV	O Yes O No

Chronic Renal Failure (eGFR <60ml/min/1.73m^2)	O Yes O No
Concurrent Neurotoxic Drug	O Yes O No
Concurrent Radiotherapy and/or Surgery	O Yes O No
Habit to Alcohol Use	O Yes O No
Smoking Status	O Current O Former O Never
Anemia	O Yes O No
Hypoalbuminemia	O Yes O No

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