EFFECT OF HYDRATION WITH ELECTROLYTES SUPPLEMENTATION ON CISPLATIN INDUCED NEPHROTOXICITY AMONG PATIENTS WITH SOLID TUMORS AT OCEAN ROAD CANCER INSTITUTE

Tatu Estomih Lyimo (B.Pharm)

M. Pharm. (Hospital and Clinical Pharmacy) Dissertation

Muhimbili University of Health and Allied Sciences,

October, 2019

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Department of Clinical Pharmacy and Pharmacology

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By,

Tatu Estomih Lyimo (B.Pharm)

A Dissertation Submitted in (partial) Fulfilment of the Requirements for the Degree of Master of Pharmacy (Hospital and Clinical Pharmacy)

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October, 2019

CERTIFICATION

The undersigned certify that he has read and hereby recommend for acceptance by Muhimbili University of Health and Allied Sciences a dissertation entitled, '**Effect of hydration with electrolytes supplementation on cisplatin induced nephrotoxicity among patients with solid tumors at ocean road cancer institute'** in fulfillment of the requirements for the degree of Master of Pharmacy (Hospital and Clinical Pharmacy) of Muhimbili University of Health and Allied Sciences.

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Prof. Omary Minzi (Main Supervisor)

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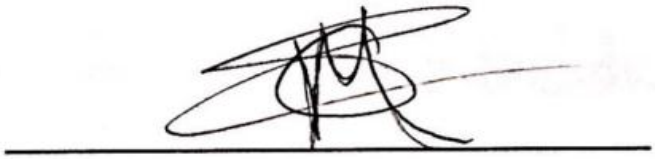
Date



Dr. Christina Malichewe

Co-Supervisors

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Date

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Dr. Francis Furia

Co-Supervisors

_____

Date

DECLARATION

I, *Tatu Lyimo* declare that this dissertation is my own original work and has not been submitted else where for examination, award of a degree or publication.

Signature_____ Date_____

ACKNOWLEDGEMENT

I have been guided and encouraged by wonderful people throughout my study period. I wish to thank you very much. There have been so many I will name just a few.

My sincere gratitude goes to my supervirsors; Professor Omary Minzi, Dr. Francis Furia and Dr. Christina Malichewe for their guidance and assistance, from my first approach with the concept for the clinical trial, throughout the proposal preparation and the outcome assessment to the writing and dissertation completion. Together they have made a near perfect supervisory team.

Special thanks are given to the management and staff at ORCI. There are not enough words to describe your excellent support. Dr. Ndumbalo Jerry, for the site supervision and coordination support, Dr. Nazima Dharsee who grants the authority to conduct a clinical trial at ORCI and organized the training programme for the research staff. Pharmacist Albina, my sister you are so humble. I appreciate your quick response in solving all challenges concerning availability of study drugs. Sister Stellah, my research nurse, thanks for all your hard work. You made this study happen. Dr. John, you have been the pillar of this study by allocating the study drugs. Thanks.

I would like to acknowledge all the staff members of the department of clinical Pharmacy and Pharmacology; Manase Kilonzi, Ritah Mutagonda, Hamu Mlyuka, Alphonce Marriale and Wigilia Mikomangwa for their tireless assistance and encouraging, I learned many principles with regard to the research activities.

I thank my classmates; Sarah, Ritah and Buganda for their encouragement throught my studies. I also thank my colleque George Bwire, Fatma Felix and Bertha Malya for their contributions in my study.

My parents, I owe you appreciation for your understanding, love and prayers.

Finally I am grateful for the sponsorship offered to me by the Ministry of Health, gender, elderly and children that has enabled me to pursue my studies at Muhimbili University of Health and Allied Sciences (MUHAS). Without financial help, the clinical trial and so the Master Degree would not have been possible.

DEDICATION

I am grateful to the almighty God for giving me health and knowledge to carry out this work. I dedicate this dissertation to my husband Mr Shadrack Masalu and children; Hope, Adin and Noela for their love and support, they influenced my life and thinking in a very positive way.

ABSTRACT

BACKGROUND: Nephrotoxicity remains a problem for patients who receive cisplatin based chemotherapy. Electrolyte derangements are known as a complication to chemotherapy with cisplatin and likely to enhance nephrotoxicity.

AIM: To evaluate the effects of pre-hydration with a solution containing magnesium sulfate, potassium chloride and calcium gluconate on cisplatin induced nephrotoxicity in cancer patients receiving cisplatin chemotherapy at Ocean Road Cancer Institute.

METHODOLOGY: 99 patients diagnosed with cancer and who were to receive cisplatin based chemotherapy at ORCI at a dose of ≥50mg were randomly assigned to receive either intravenous electrolyte supplementation plus cisplatin as intervention arm or cisplatin in normal saline alone as control arm. Serum creatinine (SCr) was measured at every visit. The follow-up period was 6weeks. The primary outcome measure was incidence of acute kidney injury grade I or higher as defined by the Common Terminology Criteria for Adverse Events version 4.0.

RESULTS: A total of 99 patients were recruited, where 49 patients (49.5%) were randomized to receive NaCl + electrolytes (treatment group) while 50 patients (51.5%) received NaCl alone (control group). The incidence risk of a grade I or higher Cisplatin-Induced Nephrotoxicity (CIN) was 20.41% (n=10) in the treatment group and 54% (n=27) in the control group. Patients received NaCl alone were 2.6 times more likely to get CIN than those who received NaCL + Electrolyte [Realative Risks (RR); 2.6, 95%CI; 1.5-4.9, $P < 0.0001$]. The most common malignancy was cervical cancer, n = 43 (87.8%) in treatment group and n= 45 (90.0%) in the control group (P = 0.590). The Kaplan-Meier analysis and the log-rank test revealed that electrolytes supplementation was associated with extended survival without cisplatin-induced nephrotoxicity [P = 0.0004; Hazard ratio (HR) 0.3149; 95% CI 0.165 to 0.6011].

CONCLUSION: Hydration with magnesium sulfate, potassium chloride and calcium gluconate decreases the risk of cisplatin nephrotoxicity. A randomized controlled trial with larger sample size is recommended to evaluate the robustiness of this protocol.

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LIST OF ABBREVIATIONS

CBC	Compete Blood Count
CDDP	Cis-diamminedichloroplatinum or Cisplatin/Cisplatinum
CIN	Cisplatin Induced Nephrotoxicity
CP	Cisplatin, Paclitaxel
CrCl	Creatine Clearance
CRF	Case Report Form
GFR	Glomerular Filtration Rate
GLOBOCAN	Global Cancer network
LFTs,	Liver Function Test
NCCN	National Comprehensive Cancer Network
ORCI	Ocean Road Cancer Institute
PID	Participant Identification Number
PTH	Parathyroid Homone
RFTs,	Renal Function Test
ROS	Reactive Oxygen Species
SCr	Serum Creatine
SPSS	Statistical Packages for Social Sciences
WBC	White Blood Cell

DEFINITION OF TERMS

Cancer: Is a group of diseases characterized by uncontrolled growth and spread of abnormal cells

Nephrotoxicity: Is defined as serum creatinine elevation > 1.5 times that at baseline (grade ≥ 1) from 4 to 7 days after injection of chemotherapeutic agent (according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.)

Incidence: Is the number of new cases of the condition over a specified period of time.

Prevalence: Is the proportion of the population that has the outcome of interest at a specific time.

Preventive Strategies: Includes drug and non drug measures used to reduce nephrotoxicity of cisplatin. These include hydration with Normal Saline, forced dieresis with furosemide, using magnesium sulphate, amifostine, and potassium chloride and stopping the drug in cases of kidney damage.

CHAPTER ONE

1.1 INTRODUCTION

Cancer is a health problem affecting many people worldwide. Global burden of cancer is high and it is growing still larger. According to Global Cancer network (GLOBOCAN), about 14.1 million new cancer cases and 8.2 million cancer related deaths occurred in 2012 worldwide compared with 12.7 million and 7.6 million, respectively, in 2008 (1). Cancer has moved from the third leading cause of death in 1990 to the second leading cause behind cardiovascular disease in 2013(2). According to WHO report in 2010, deaths from cancer in the developing world were likely to grow from 6.7 million in 2015 and 8.9 million in 2030 if no action is taken (3).

More than 70% of all cancer deaths occur in developing world. This is because resources for prevention, diagnosis and treatment of cancer are limited (3). ORCI has 3 firms with a total of 270 hospital beds. The average number of new cases per day is 10 to 15 patients. In fact, the true magnitude of the cancer situation in Tanzania is unknown, however more than 3000 new cases are recorded in ORCI-based registry every year; and that is estimated to be only 10% of cancer incidence in the country (4).

Based on incidence rate, solid tumors are the most common type of cancers, and include prostate, breast, cervix, ovarian, head and neck and bladder cancers (2). At present, cisplatin is the most widely used chemotherapeutic agent to treat solid tumors (5). It can be used alone or with other anticancer agents and forms the backbone of majority of chemotherapeutic regimens used in many malignancies: Cisplatin can be used as first-line treatment, as adjuvant, or even as neoadjuvant therapy of other procedures such as surgery or radiotherapy (6). However, severe side effects such as nephrotoxicity, electrolyte disturbances, ototoxicity, neurotoxicity and bone marrow suppression have been reported to accompany its administration(7).

Of these various side effects, nephrotoxicity is of great concern. Studies have shown that the prevalence of cisplatin nephrotoxicity is high, occurring in about one-third of patient undergoing cisplatin treatment (8). It is a dose-limiting toxicity which results into irreversible decline in glomerular filtration rate, and can be life threaterning to the patient. As an altenative, development of cisplatin analogues with less nephrotoxicity but equal efficacy has been attempted and led to the introduction of carboplatin and oxaliplatin into clinical use (9).

In spite of these attempts cisplatin still yields a higher response rate and a better probability of survival than a chemotherapy containing other alkylating agents. Hence cisplatin remains an important component of various chemotherapy protocols due to its efficacy, wide spread availability and affordability (10).

A number of measures have been developed in recent years to reduce or prevent the occurrence of CIN. The main protective measures currently employed in clinical practice are based on avoiding the excessive exposure of kidneys to cisplatin basically by hydration/diuresis, reducing the maximum circulating concentration of ciplatin by fractionation of the dose and slowing the rate of infusion when the renal function is altered (6).

While these approaches have reduced the occurrence of CIN, they have not completely prevented it so the prevalence is still recognized to be high. The worldwide prevalence of CIN is between 28-36% in patients who received a single dose cisplatin ($50mg/m^2$) (11) while it is more prevalent in developing countries. A study in Kenya reported a percentage of occurrence of 58.5%, mostly grade 2 nephrotoxicity among patients receiving first cycle of cisplatin based regimen (8).

The most common electrolyte abnormality associated with cisplatin is hypomagnesemia due to renal magnesium wasting. Others include hyponatremia, hypokalemia, hypocalcemia and hypophosphatemia (12). A study done in Denmark by Lajer et al concluded that cisplatin treatment caused significant Mg and K depletion in the majority of patients and, in most patients, this depletion was observed despite normal corresponding P-values. Therefore, due to

inability to monitor these electrolytes routinely during treatment, routinely introducing Mg and K supplementation in these patients from the start of treatment should be considered (13).
Research on the pathogenesis of cisplatin induced nephrotoxicity during recent years, showed there is growing evidence linking the electrolytes derangement and cisplatin induced nephrotoxicity. It showed that Cisplatin induces magnesium depletion, which in turn enhances cisplatin nephrotoxicity in addition to the direct cytotoxic damage of cisplatin to renal cells **[(14),(15)].** Further more, magnesium depletion leads to impaired sodium, calcium and potassium regulatory mechanisms and cisplatin administration results in further wasting of sodium, potassium, and magnesium (12).

Following these findings, researchers have investigated the protective effect of electrolytes supplementation during cisplatin treatment. Although the results have been variable, some studies demonstrated that electrolytes supplementation added to volume hydration during cisplatin treatment can provide a combinatory strategy to significantly reduced frequency and severity of renal toxicity and show no harmful effects in patients receiving cisplatin treatment (16).

Therefore, the current prospective interventional study sought to establish any potential benefits of electrolytes supplementation in ameliorating cisplatin induced nephrotoxicity.

1.2 LITERATURE REVIEW

1.2.1 Cancer

Cancer is a desease where cells grow abnormally, out of control and in the wrong place. When cells are damaged they can start growing in a way that is not normal. The uncontrolled cells may form a lump called a tumor, may travel inside the blood vessel (leukemia) or in the lymph node (lymphoma). There are four stages of cancer. Stage 1, stage 2, stage 3 and stage 4. Stages explain how much cancer is in a person`s body and where it is located. Stage 1 and stage 2 means that the cancer is in an early phase, still small and responding well to treatment. Stage 3 and 4 show that the cancer cells have travelled in nearby other organs or have spread through the blood vessels and it is more difficult to treat.

It is difficult to know why certain people get cancer and others don`t. However the causes of cancer can be explained by considering things that damage the cells so they can grow into tumours. These insights are termed as risk factors, they include some infections eg HIV, HPV and hepatitis B virus, smoking, unhealthy lifestyle such as being overweight, limited physical exercise, too much alcohol, too much sugar and red meat, not enough vegetables and fruits, pollutions and toxins in the environment. In addition, family history of cancer can be a risk to development of cancer. Chronic inflammations, hypoxia, chemicals, radiations etc may trigger production of Reactive Oxygen Species (ROS). ROS production has been strictly associated with cancer pathogenesis (17).

Cancer pathogenesis may be described as a multistep process including transformation, growth promotion and, malignant progression. During the natural history of cancer a large number of genes, molecules, and pathways contribute first to transformation and promotion then to the manifestation of the malignant cancer phenotype; most of these molecules and pathways interact with reactive oxygen species (ROS) in the cytosol, nucleoplasm, and intra or- ganellar space (17)

A transformed cell is identified by the loss of control of proliferation and deregulation of apoptosis producing an excess of cell number and forming a mass (tumor). The disruption of cell cycle and apoptosis regulation is due to mutations of genes with a gain-of-function

(oncogenes) and a loss-of-function (oncosuppressor genes), both leading to an excessive proliferative signal [(18),(19)]. The presence of ROS is a constant feature in living cells metabolizing O_2. ROS concentration and compartmentation determine their physiological or pathological effects. ROS over production is a feature of cancer cells and plays several roles during the natural history of malignant tumor. ROS continuously contribute to each step of cancerogenesis, from the initiation to the malignant progression, acting directly or indirectly (20).

The three most common type of treatment for cancer are surgery, chemotherapy and radiotherapy. Chemotherapy is the use of strong drugs to kill cancer cells. There are many types of chemotherapy, depending on the type of cancer, stage and the patient. Some times chemo is the only treatment given, but often it is given before or after surgery or together with radio therapy.

1.2.2 Platinum based cancer chemotherapy

Since the discovery of the activity of one of the most successful anticancer compound cis-diaminedichloroplati- num (II)[cis-(NH3)2PtCl2] clinically called cisplatin, thousands of platinum complexes have been synthesized and evaluated for their anticancer activity. However, a few of these complexes have entered clinical trials of which five are currently approved: cisplatin and carboplatin world-wide, oxaliplatin, in a few countries, nedaplatin in Japan, and Lobaplatin in China (9).

Cisplatin is a metallic (platinum) coordination compound with a square planar geometry (Figure 1). It is a white or deep yellow to yellow-orange crystalline powder at room temperature. It is slightly soluble in water and soluble in dimethylprimanide and N,N-dimethylformamide. Cisplatin is stable under normal temperatures and pressures, but may transform slowly over time to the trans-isomer. Cisplatin has a molecular weight of 301.1 gm/mol, a density of 3.74 g/cm3, a melting point of 270° C, a log Kow of -2.19 and a water solubility of 2.53 g/L at 25° C (21)

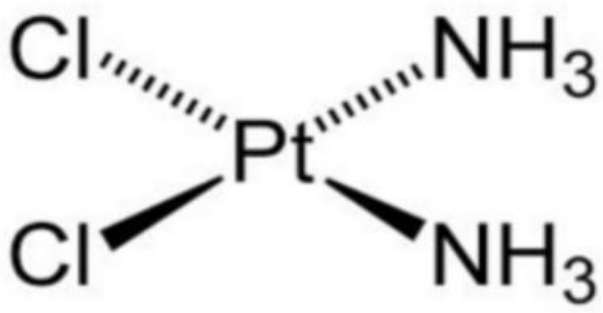

Figure 1: Structure of the anticancer drug, Cisplatin.

Platinum compounds are among the most used DNA-damaging anticancer drugs, Its mode of action has been linked to its ability to crosslink with the purine bases on the DNA; interfering with DNA repair mechanisms, causing DNA damage, and subsequently inducing apoptosis in cancer cells (21). However, they can also be tailored to target biological substrates different from DNA, for instance enzymes involved in cancer progression (22).

Currently, cisplatin is one of the most widely used antitumor drugs. It is highly effective in treating testicular, ovarian, bladder, cervical, head and neck, and small-cell and non- small cell lung cancers [(9)(22)(23)]. Despite its activity in many cancers, cisplatin is ineffective in others e.g. leukemia, renal and gastrointestinal cancers. The major barrier to cisplatin efficacy is perhaps the drug resistance, which can be either intrinsic or acquired. That means for the latter case that many cancers, including ovarian cancer, initially responsive to cisplatin become resistant to it. It also has major toxicity limitations of which nephrotoxicity is the most notable, although nausea and vomiting, peripheral neuropathy, and myelotoxicity can also raise major concerns (9)

Cisplatin Pharmacokinetics

Cisplatin injection USP is a single-dose vial containing 50 mg of Cisplatin as white to light yellow lyophilized powder for reconstitution. For preparation of the infusion solution, it is recommended that the reconstituted solution be further diluted in 1 to 2 L of a compatible infusion solution such as isotonic saline (0.9%NaCl). Cisplatin injection is administered by

slow intravenous infusion. Dosage depends on type of cancer and goal of treatment; it ranges from 20mg/m^2 to 120mg/m^2.
Cisplatin is usualy administered in cycles with rest periods in between. A cycle may last 1 or 2 days. A cycle of treatment may be administered every 1 to 4 weeks. A whole course of treatment may comprise several cycles. Each course of cisplatin is different but usually comprise 4 to 6 cycles.

After injection (oral administration is not possible due to highly gastric acidity) cisplatin binds to plasma proteins and is renally excreted (30-70%) (9). The remaining fraction is transported by the blood in an unaltered form. After passive transport of neutral cisplatin through cell membranes of different organs or tumor cells, it is rapidly hydrolyzed due to the markedly lower chloride concentration in intracellular regions. The hydrolysis reaction is the rate-determining step for DNA binding. Within cells, about 40% of the platinum is present as [cis-Pt (NH3)2Cl(H2O)]+ which is assumed to be the active form of the antitumor agent. Furthermore, the cationic species would be likely to approach and coordinate to the negatively charged DNA (9).

During and shortly after intravenous administration of cisplatin, rapid renal excretion of unbound cisplatin takes place at a clearance rate higher than the glomerular filtration rate, which was attributed to active renal tubular secretion of cisplatin. However, the cumulative urinary platinum excretion at 24 hours after administration of cisplatin is no more than approximately 25% of the administered platinum dose. This may be explained by progressive, strong and partially irreversible binding to plasma proteins (mainly albumin), whereas binding to cellular proteins and nucleic acids also takes place.

Protein binding and cellular toxicity (especially renal tubular toxicity) are influenced by the equilibrium between chlorinated and hydrated platinum species, the hydrated platinum compounds being far more reactive. The reduced renal toxicity following administration of cisplatin in hypertonic saline was ascribed to forcing this equilibrium into the direction of the less toxic chlorinated platinum species (22)

1.2.3 Cisplatin Use in Cancer Management

Cisplatin is a well-known chemotherapeutic drug. It has been used for treatment of numerous human cancers including bladder, head and neck, lung, ovarian, and testicular cancers. It is also effective against various types of cancers, including carcinomas, germ cell tumors, lymphomas, and sarcomas (21). It was discovered to have cytotoxic properties in the 1960s, and by the end of the 1970s it had earned a place as the key ingredient in the systemic treatment of germ cell cancers (24). Among many chemotherapy drugs that are widely used for cancer, Cisplatin is one of the most used ones (24). Due to drug resistance and considerable side effects, combination therapy of cisplatin with other cancer drugs have been applied as novel therapeutic strategies for many human cancers (24). The combination chemotherapy with paclitaxel, cisplatin and fluorouracil is an active and tolerable as first-line and second line therapy in Chinese patients with advanced gastric and esophagogastric (21). Other example of combination therapy with other anticancer drugs includes cisplatin and mitomycin, ciplatin and gemcitabine, cisplatin and doxorubicin, cisplatin and paclitaxel (21).

1.2.4 Cisplatin Toxicity

The majority of therapies for malignant tumours are based on chemotherapeutic drugs with cytotoxic effects, which cause death of tumour cells by direct damage to DNA or by inhibition of cell division. Unfortunately, these drugs are mostly unspecific, therefore, their administration often causes extended tissue toxicity(25). Cisplatin remains the leading chemotherapy agent for the treatment of solid tumors. However severe adverse effects that significantly restrict its clinical use and effectiveness have been reported in literature. Several things are thought to be correlated with adverse effect of cisplatin administration such as dosage, the sites of solid tumors and interaction with other drugs. The pathway of cisplatin-induced toxicity is complex and not completely understood. However, results from several experimental studies suggest a sequential injury pathway, which includes (i) role of membrane transporters (ii) cisplatin conversion to toxic metabolites; (iii) induction of nuclear and mitochondrial DNA damage; (iv) disruption of ionic homeostasis (v) role of oxidative stress and mitochondrial dysfunction; (vi) induction of inflammation; and (vii) activation of apoptotic machinery (26).

The kidney accumulates cisplatin to a greater degree than other organs and is the major route for its excretion. The cisplatin concentration in proximal tubular epithelial cells is about 5 times the serum concentration(27). The disproportionate accumulation of cisplatin in kidney tissue contributes to cisplatin-induced nephrotoxicity (21). Cisplatin is cleared by the kidney by both glomerular filtration and tubular secretion (12). Cisplatin concentrations within the kidney exceed those in blood suggesting an active accumulation of drug by renal parenchymal cells (12).

Different researchers try to explain the mechanisms and risk factors of these toxicity, example Cisplatin Induced nephrotoxicity, it was observed that cisplatin induced nephrotoxicity has multiple pathways. Yao et al(12) reported in 2007 a detailed study on the mechanism of nephrotoxicity induced by cisplatin. They reviewed clinical and experimental literature relevant to CIN and found that unbound platinum is mainly responsible of the injury. It is filtered at the glomerulus and taken up into tubular cells where it is partially metabolized into toxic species which in turn, through different intracellular effects, cause tubular damage and tubular dysfunction characterized by sodium, potassium, and magnesium wasting (12). Indeed, in a study done by Layer et al to evaluate skeletal muscle magnesium (Mg) and potassium (K) during treatment with cisplatin, it was revealed that cisplatin treatment can lead to significant Mg and K depletion in the majority of patients (80%-95%)(13).

In a clinical study done by Arunkumar PA et al on a science behind CIN in human, electrolyte disturbances such as hypomagnesaemia (60%), hypocalcaemia (89%), hypophosphatemia (57%), hypokalemia (95%) and elevations in serum creatinine, BUN were observed after cisplatin- based chemotherapy (24).

Hypomagnesaemia is a well known side-effect in patients receiving cisplatin, the direct injury to magnesium reabsorption in the ascending limb of loop of henle, as well as the distal tubule, is the possible mechanisms behind the cisplatin induced hypomagnesaemia(24). In additional to renal tubular damage, GI losses due to decreased absorption caused by cisplatin induced vomiting and diarrhea. Hypokalemia is also a common electrolyte abnormality occurred

during cisplatin treatment; it is due to increased renal reabsorption capacity observed in response to decreased intestinal absorption of potassium(24)

Hypocalcaemia is another known side effect associated with cisplatin chemotherapy. The possible mechanism behind cisplatin induced hypocalcaemia might be excessive urinary loss of calcium, decreased renal uptake of calcium due to the proximal tubular damage, due to low tissue response of parathyroid hormone and low serum magnesium levels. In a study done by Arunkumar PA et al a significant hypocalcaemia was observed in 16 patients (89%) with various types of cancers. There was significant decrease in calcium level in both female and male patients with carcinoma of oesophagus and cervix after 5 cycles of cisplatin therapy (24). To prevent this complication, electrolyte monitoring and continuous oral calcium substitution was adviced for patients undergoing cisplatin therapy (24). In low serum magnesium levels, parathyroid gland function is abnormal, largely because of impaired release of PTH. In fact, low serum magnesium levels impaire magnesium-dependent adenyl cyclase generation of cyclic adenosine monophosphate (cAMP), which mediates the decreased release of PTH. Hypomagnesemia also alters the normal heteroionic exchange of calcium and magnesium at the bone surface, leading to an increased bone release of magnesium ions in exchange for an increased skeletal uptake of calcium from the serum, leading to low serum calcium level which is a classic sign of severe hypomagnesemia. In addition, because the formation of calcitriol involves a magnesium-dependent hydroxylase enzyme, calcitriol concentrations are reduced in magnesium deficiency, possibly affecting calcium reabsorption.The extracellular fluid (or plasma) calcium concentration is tightly controlled by a complex homeostatic mechanism involving fluxes of calcium between the extracellular fluid (ECF) and the kidney, bone, and gut. These fluxes are carefully regulated by three major hormones: parathyroid hormone (PTH), calcitonin, and 1,25-dihydroxyvitamin D[1,25(OH)2D3]. Important cellular functions are dependent on the maintenance of the extracellular calcium concentration within a narrow range. Disturbances of this tightly regulated homeostatic system leads to disorders of calcium metabolism(28). The biological actions of PTH include (a) stimulation of osteoclastic bone resorption and release of calcium and phosphate from bone, (b) stimulation of calcium reabsorp- tion and inhibition of phosphate reabsorption from the renal tubules, and (c)

stimulation of renal production of 1,25(OH)2D3, which increases intestinal absorption of calcium and phosphate(28). The renal 1Alpha-hydroxylation of 25-hydroxyvitamin D (1,25(OH)2D3) is the major recognized control point in vitamin D metabolism, responding to ambient phosphate concentrations, circulating PTH concentrations, and calcium concentrations. In a drug induced nephtotoxicity or else, the activity of 1Alpha- hydroxylase is abolished. Furthermore, a deficit of calcitriol occurs early in Chronic Renal Failure, which in turn leads to a significant increase in PTH. Phosphorous restriction, together with calcium supplementation, ameliorated the hyperparathyroidism of patients with early renal failure (28)

Understanding the mechanisms of injury especially on the signaling pathways which leads to tubular cell death and inflammation, has led to multiple approaches to prevention. To further understand the mechanism of nephrotoxicity, Taguchi et al (29) examined recent research and reported that exposure of tubular cells to cisplatin activates signaling pathways that are cell death promoting (Mitogen-Activated Protein Kinases [MAPK], p53, Reactive Oxygen Species [ROS]) or cytoprotective (p21). In the meantime, cisplatin induces TNF-α production in tubular cells, which triggers a robust inflammatory response, which further contributing to tubular cell injury and death.

1.2.5 Prevalence of cisplatin – induced nephrotoxicity

In a study done in Indonesia nephrotoxicity among patients receiving Cisplatin regimen was found to occur in more than one-third (>33.3%) of patients after the fourth cycle of chemotherapy and worsened after each cycle despite preventive strategies such as hydration (30). Muthoni et al reported a prevalence of nephrotoxicity at 37 % in a local study of assessment of nephrotoxicity profile of pediatric patients at Kenyata National Hospital(6). Another study in Kenyatta National Hospital Kenya revealed a prevalence of cisplatin - induced renal toxicities of 58.5%, mostly grade 2 nephrotoxicity, with mean glomerular filtration rate of 59.3 ml/min/1.73m2 (±20.6) (8).

In a study done in Osaka Japan it was found that 32% (127/401) of individuals who received cisplatin at a dose of at least 60 mg/m^2 developed acute nephrotoxicity despite the adoption of conventional measures of hydration and osmotic dieresis (31). Although the nephrotoxicity

was transient and reversible in most cases, 43% (55/127) of the patients with acute nephrotoxicity went on to develop irreversible renal failure, indicating that the conventional prophylactic procedures were not sufficient to prevent cisplatin-induced nephrotoxicity in a subset of patients (31). In another study by Songul Tezcan et al, among the patients that receive a single dose (50 mg/m^2) of cisplatin, nephrotoxicity was observed in 28% - 36% of the patients (11).

1.2.6 Risk Factors for Cisplatin Nephrotoxicity

1.2.6.1 Cummulative amount of cisplatin

Dose of cisplatin > 20 mg/m2 significantly increased serum creatinine concentration and cause nephrotoxicity in a dose-dependent manner(32). In a study done by Kayser Caglar *et al* it was found that a cumulative dose of cisplatin is a strong risk factor for the development of nephrotoxicity in patients who receive high doses cisplatin (33). In a study done in Newcastle, nephrotoxicity was less severe in children who received cisplatin courses at a dose rate of 40 mg m^2 than in those who received higher dose rates (34). Another study done at St. Anna Hospital (Ferrara, Italy), the overall results showed that the main factor influencing the severity of the adverse effects was the dosage of cisplatin administered (25). A multivariate logistic regression analysis indicated that a high dose of cisplatin (≥ 80 mg/m^2), was a significant risk factor for cisplatin-induced nephrotoxicity (32). However, the decline of renal function induced by cisplatin ≥60 mg/m^2 was affected by many other factors such as age and hypertension (30).

1.2.6.2 Patient factors

A Comprehensive Review on the Genetic Regulation of Cisplatin-induced Nephrotoxicity, two recent studies, discovered a micro RNA (miRNA) biomarkers from the urine-derived genetic materials, expression level of one or more miRNAs correlates with renal damage (35). Urinary TIMP2·IGFBP7 measured in specimens gathered after platinum based chemotherapy may be a useful tool to early identify patients who are at risk for developing platinum-induced AKI (36). Multivariable analysis revealed that a relatively poor performance status (an Eastern

Cooperative Oncology Group performance status of 2) was significantly associated with an increased risk for cisplatin nephrotoxicity (31)

In a study to analyze the influence of nongenetic factors, patient age ≥50 years was found to increase susceptibility of cisplatin induced renal function decline or nephrotoxicity (37). A multivariate logistic regression analysis indicated that old age (≥ 65 years) was a significant risk factors for cisplatin-induced nephrotoxicity.(32). In a review done by Mehdi Nematbakhsh *et al* suggested that Cis-diamminedichloroplatinum (CDDP) induced nephrotoxicity is gender related and it seems female gender involves with the lower risk of nephrotoxicity after CDDP therapy (38). However, Estrogen may increase the risk of renal toxicity after CDDP therapy, so CDDP therapy in women is recommended when the serum level of sex hormone estrogen in not high in the body (38).

1.2.6.3 Type of tumor

With regard to tumor type, it was found that individuals with esophageal cancer were at a significantly higher risk for cisplatin- induced nephrotoxicity than were those with lung cancer (31).

1.2.6.4 Concurrent medications

NSAIDs which are commonly administered to manage cancer-related pain was associated with cisplatin-induced nephrotoxicity (31). In a study to evaluate the prevalence of Chronic kidney disease (CKD) risk factors in patients who received cisplatin, it was revealed that patients with more risk factors for CKD including NSAID use, tended to have a greater risk of developing cisplatin-induced AKI (39). A multivariate logistic regression analysis indicated that the use of mannitol were significant risk factors for cisplatin-induced nephrotoxicity (32).

1.2.6.5 Presence of other diseases

A study done in Japan revealed that cardiac disease, diabetes mellitus and lower baseline serum albumin (Alb) values conferred a higher risk for nephrotoxicity (40). A multivariate logistic regression analysis indicated that low serum albumin level (≤ 3.5 g/dl) was a significant risk factors for cisplatin-induced nephrotoxicity(32). Recent evidence has

demonstrated that patients with chronic kidney disease (CKD) have an increased risk of developing cisplatin induced acute kidney injury (AKI) (39).

1.2.7 Potential of Electrolyte supplementation for prevention of CIN

Electrolyte supplementation has been found to prevent cisplatin induced electrolyte wasting and hence reduction on the incidence and severity of nephrotoxicity in patient undergoing cisplatin based chemotherapy. A cross sectional prospective study was performed on cancer patients treated in Shafa Hospital, Ahvaz, Iran from November 2009 to March 2010. The patients were under at least 50 mg/m^2 cisplatin. All patients received 1000 mL isotonic saline plus 20 mEq of KCl and 2 g of MgSO4 during 2-3 hours before, and 500 mL of the same solution over the two hours after administration of cisplatin. Hypokalemia and hypomagnesemia were not observed in any patient, and it was concluded that the new protocol was able to decrease the rate of cisplatin nephrotoxicity from about 20% to 6.6%.(41)

Another study done in Kenya by Marius et al(42) to evaluate the effect of intravenous magnesium preloading supplementation on cisplatin-induced nephrotoxicity in cancer patients on cisplatin combination chemotherapy at Kenyatta National Hospital and Texas Cancer Centre, showed that, there was a significant decrease in the incidence of CIN in the Magnesium Preloading Group, compared to the Non-Magnesium Preloading group (12.12 % vs 33.13%, respectively. Further more, intravenous magnesium sulfate supplementation also reduced the severity of CIN as it significantly reduced the mean maximum change in serum creatinine and the mean maximum change in creatinine clearance (42).

1.2.7.1 Possible mechanisms of protective effects of electrolytes supplementation on neprotoxicity:

Most patients undergoing cisplatin treatment develop renal problems, including acute kidney injury (AKI) within days and chronic kidney disease (CKD) later. The major pathological feature of cisplatin nephrotoxicity is tubular cell death in the forms of apoptosis and necrosis. The proximal tubules and the thick ascending limb of the loop of Henle are particularly sensitive to cisplatin injury, partly due to cisplatin uptake and accumulation in these renal tubules at an extremely high concentration via specific transporters. Cisplatin enters renal cells

by passive and/or facilitated mechanisms. Exposure of tubular cells to cisplatin activates signaling pathways that are cell death promoting (MAPK, p53, ROS, and so on) or cytoprotective (p21). Meanwhile, cisplatin induces TNF-a production in tubular cells, which triggers a robust inflammatory response, further contributing to tubular cell injury and death. Cisplatin may also induce injury in renal vasculature, leading to ischemic tubular cell death and decreased glomerular filtration rate (GFR). Together, these pathological events culminate in acute renal failure(43).

By understanding all the mechanisms of renal damage by cisplatin, different approaches have been documented to afford protective effects against cisplatin AKI(12) Scientists thought that inhibition of some of the cell death signaling pathways that are common to normal and cancer cells, for example the DNA damage response leading to p53 activation, would reduce the efficacy of cisplatin in cancer therapy (43). Therefore, identification of molecular targets and development of normal tissue-specific protective strategies without compromising the anti-cancer effects would significantly improve the therapeutic window and efficacy of cisplatin chemotherapy(44). In this regard, Solanki et al. verify an important finding that electrolytes, specifically magnesium supplementation may protect kidneys while enhancing the therapeutic effects of cisplatin in cancer(45).

Electrolytes are naturally occurring elements and compounds in the body. They control important physiologic functions therefore need to be maintained in an even balance for the body to function properly. For example magnesium is an important cofactor for numerous enzymes that regulate a variety of cellular processes. It plays a fundamental role in many functions of the cell, including energy transfer, storage, and use; protein, carbohydrate, and fat metabolism; maintenance of normal cell membrane function; and the regulation of parathyroid hormone (PTH) secretion (46). Magnesium homeostasis is tightly regulated by the kidney. Earlier studies suggest that cisplatin induces hypomagnesemia in 40-90% of patients receiving the treatment and magnesium loss in turn aggravates cisplatin nephrotoxicity (47).

Mechanistically, the renoprotection of magnesium may be associated with its inhibitory regulation on oxidative stress, inflammation, and cell death signaling pathways that have been shown to contribute to the pathogenesis of cisplatin nephrotoxicity.

Solanki et al. has recently suggested a regulatory role of magnesium on renal accumulation of cisplatin (15),(45). Magnesium deficiency promoted cisplatin accumulation in the kidneys by reducing the renal expression of cisplatin efflux transporters including MRP2, MRP4 and MRP6. Conversely, magnesium supplementation reversed the reduction of cisplatin efflux and suppressed cisplatin accumulation (15),(45). Notably, magnesium did not appear to affect the expression of cisplatin transporters and cisplatin accumulation in tumor cells (45). Further studies need to determine how magnesium specifically regulates cisplatin transporters in renal tubular cells and not in tumor cells.

The renoprotective effect of Mg has also been evidenced by Saito and collaborators in cisplatin-treated cancer patients in which premedication with Mg was associated with lower nephrotoxicity measured in terms of changes in serum creatinine and creatinine clearance (48). The same authors investigated the mechanism underlying this effect, finding that Mg prevents the downregulation of renal TRPM6 while inhibiting the organic cation transporter 2 (Oct2); both actions lead to prevention of both Mg wasting and accumulation of platinum.

Regardless of the suggestions that magnesium supplementation may represent a clinically applicable approach for kidney protection during cisplatin chemotherapy, cisplatin has multiple targets in cells and thus blocking a single injurious event may only have partial protective effects in the kidneys. This is clearly shown by the studies conducted thus far. No matter whether inflammation, accumulation, injury signaling, or cell death pathway is blocked, the protective effects can vary from marginal to impressive levels, but rarely complete. Therefore, the partial effects by individual approaches suggest that it may be possible and necessary to use several agents together to achieve a clinically meaningful outcome (43).

Furthermore, an Asian pacific Journal of tropical biomedicines describes a clinical study done by Arunkumar PA et al on a science behind CIN in human. The study aimed to investigate the relationship between serum electrolyte changes and cisplatin induced nephrotoxicity. It was concluded that, acute nephrotoxicity was observed in patients with different types of cancers undergoing cisplatin based chemotherapy due to electrolyte disturbances (24) The study also indicate that the frequency and severity of cisplatin nephrotoxicity may be reduced by slow intravenous electrolyte infusions and maintaining the hydration; before, during and immediately after the administration of cisplatin. However frequent measurement of serum electrolytes and appropriate replacement are recommended (24)

Potassium is the major intracellular cation, responsible for the maintenance of a normal charge difference between intracellular and extracellular environments. Its homeostasis is also maintained by renal and intestinal excretion as well as shifts between the extracellular and intracellular fluid compartments. Since platinum agents are nephrotoxic, emetogenic and diarrheagenic, they have the potential to induce potassium wasting. However, low potassium tends to coexist with low magnesium since magnesium is a cofactor of ATP, with the Mg2+ ion bound to the negatively charged oxygen atoms of the phosphate groups. Therefore, when the concentration of ionized magnesium is decreased due to platinum administration, the Na+–K–ATPase (i.e., sodium potassium pump) is inhibited due to decline in adenosine triphosphate (ATP) induced by hypomagnesemia; as a result, the cells lose potassium, which is excreted in the urine due to release of the Mg2+-dependent inhibition of the potassium channels of the ascending limb cells (47). Together with other functions, potassium supplementation target to maintain the intergrity of this sodium potassium pump and reverse the reabsoption defect induced by cisplatin chemotherapy.

Cisplatin, under low intracellular chloride ion concentrations, has been shown to hydrolyze into variously charged reactive species including monoaqua [cis-(NH) PtCI(HO)]+ and diaquated [cis-(NH)Pt(HO)]2+ forms (49). These hydrolyzed forms of cisplatin have been shown to be 1,000 times more reactive than normal cisplatin, and act through the inhibition of mitochondrial respiration by uncoupling oxidative phosphorylation. This result in an efflux of

calcium from the mitochondria and a temporary increase in the cellular calcium levels, which is thought to play a significant role in the disruption of normal calcium homeostasis, and hence cell function.

Further more, Calcium homeostasis in the extracellular fluid is tightly controlled and defended physiologically. The extracellular fluid (or plasma) calcium concentration is tightly controlled by a complex homeostatic mechanism involving fluxes of calcium between the extracellular fluid (ECF) and the kidney, bone, and gut. These fluxes are carefully regulated by three major hormones: parathyroid hormone (PTH), calcitonin, and 1,25-dihydroxyvitamin D[1,25(OH)2D3]. Important cellular functions are dependent on the maintenance of the extracellular calcium concentration within a narrow range. Disturbances of this tightly regulated homeostatic system leads to disorders of calcium metabolism (28). The biological actions of PTH include (a) stimulation of osteoclastic bone resorption and release of calcium and phosphate from bone, (b) stimulation of calcium reabsorp- tion and inhibition of phosphate reabsorption from the renal tubules, and (c) stimulation of renal production of 1,25(OH)2D3, which increases intestinal absorption of cal- cium and phosphate (28). The renal 1@-hydroxylation of 25-hydroxyvitamin D (1,25(OH)2D3) is the major recognized control point in vitamin D metabolism, responding to ambient phosphate concentrations, circulating PTH concentrations, and calcium concentrations. In a drug induced nephtotoxicity or else, the activity of 1@- hydroxylase is abolished. Furthermore, a deficit of calcitriol occurs early in Chronic Renal Failure, which in turn leads to a significant increase in PTH. Therefore, phosphorous restriction, together with calcium supplementation, ameliorated the hyperparathyroidism of patients with early renal failure (28).

In summary, cisplatin's disruption of calcium homeostasis initiates primary events such as lipid per oxidation and enzyme inhibition. These events damage the cells through mitochondrial damage, inhibition of mitochondrial function, depletion of adenosine triphosphate (ATP) and other cofactors. This probably leads to apoptosis and tissue necrosis. Thus, it seems that elevated calcium levels, via calcium supplementation, may act as another

means of cytoprotection, by competing for binding sites with cisplatin and prevent various toxicities associated with it (21).

1.2.7.2 Adult Electrolyte Replacement Protocols:

Patients must meet the following criteria prior to initiation of the electrolytes supplementation; SCr < 2 mg/dL and body Weight > 40 kg. The electrolyte replacement protocols for all levels of care includes Calcium gluconate, Magnesium sulfate, Potassium chloride, or Potassium Phosphate and these may be ordered individually or in combination (50).

For Potassium supplementation; recommended rate of infusion is 10 mEq/h, maximum rate of intravenous replacement is 20 mEq/h with continuous ECG monitoring (the maximum rate may be increased to 40 mEq/h in emergency situations). Maximum Concentration for Central IV administration = 20 mEq/50 mL and maximum Concentration for Peripheral IV administration = 10 mEq/50 mL. Depending on the baseline Serum Potassium Level, a dose of 10 mEq IV can be administered over 1 hour, 2 to 3 times a day without any need of additional monitoring (50).

For Magnesium; infusions should be no faster than 1gm of magnesium sulfate every 30 minutes. A dose of 2 grams per day Magnesium Sulfate IV can be administered over 1 hour without any need of additional monitoring (50). For calcium gluconate; administration via a central line is preferred; however, it may be given peripherally with adequate IV access. Maximum rate = 3 gm IV over 10 minutes. A dose of 1 gram IV over 1 hour can be given without any addition monitoring (50).

CHAPTER TWO: STUDY OBJECTIVES

2.2 STATEMENT OF RESEARCH PROBLEM

Cisplatin has clinical benefit for several types of solid tumors such as lung, testicular, head and neck, ovarian, cervical and breast cancers. However, its clinical utility is limited by nephrotoxicity, the chief dose-dependent side effect. Electrolyte depletion is also known as a complication to chemotherapy with cisplatin and likely to enhance nephrotoxicity.

Electrolytes supplementation before the administration of cisplatin has been applied as a new hydration protocol in order to reduce the incidence and severity of cisplatin induced nephrotoxicity in patient undergoing cisplatin based chemotherapy. This intervention was also recommended by the National Comprehensive Cancer Network (NCCN) in January 2011. Since its application, several studies have reported on its efficacy and safety. For example, a recent study shows that Magnesium preloading before cisplatin administration significantly reduces cisplatin-induced nephrotoxicity (51). A Systematic Review of Strategies to Prevent Cisplatin-Induced Nephrotoxicity shows that magnesium supplementation (8–16 milliequivalents) may limit cisplatin-induced nephrotoxicity (52)

At ORCI, the pre-hydration protocol with normal saline 3000mls is done as per Tanzania standard treatment guideline(4), However, electrolyte supplementation to all cancer patients receiving cisplatin is not routinely done despite its indication in the Institution Guideline. Currently the normal practice is to give electrolyte supplement with hydration to those patients with signs and symptoms of deficiency only. So it is usually done intermittently at the beginning or in between treatment depending on when the patient develops signs and symptoms of derangement. Therefore, the pre-hydration with solution containing electrolyte supplements as a preventive measure against cisplatin induced nephrotoxicity is not routinely done while the magnitude of nephrotoxicity among patients receiving high dose cisplatin seem to be high (clinical judgment).

However, in Tanzania there is little information to establish an association between electrolytes pre supplementation during cisplatin based chemotherapy and reduction of nephrotoxicity. This limit the acceptance and routine application of this intervention in our

clinical setting while the need for more preventive measures is of such great importance. Yet, there is little information on the incidence of both Cisplatin induced Nephrotoxicity and electrolyte derangement among patients receiving Cisplatin chemotherapy at ORCI. Therefore, this study aimed to evaluate the renoprotective effect of electrolytes pre-supplementation on cisplatin-induced nephrotoxicity among cancer patients receiving cisplatin based chemotherapy at Ocean Road Cancer Institute.

2.3 RATIONALE OF THE STUDY

Since nephrotoxicity is one of the main reasons to stop or change chemotherapy regimen and this toxicity is enhanced by electrolyte depletion, it may be reasonable to add electrolytes (calcium gluconate, potassium chloride and magnesium sulfate) infusions as part of the chemotherapy regimen at the beginning of treatment for the purpose of preventing or reducing the incidence of nephrotoxicity.

This study establishes potential benefits of electrolytes supplementation in ameliorating CIN. By diminishing this major dose-limiting toxicity of cisplatin and reducing the need for dose reduction, this intervention will serve to maintain the therapeutic index, enhance the dose-dependent antitumor efficacy of cisplatin and improve treatment outcomes.

This study therefore, offers direct locally derived evidence for its introduction into practice. Futher more the information obtained will be used by the ministry of health in review of policy guidelines and also save as literature repository for different research community.

2.4 RESEARCH HYPOTHESIS

‘There is no significant difference in the occurrence and severity of nephrotoxicity among patients receiving pre-hydration with a solution containing electrolyte supplementation to patients who do not receive electrolytes prehydration supplementation as a renoprotective measure against CIN’.

2.5 STUDY QUESTIONS

1. Is there any significant difference in the incidence of nephrotoxicity among patients receiving normal saline hydration without electrolytes (control group) to those receiving normal saline plus electrolytes supplementation (intervention group)?

2. What are the risk factors that influence the degree of Cisplatin Induced Nephrotoxicity and electrolyte changes in both comparison groups?

2.6 STUDY OBJECTIVES

2.6.1 Broad objective*:*

To evaluate the effect of pre-hydration with magnesium sulfate, potassium chloride and calcium gluconate on cisplatin-induced nephrotoxicity among cancer patients receiving cisplatin based chemotherapy at Ocean Road Cancer Institute.

2.6.2 Specific objectives

1. To assess and compare the incidence risk of nephrotoxicity among cancer patients on cisplatin-based chemotherapy receiving a pre-hydration solution of normal saline with/without electrolytes supplements.

2. To determine the influence of various risk factors such as age, sex, co-mobidity and concurrent medications on the incidence and severity of Cisplatin Induced Nephrotoxicity in both comparison group.

CHAPTER THREE: METHODOLOGY

3. CONCEPTIAL FRAMEWORK

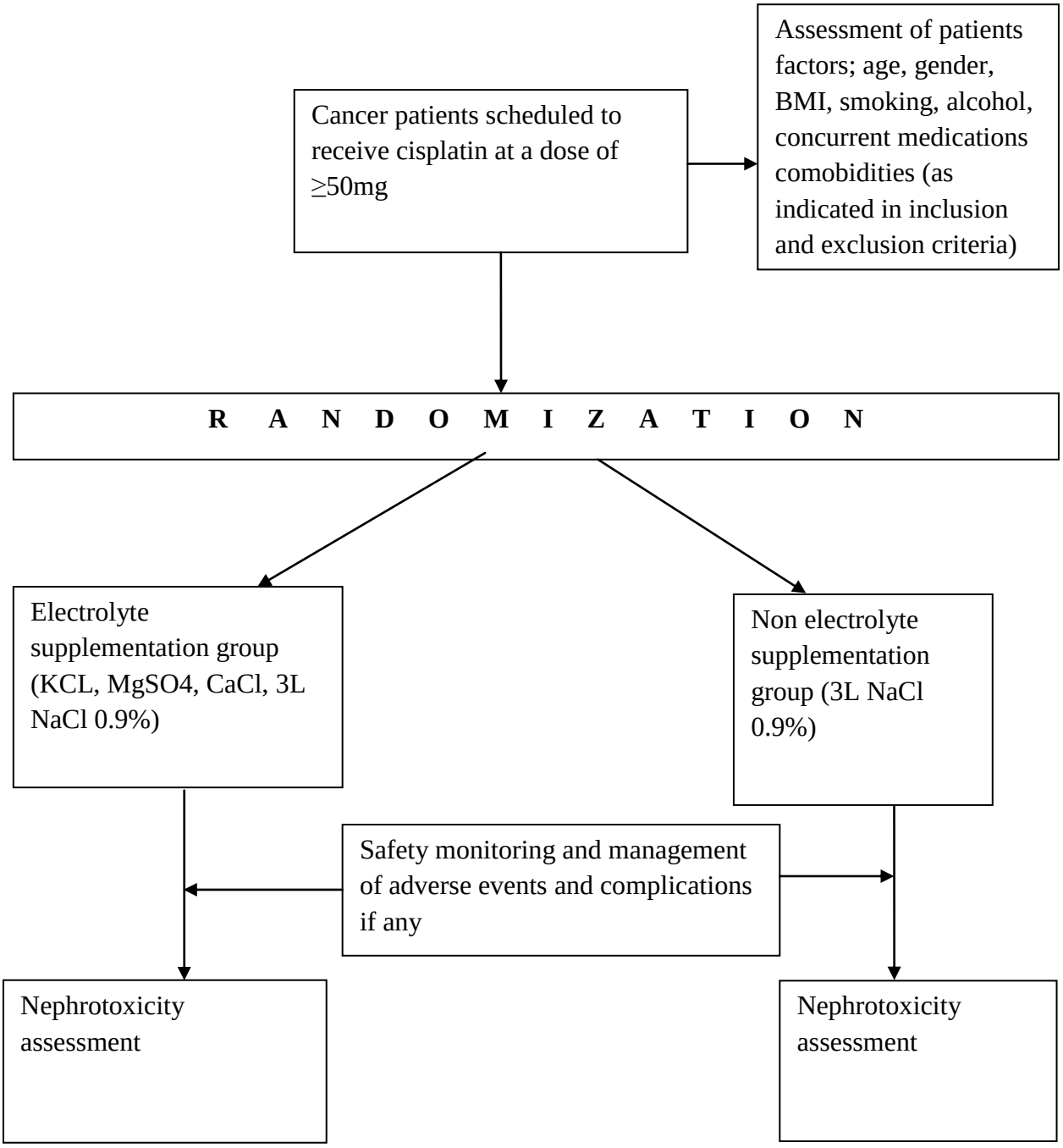

Figure 2: Conceptial framework

3.1 STUDY AREA

The study was conducted in Dar es Salaam at Ocean Road Cancer Institute (ORCI) between January 2019 and June 2019. ORCI is the only public healthy facility in Tanzania where patients can obtain advance comprehensive treatment for cancer. It serves patients across all regions in the country that are referred from other hospitals or institutions for specialized health care.

Due to these high demands for services, ORCI has a number of oncology specialists and is well equipped with advanced diagnostics and treatment facilities. The in patient department is divided in three firms with a total of 270 patient`s beds. Records indicated that there are approximately 10 -15 new cancer patient every day. Infact the true magnitude of the cancer situation in Tanzania is unknown, however more than 3000 new cases per year are recorded in ORCI- based registry(4).

3.2 STUDY DESIGN

This study was a two armed, prospective, randomized controlled, double blind, superiority trial, to evaluate the reno-protective effect of intravenous electrolytes supplementation in reducing the incidence and severity of cisplatin induced nephrotoxicity among chemotherapy-naive cancer patients following the course of standard cisplatin based chemotherapy.

3.3 PARTICIPANT SELECTION

3.3.1Target Population

The participants for this study were chemotherapy-naive patients aged 18-70 years old, diagnosed with solid tumor and who were prescribed to receive cisplatin at a dose of ≥50mg as part of their chemotherapy regimen at ORCI.

Study eligibility criteria were set out to ensure that cancer patients recruited were able to complete the course of treatment. Patient history such as medical and medication history was noted so as to ensure that patients who participated were not likely to develop acute kidney injury or any serious complications requiring urgent.

3.3.2 Patient Inclusion Criteria

Patients were considered eligible for enrolment into this study if they met the following criteria:

- Patient aged between 18 and 70 years
- Patients that had confirmed diagnosis of a solid tumor such as carcinoma of oesophagus, head and neck, cervix, lung and breast.
- Patients who had not received any prior cancer chemotherapy and were to receive their first course of cancer chemotherapy that included cisplatin (≥50mg).
- Adequate renal function prior to start of chemotherapy (baseline SCr ≤ 115.00µmol/L).
- Adequate bone marrow function
    - WBC ≥ 4.00 ×10^3/µl
    - Netrophil count ≥ 2.00 ×10^3/µl
    - Lymphocyte count ≥ 0.8 ×10^3/µl
    - Plateletes count ≥ 100.0 ×10^3/µl
    - Hemoglobin (Hb) ≥ 11.0g/dl
- Adequte Electrolytes balance
    - Serum potassium 3.5 - 5.5 mmol/L
- Signed informed consent

3.3.3 Patient Exclusion criteria

The exclusion criteria for the study were as follows:

- Medical signs and/or symptoms of active infectious disease eg hiv
- Evidence of any other disease/metabolic disorder that in the opinion of the investigator would have put the participant at high-risk of treatment-related complications or prevented compliance with the study protocol. Example uncontrolled hypertension or diabetes mellitus, heart failure, hyperuricemia
- Patients with exposure to contrast media in the two weeks prior to cisplatin administration.

- Patients who had used potentially nephrotoxic drugs (non-steroidal anti-inflammatory drugs, aminoglycosides, amphotericin B, angiotensin-converting-enzyme inhibitors such as captopril and enalapril and angiotensin receptor blockers such as losartan) in the two weeks prior to cisplatin therapy.
- Patients taking oral magnesium, potassium or calcium containing agents
- Patients on drugs that falsely elevated serum creatinine such as sulfonamides
- Pregnant women

3.4 SAMPLE SIZE CALCULATION

The sample size was determined on the basis of the primary hypothesis that the occurrence of CIN among patients receiving the standard cisplatin based chemotherapy together with IV electrolytes supplementation will be significantly different from that among patients on standard cisplatin based chemotherapy and who do not receive IV electrolyte supplementation. In this regard, occurrence of CIN as manifested by the development of AKI grade I or higher (as defined by the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0) was chosen as the primary outcome of interest.

In order to calculate the target sample size, estimated proportions of CIN occurrence in control and intervention group was needed. These figures were estimated from previous studies. The study done in Indonesia nephrotoxicity among patients receiving Cisplatin regimen was found to occur in more than one-third (>33.3%) of patients after the first cycle of chemotherapy and worsened after each cycle despite preventive strategies such as hydration (30). An initial evaluation of protective Effect of Forced Hydration with Isotonic Saline, Potassium Chloride and Magnesium Sulfate on Cisplatin Nephrotoxicity which was done in Iran showed that the new protocol was able to decrease the rate of cisplatin nephrotoxicity from about 20% to 6.6%, a 67% absolute reduction (41).

This study was an initial evaluation which was done in our country; based on previous studies and clinical judgment, we adopted a 33% prevalence of cisplatin induced nephrotoxicity in patients treated with the standard hydration preventive measure in ORCI. With a new intervention of electrolyte supplementation, we assumed an absolute reduction of 67% in the

occurrence of CIN. Therefore, a reduction from 33% to 10.9% was considered clinically significant, with the precision of 0.05, 80% power. This level of potential error and statistical power are conventionally considered acceptable in routine health care research.

The sample size for this study was calculated using the formula below which was described by Chan(53) for estimating sample sizes for superiority trials with a dichotomous outcome of interest:

$$m \text{ (size per group)} = c \times \frac{\pi 1 (1 - \pi 1) + \pi 2 (1 - \pi 2)}{(\pi 1 - \pi 2)^2}$$

Where:

c = 7.9 for 80% power and $\pi 1$ and $\pi 2$ are the proportion estimates

$\pi 1$ = prevalence of nephrotoxicity in the control group which was 0.33 obtained from previous studies and clinical judgment

$\pi 2$ = prevalence of nephrotoxicity in the intervention group which was 0.109

$$m \text{ (size per group)} = 7.9 \times \frac{0.33 (1 - 0.33) + 0.109(1 - 0.109)}{(0.33 - 0.109)^2}$$

$$m \text{ (size per group)} = 7.9 \times \frac{0.2211 + 0.097119}{0.048841} = 51.47$$

Hence a minimum of 52 x 2 = 104 patients was required for this study, 52 in each comparison group. We assumed a non-response rate of 10%, then this number was adjusted upwards to account for an expected 10% loss to follow up rate by using the following formular(53).

$$n' = \frac{(n \times 100\%)}{(100\% - 10\%)} = \frac{104 \times 100}{90} = 115.55$$

The adjusted minimum required sample size was 116; 58 patients in each comparison group.

3.5 RECRUITMENT OF STUDY PARTICIPANTS

3.5.1Recruitment strategies:

Prior to starting recruitment procedure, an announcement of the study was made to the oncology physicians and oncology pharmacists at the study site. Following this announcement, sensitization meetings were held with study staff to improve their understanding of the study aims and protocols, thus ensuring cooperation. In addition, summary of the study recruitment procedures and eligibility criteria were placed in every physician office to ensure adherence with recruitment protocols.

3.5.2 Recruitment procedure

The attending physician initially identified potential participants who were scheduled to receive cisplatin contained chemotherapy regimen. All potential patients were clinically assessed by the physician. Following clinical assessment, blood samples were drawn for baseline investigations. Once the patient met the eligibility creteria, the initial information regarding the study to the patient were given by the attending physician with subsequent counseling by the researcher.

A potentially suitable patient for the study was selected by the research clinician in collaboration with the principal investigator (PI) based on the inclusion and exclusion criteria. These patients were invited and counseled regarding enrollment in the study. They were then be given time to consider the issues and discuss it privately with their relatives. If the patient was willing to take part in the study, then he/she was invited to sign the consent form. Thereafter, his/her file was labeled with a green sticker for easy identification and follow- up by the principal investigator. A signed copy of the consent form was also given to each participant.

Any patient who hesitates to participate or to provide proper information regarding enrollment criteria in question was not enrolled.

Consenting participants were provided with a study information sheet (Apendix I) and the details of the study. When all inclusion and exclusion criteria were addressed and the

eligibility of the participant was confirmed, the participant was randomly assigned to one of the two comparison groups as described bellow.

3.5.3 Randomization Procedures

Randomization took place after written consent was obtained from the study participants. The study needed only chemotherapy naïve new patients therefore participants were recruited, enrolled and randomized as they came to the clinic. It was an ongoing process until the required sample size was obtained. Patients, who fulfilled the eligibility criteria, agreed to participate and signed the consent, were randomly allocated into one of the two study groups; an experimental group that received electrolyte supplementation plus cisplatin and a control group that received cisplatin in normal saline supplementation only.

3.5.3.1Random sequence generation

The allocation procedure was based on a simple random sampling technique. The study biostastistician used a computer program to generate a sheet of allocation sequence, randomly indicating treatment and control arms. Once the randomization sheet was generated, the biostastistician used this sheet to create a sequentially numbered, sealed envelopes each containing a slip indicating which of the two different interventions an assigned patient was to receive. The envelopes were provided securely to the research coordinator (research doctor).

3.5.3.2 Allocation – Implementation and blinding mechanism

Following successful recruitment and enrollment, on day 1 of patient treatment the appropriate envelope in sequence was taken and the patient name was written beside the number of the envelope. This number became the ID number of the patient and it was then written on a sticker which was placed on the file of the patient for easy follow-up. The envelope was then handed over to the chemotherapy pharmacist by the research coordinator (research doctor). Once the envelope had been opened by the chemo-pharmacist the allocation was made open and the details of treatment were noted on the allocation slip contained in the envelope. The envelope and the allocation slip were then kept under lock and key by the pharmacist. No envelopes were opened out of sequence and no envelopes were skipped. The treatment

allocation was kept secret from the patient, investigator, laboratory and study personnel till completion of the study.

Once the group allocation for a patient was made, the chemo-pharmacist (not involved in care of the trial patients and independent of the investigator) prepared the corresponding pre – hydration infusion and labeled the infusion bottles with the patient`s ID and date. The infusion bottles carried no indication of whether they contained electrolytes supplements or not and were made available to the research nurse immediately before administration. The pre-hydration solutions were administered at the same rate for intervention and control group by the research nurse. The principal investigator confirmed that the administration of the pre-hydration infusion was done as planned. The principal investigator was there at chemotherapy ward every day making sure that all patients with files containing green stickers were well attended.

3.6 INTERVENTIONS AND TREATMENT PROTOCOL

3.6.1 Supply of Study Medications

Drugs and medical supplies were provided by the hospital pharmacy in their commercially available form.

The main study drugs were:

- 10 ml of 50 % Magnesium sulfate
- 10ml of 15% Potassium chloride
- 10ml of 10% Calcium gluconate
- Cisplatin 50 mg /50 ml

Other drugs included:

- Granisetron 1mg/ml injection
- Dexamethasone 4mg/ml injection
- Ondansetron 8mg tablet
- Dexamethasone 4mg tablet

3.6.2 Preparation of the intervention and control pre-hydration solutions

- The pre-hydration solutions were prepared by the hospital chemotherapy pharmacist in the chemotherapy mixing unit. A total of 3L Normal Saline infusions were given to each patient in both groups before chemotherapy:
    - For the treatment group, each electrolyte supplement was diluted in a separate liter of normal saline; Potassium chloride (KCl) 20 mmol (1.5g) was diluted in 1L normal saline, Magnesium sulfate 8 mEq (1g) was diluted in 1L normal saline and calcium gluconate (1g) was diluted in 1L normal saline.
    - The control group received 3L normal saline without additional electrolytes

  The solutions were prepared on the day of administration and the pharmacist ensured proper mixing by slowly shaking the bottle for approximately 10 times.

3.6.3 Delivery of treatments and interventions

For Intervention Arm

The most important part in this trial was the administration of Magnesium sulfate, potassium chloride and calcium gluconate as part of the pre-hydration solution. As per the NCCN recommendation; Potassium chloride (KCl) 20 mmol (1.5g), Magnesium sulfate 8 mEq (1g) and calcium gluconate (1g) each diluted in 1litre of normal saline were administered for the intervention group as pre-treament supplementation before administration of cisplatin.

The total volume of pre-hydration solution administered to the patients was equal both in experimental and control group. Each patient received a total volume of 3000 ml of intravenous normal saline 0.9%. Besides pre-hydration, participants were encouraged to drink a minimum of 500 ml of water daily, following administration of cisplatin.

The pre-hydration solutions were administered to the participants in both arms by the research nurse.

Participants randomized to the intervention arm were given the following treatment:

Details on patient treatment

On Day 1

1. Antiemetic prophylaxis

Prior to commencing chemotherapy, standard antiemetic prophylaxis was administered. A 5-HT3 receptor antagonist (granisetron) 3 mg, and dexamethasone (8 mg) mixed together with 50 mL of Normal Saline were administered by 15-minute I.V. infusion as a single dose at least 30 minutes before initiation of chemotherapy.

2. Pre-hydration with MgSO4, KCl plus Calcium gluconate supplementation

Following the antiemetic prophylaxis, Potassium chloride (KCl) 20mmol (1.5g), Magnesium sulfate 8 mEq (1g) plus calcium gluconate (1g) each diluted in 1litre of normal saline as described previously (section 6.3.2) were administered in sequence by IV infusion, where each infusion was run for 2 hours.

3. Cisplatin and Other cytotoxic drugs

The patient-specific cisplatin-based chemotherapy regimens varied from patient to patient as prescribed by the medical oncologist. Some patients receive only cisplatin while others were prescribed a cisplatin-based regimen that contains two or three cytotoxic drugs. The cytotoxic drugs were prepared as per manufacturer's instructions and administered as per prescription. 30minutes after hydration, Cisplatin dose was diluted in 1L of 0.9% NaCl solution and administered by IV infusion over 90 minutes. All participants received a cisplatin dose $\geq$ 50 mg.

4. Post hydration

Following cisplatin administration, 1 liter 0.9% sodium chloride was administered by IV infusion over 2hrs immediately after cisplatin chemotherapy. There-after patients were advised to drink more than 500mls of water every day.

On day 2-5

Delayed antiemetic prophylaxis was prescribed with Dexamethasone tablet 4 mg orally twice daily plus ondansetron tablet 8 mg twice a day. The antiemetic prophylaxis was continued until day 5 after cisplatin administration.

The same intervention was given before commencing chemotherapy for the second cycle of treatment. Treatments given to patients in the intervention group were summarized in the Table below.

Table 1: Intervention treatment: Drugs administered, day, route and rate of administration.

Day	Treatment	Drug	Route	Time
Day 1	Acute antiemetic prophylaxis	Dexamethasone 8mg plus granisentron 3mg in 50ml N/S	iv	30min
	Pre-hydration	Potassium chloride (KCl) 20mmol (1.5g) Magnesium sulfate 8 mEq (1g) plus calcium gluconate (1g) each in 1000 ml Normal saline	iv	120min
	Cisplatin	Cisplatin as prescribed, diluted in 1000ml Normal saline (NaCl 0.9%)	iv	90min
	Other Cytotoxic drugs	Per prescription	Per prescription	Per prescription
	Post hydration	Normal saline 1000ml		120min
Day 2 - 5	Delay antiemetic prophylaxis Additional hydration	Dexamethasone 4mg tablet Ondansetron 8mg tablet fluid intake of > 500mls daily	Orally twice a day Oral	5 days

For Control Arm

Patients who were allocated in the control arm did not receive electrolytes [Potassium chloride (KCl) 20 mmol (1.5g), Magnesium sulfate 8 mEq (1g) and calcium gluconate (1g)]. Instead, they received the same treatment as the intervention group except that their pre-hydration solution contained only Normal saline 0.9% solution.

3.6.4. Participant follow-up

Following administration of treatment on day 1, patients attended visit on day 5 for review which included:

1. Recording any Adverse Experiences
2. Reviewing of antiemetic drugs compliance
3. Recording changes to concomitant medications.
4. Performing physical examination
5. Performing and recording vital signs.
6. Collecting blood for laboratory checkup including Serum Creatinine, urea and complete blood count

On day 6, a fully laboratory workup (hematology & chemistry) was obtained and reviewed to prepare the patient for the second cycle of treatment. On day 7 the patient received treatment again as per study protocol then follow-up and review process was started again. After completion of a fifth cycle, the patient was officially handed over by the principal investigator to the oncology physician for continuation of other treatments.

3.7 DATA COLLECTION

A Case Report Form (CRF) available in Appendix II was used as data collection tool to collect data of interest. It was designed to record all observations and other relevant data for each participant. In this Study, participants attended the clinic weekly for about 4-6 times depending on the number of cycles prescribed. For the purpose of this study; patients were assessed in three consecutive visits post treatment. In every visit of patient assessment, the information was entered into a Case Report form. When the information corresponding to a particular visit was available, study parsonnel entered data from the source document (eg

printed lab results) into a case report form. The data collected in a case report form were as follows:

3.7.1 Social Demographic Information

Participant's socio-demographic information of interest such as gender, age, weight, smoking status, alcohol intake etc, were obtained by patient interview and also assessment of patient history which was written in the patient file. These data were recorded on the CRF at baseline screening.

3.7.2 Concomitant Medications

All concomitant medications and concurrent therapies were documented at baseline/screening on the CRF and reviewed at every visit. Dates of medications, dose, and frequency of administration were all captured.

3.7.3 Medical History

Relevant medical history, including history of current disease, and information regarding underlying diseases were recorded on the CRF at baseline investigation.

3.7.4 Adverse Events Information

Information regarding occurrence of adverse events was captured throughout the study. Duration (start and stop dates and times), severity/grade, outcome, treatment and relation to study drug were assessed and recorded on the CRF.

3.7.5 Laboratory Measurements

Complete Blood Count (CBC), renal function tests (RFT), Urine analysis (Proteinuria) and Serum electrolytes profiles as detailed on section 5 of the CRF, all were performed at baseline screening. Except for serum electrolyte which was only done during baseline investigation, all other tests were also perfomed at every visit of the patient, the results of which were recorded on CRF. All laboratory investigations were performed at ORCI laboratory unity. The first step in acquiring a quality lab test result for any patient is the specimen collection procedure. During the study period, blood specimen was collected by a qualified phlebotomist in the laboratory on day 5 following treatment in every visit of the patient. A phlebotomist used a

needle to collect blood sample from a vein in patient arm. For a Complete Blood Count (CBC), the blood sample was processed by a hematology analyzer whereby WBC, Neutrophils, Lymphocyte, Plataletes and Hemoglobin values were obtained. For renal function tests (RFT) the whole blood was processed by a Start Sensor Express machine while Serum electrolytes were obtained from electrolyte analyzer. Urine was also collected in an appropriate container and the analysis test performed using a dipstick urinalysis whereby the values of protein reading were either negative or trace.

3.8 DATA MANAGEMENT AND ANALYSIS

3.8.1 Data Management

The hard copy data forms were stored in a lockable cabinet in the Principal Investigator's office during collection and the information regarding patient identity was confidential, information such as the name was not included in the data collection forms instead study serial numbers (Patient ID) were used. Completed Case Report Forms were checked for completeness and accuracy by the investigator and then data were entered electronically into a password protected Microsoft excel computer database. All changes to this study database were documented after information had been captured using case report forms. The database was backed up on a separate media, once the updates were done. All forms related to study data were stored in a locked cabinet.

3.8.2 Data Analysis

Statistical analyses were conducted on modified intention - to treat (mITT) bases. All participants who were enrolled and randomized to one of the two groups and received the allocated intervention as prescribed by the study protocol with at least one post baseline investigation were included in the evaluation of primary outcome. Any patient who did not receive the allocated intervention as per study protocol was excluded from the analysis.

The descriptive statistics was done. Baseline characteristics were summarized using measures of central tendency such as means plus standard deviations for normally distributed data and median plus ranges for non-normally distributed continuous variables. Frequencies and

percentages were used to summarize categorical variables. The incidence of acute kidney injury (AKI) between the two groups and association between categorical variables and groups were compared using a chi-square test respectively. In addition, analysis of variance (ANOVA) was used to compare the elevation of Scr level between the groups. Cofounding variables were controlled using regression analysis where variables with $P < 0.2$ on univeriate analysis were entered into multilogistic regression analysis.

The survival analysis was performed using the Kaplan Meier and the different in time to event was analyzed using log-rank test. A value of $P < 0.05$ was considered statistically significant. All analyses were performed using SPSS version 23 and GraphPad Prism 8.2.0.

3.9 ETHICAL CONSIDERATIONS

3.9.1 Informed Consent

To ensure that the patients were given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the trial, the principal investigator before consenting, did a physical talk with the patient explaining the trial in details including reading and describing the consent form. The PI asked questions to ensure if the patient got the information correctly. Patients were also be notified that they are free to discontinue from the trial at any time. The patients were given the opportunity to ask questions and were allowed as much time as they required to discuss and consider the information provided. A copy of Participant Consent form was also given to the patient to read.

3.9.2 Confidentiality

Participant confidentiality was strictly held in trust by the research staff. This confidentiality was extended to cover testing of biological samples in addition to the clinical information relating to participants. The study protocol, documentation, data and all other information generated were held in strict confidence. No information concerning the study or the data was released to any unauthorized third party.

3.9.3 Ethical Clearance

Ethics approval for this study was granted by the Muhimbili University of Health and Allied Sciences Research and Publication committee and the National Institute of Medical Research (NIMR). The Permission to conduct the study in the hospital was granted by the Director of Academic and Research of Ocean Road Cancer Institute.

CHAPTER FOUR

RESULTS

4.1 Participants Enrollment, Allocation And Followup

Between January 2019 and June 2019, 220 new patients were screened of whom 119 were excluded for they did not fulfill the inclusion criteria. Among them 13 patients with age above 70yrs, 97 patients were HIV positive on ART and 9 patients with SrCr exceeding the eligibility limits (>115.00μmol/L) so were excluded. One hundred and one patients (101) were randomized to receive either IV electrolyte supplementation plus cisplatin (n = 49) as intervention arm or cisplatin in normal saline supplementation (n = 52) as control arm.

Two patients in the control group (n = 52) did not show up on day 2 therefore did not receive the complete intervention as prescribed by the study protocol. These two subjects were considered as significant deviations from the protocol and were discontinued from the study. Therefore, a total of 99 patients were followed up and all 99 patients (100%) competed the prescribed cycles of treatment (6weeks follow up) and their data were available for analysis. This is summarized in the flow diagram below (**Figure3**).

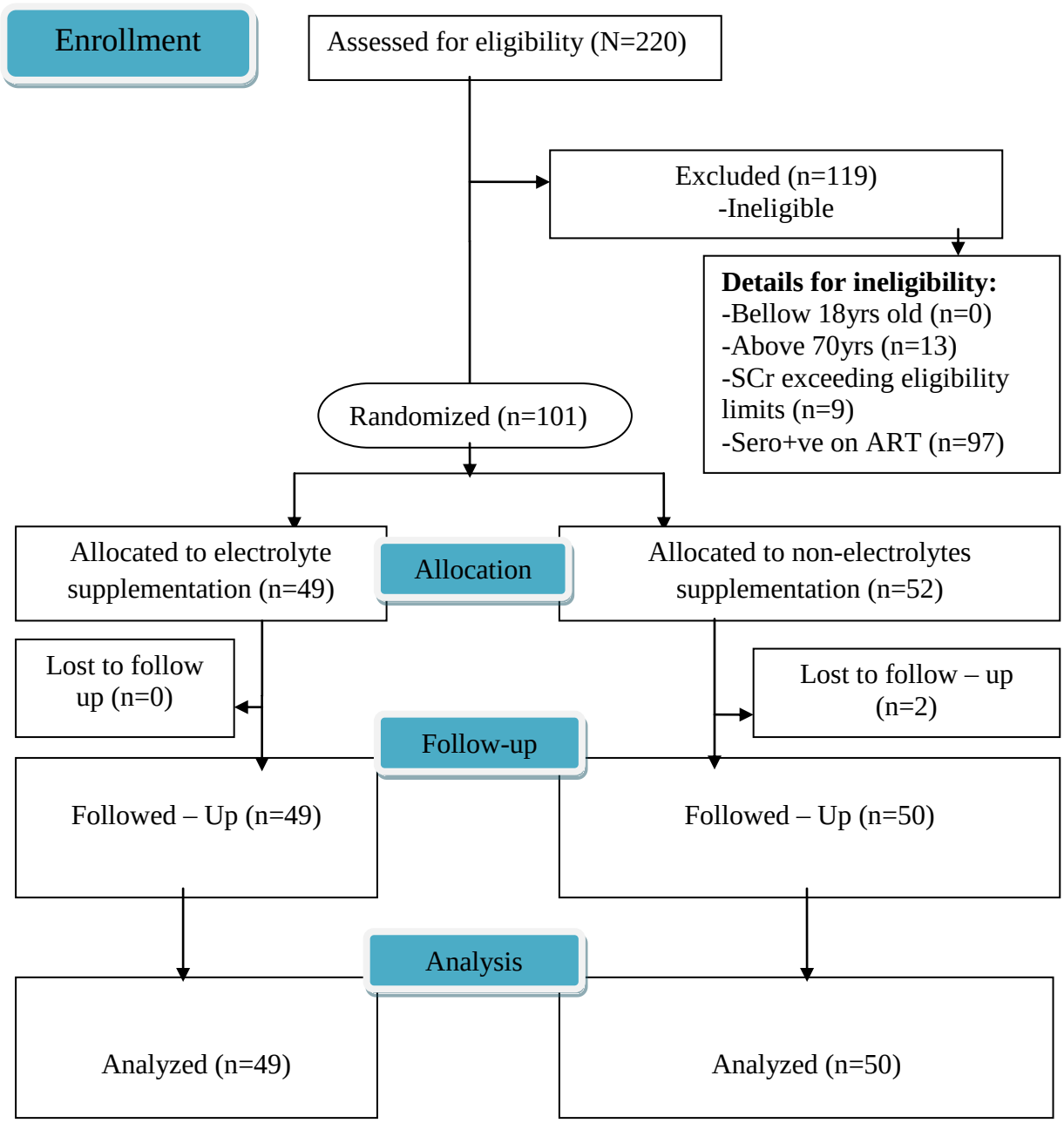

Figure 3: Flow diagram outlining participant enrollment, allocation and follow up

4.2 Participants Baseline Characteristics

A total of 99 patients were recruited, where 49 patients (49.5%) were randomized to receive NaCl + electrolyte (treatment group) while 50 patients (51.5%) received NaCl alone (control group). The majority of participants were females as observed in the treatment group (n = 45, 91.8%) and the control group (n = 48, 96.0%) however the difference was not statistically significant (P = 0.392). In terms of age distribution, the majority of patients in both groups were those with age between 46 – 64 years and the distribution was statistically significant (P = 0.014).

Most of the participants recorded BMI of 18.5 – 24.9 kg/m^2 as observed in the treatment group (n = 23, 46.9%) and in the control group (n = 22, 44.0%) (P = 0.942). The study found most of the patients were non-smokers and non-alcohol users by more than 90% whereas majority of the patients in both groups reported no use of traditional medicines (P = 0.168).

The most common malignancy was cervical cancer, n = 43 (87.8%) in treatment group and n= 45 (90.0%) in the control group (P = 0.590), others included esophageal and oral cancers. In addition, most of the patients reported the use of Cisplatin alone regimen by more than 90% where the most used dose was between 50 – 60 mg in both groups although it was not statistically significant (P = 0.441) (Table 2).

Table 2: Participants Social Demographic and Clinical characteristics according to Electrolyte exposure

Characteristics		**Treatment arms**		P value
		NaCl + Electrolyte n (%)	**NaCl alone n (%)**	
Sex	Male	4 (8.2)	2(4.0)	0.392
	Female	45 (91.8)	48 (96.0)	
Age (years)	30 - 45	18 (36.7)	7 (14.0)	0.014
	46 - 64	21 (42.9)	35 (70)	
	>65	10 (20.4)	8 (16.0)	
BMI (kg/m^2)	<18.5	6 (12.2)	5 (10.0)	0.942
	18.5 – 24.9	23 (46.9)	22 (44.0)	
	25 – 29.9	13 (26.5)	14 (28.0)	
	≥30	7 (14.3)	9 (18.0)	
Smoking status	Yes	2 (4.1)	1 (2.0)	0.552
	No	47 (95.9)	49 (98.0)	
Alcohol use	Yes	4 (8.2)	5 (10.0)	0.753
	No	45 (91.8)	45 (90.0)	
Traditional medicine use	Yes	4 (8.2)	1 (2.0)	0.168
	No	45 (91.8)	49 (98.0)	
Co-mobidity	Yes	6 (12.2)	6 (12.0)	0.640
	No	43 (87.8)	44 (98.0)	
Type of cancer	Cervical	43 (87.8)	45 (90.0)	0.590
	Esophageal	4 (8.2)	1 (2.0)	
	Oral	1 (2.0)	2 (4.0)	
	Others	1 (2.0)	2 (4.0)	
Chemotherapy regimen use	Cisplatin alone	47 (95.9)	46 (92.0)	0.418
	Cisplatin contained regimen	2 (4.1)	4 (8.0)	
Cisplatin dose (mg)	50-60	25 (51)	25 (50)	0.441
	61-70	20 (40.8)	15 (30)	
	71-80	2 (4.1)	7 (14)	
	81-90	0	0	
	>90	2 (4.1)	3 (6)	

4.3 Comparison of SCr level between the two treatment arms

The SCr level between the treatments arms were compared in terms of follow-up days (day 0, 7, 14, 21 and 28). At day 7 there was a slightly difference between the treatment arms although it was not statistical significant (P > 0.05). But at day 14 and 21, the difference in SCr elevation between those in NaCl + Electrolyte arm as compared to those who received NaCl alone was statistically significant (P = 0.0001). However, when the provision of electrolytes was stoped at day 21 the follow-up on day 28 the Scr level became comparable between the treatments arms (Figure 4).

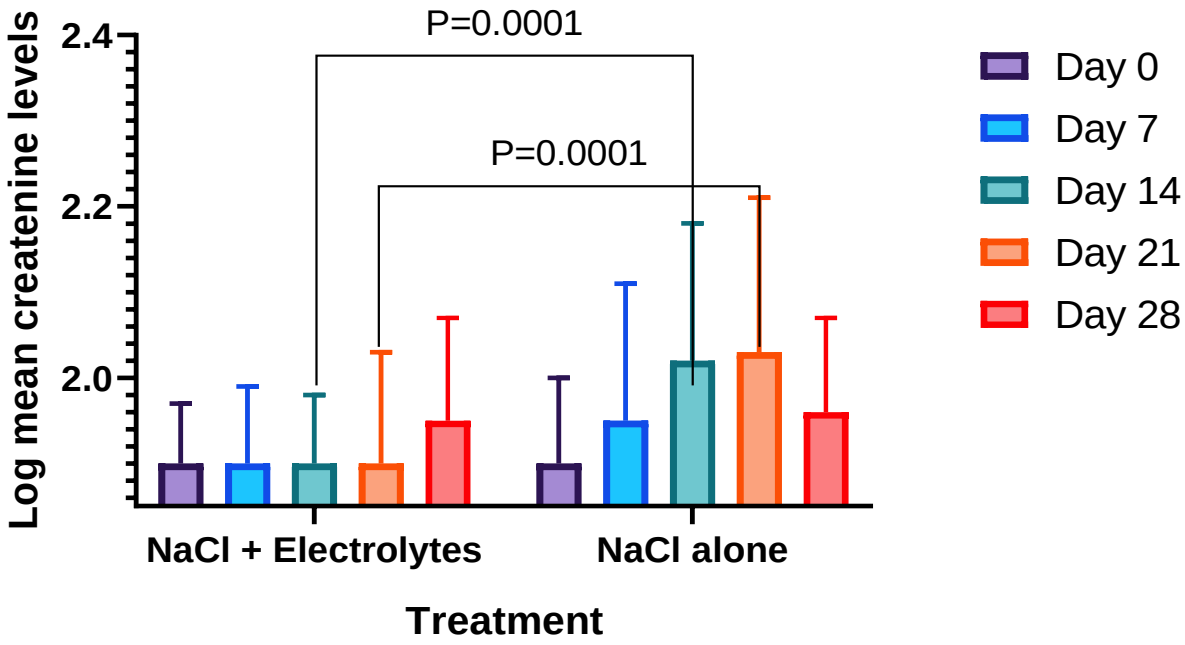

Figure 4: SCr levels between the two treatment arms

4.4 Incidence of Cisplatin - Induced Nephrotoxicity

On the basis of serum creatinine data collected, all patients who developed cisplatin - induced nephrotoxicity (CIN) in each comparison group were identified in every day of treatment. Analysis showed that in each day of treatment the incidence risk of CIN is higher in the NaCl alone group compared to the NaCl + Electrolyte group (Figure 5).

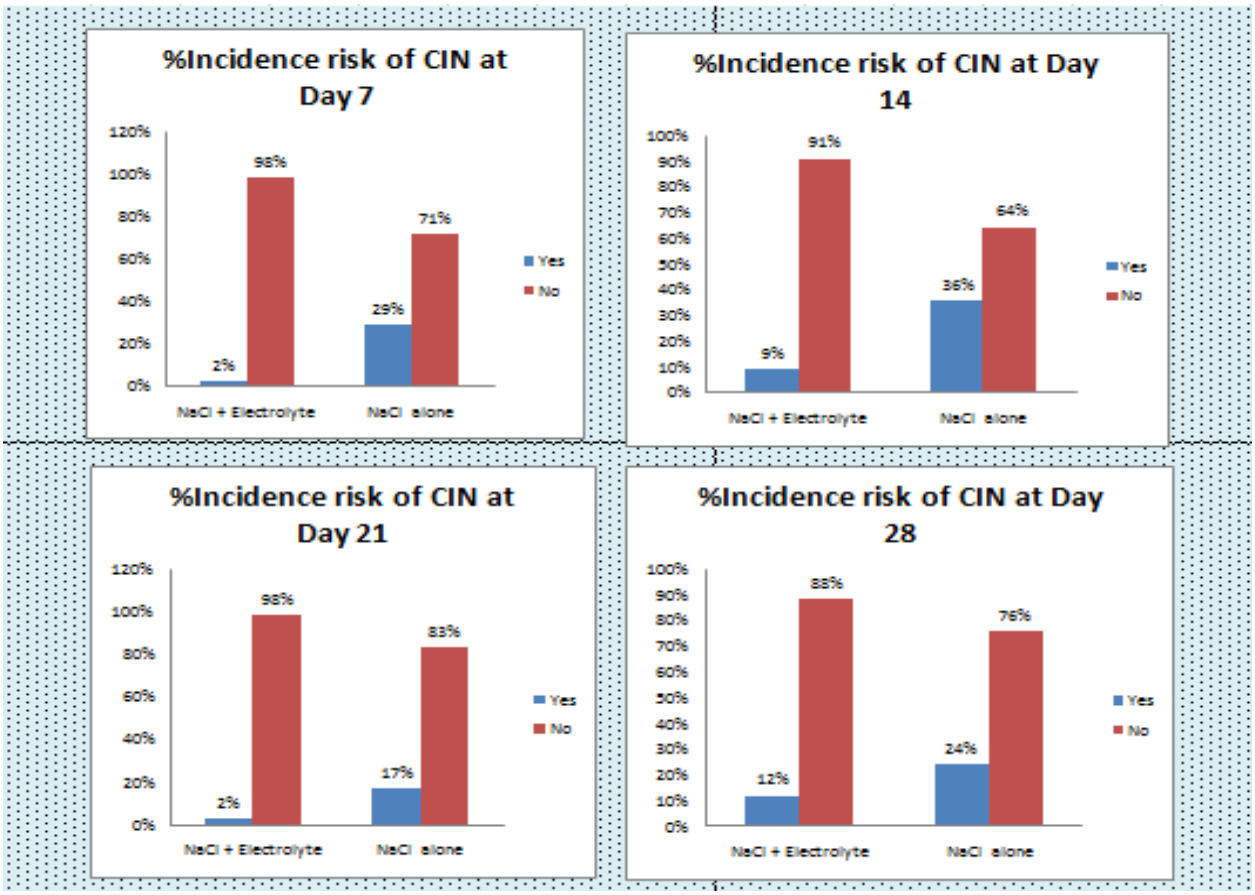

Figure 5: Incidence of CIN (CTCAE Grade I and above) in the NaCl + electrolyte group and NaCl alone group

4.5 Cumulative Incidence Of Cisplatin - Induced Nephrotoxicity

The incidence risk of a grade I or higher cisplatin-induced nephrotoxicity was 20.41% (n=10) in the NaCl and electrolyte group and 54% (n=27) in the non-electrolyte (NaCl alone) group (Figure 6). Patients received NaCl alone were 2.6 times more likely to get CIN than those who received NaCL and Electrolyte [Realative Risks (RR); 2.6, 95%Confidence Interval (95%CI); 1.5-4.9, P < 0.0001].

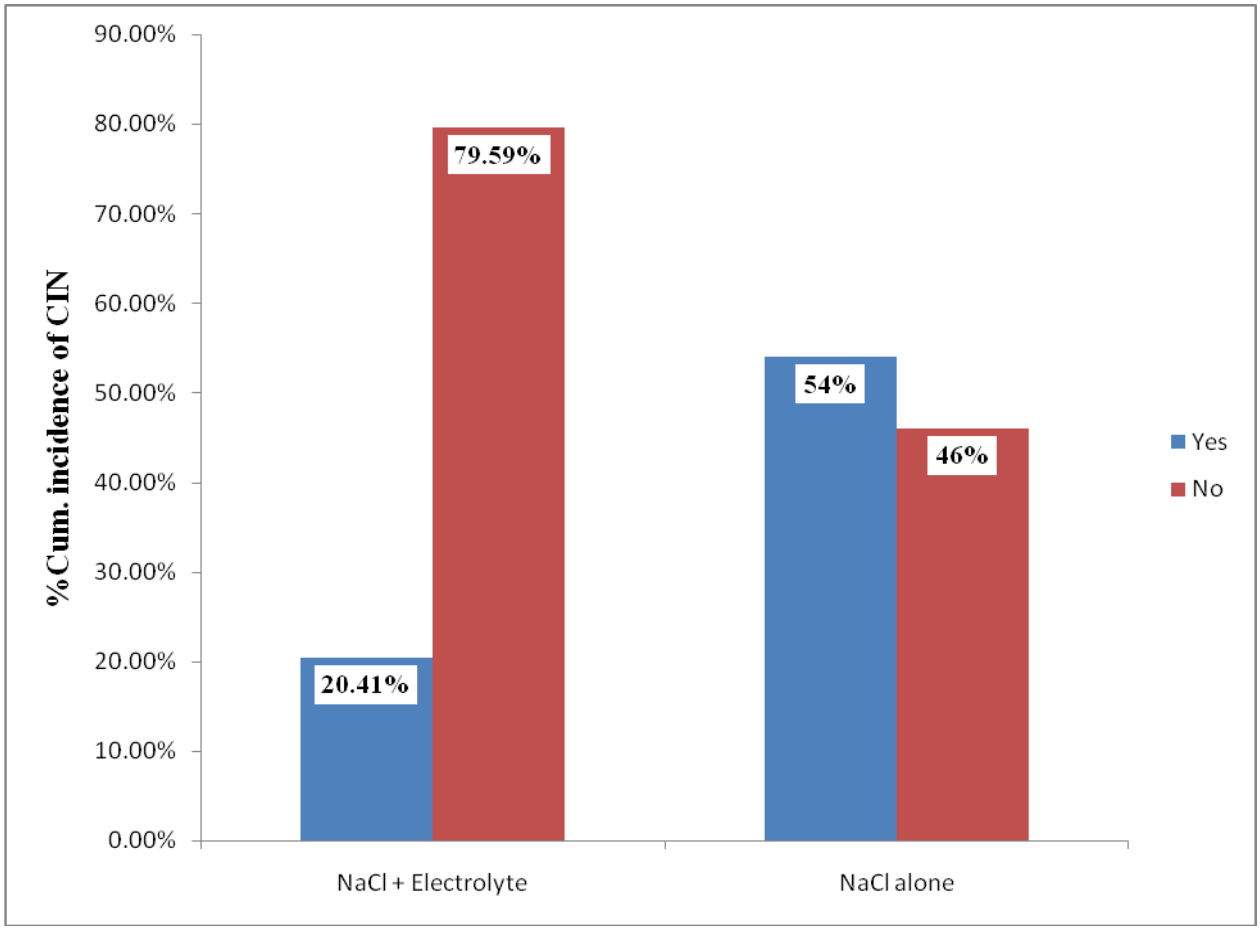

Figure 6: Cumulative Incidence of CIN (CTCAE Grade I and above) in the NaCl + electrolyte group and NaCl alone group

4.6. Assessment of adverse events

In assessing the adverse events between the groups (NaCl plus Electrolyte vs NaCl alone) the study found no statistical differences between the two groups ($P > 0.05$). Example diarrhoea was reported to 29 patients (59.2%) in NaCl plus Electrolyte group while 32 patients (64%) were reported in the group who received NaCl alone ($P = 0.622$) (Table 3).

Table 3: Table of adverse events reported during the study

Adverse event	Treatment arms		P value
	NaCl + Electrolyte n (%)	NaCl alone n (%)	
Diarrhoea	29 (59.2)	32 (64.0)	0.622
Vomiting	48 (98.0)	46 (92.0)	0.176
Anemia	1 (2.0)	1 (2.0)	-
Leucopenia	4 (8.2)	5 (10)	-
Neutropenia	1 (2)	3 (6)	-
Thrombocytopenia	1 (2)	1 (2)	0.157
Lymphopenia	2 (4.1)	2 (4)	-

-: Not estimable

4.7. Survival rate between the two treatment arms

The time from first dose of cisplatin-based chemotherapy to development of CIN was compared for the patients in the two treatment arms using the Kaplan Meier analysis (Figure 7). The analysis showed that survival rate for the NaCl+electrolyte group was consistently higher than that for the NaCl alone group at each point of analysis. The log-rank test revealed that electrolyte supplementation was associated with extended survival without cisplatin-induced nephrotoxicity [P = 0.0004; Hazard ratio (HR) 0.3149; 95% CI 0.165 to 0.6011].

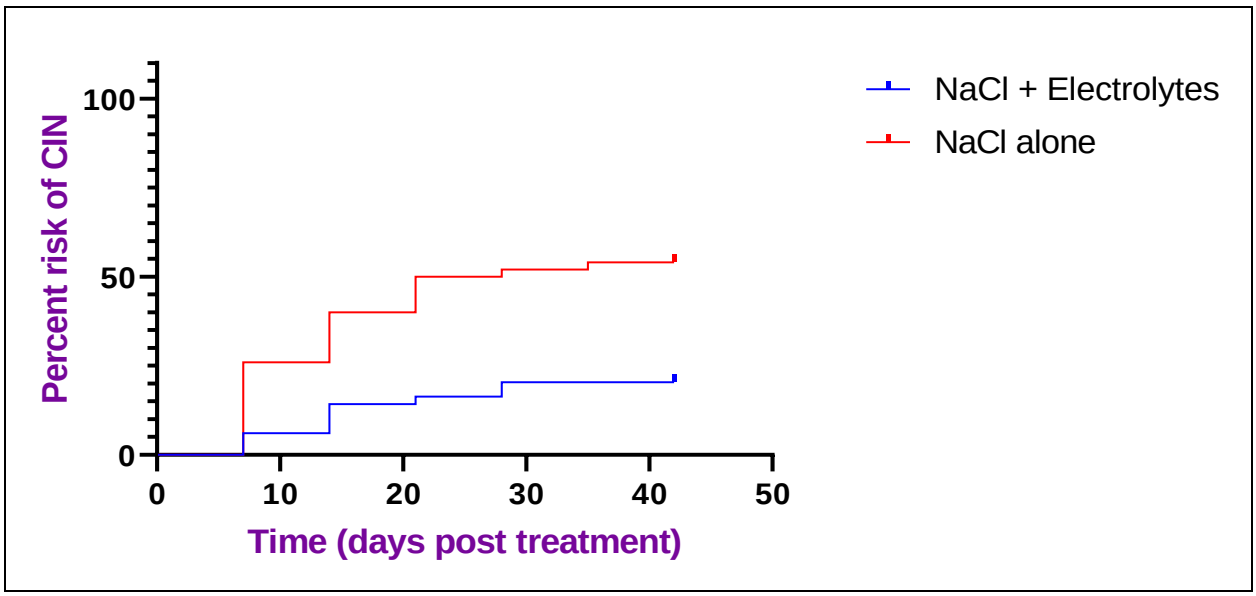

Figure 7: Kaplan Meier survival curves showing the comparison of time to CIN (survival rate) between the two treatment groups.

4.8. Comparison of blood components between the two treatment arms

The blood components such as white blood cells, neutrophills, lymphocytes, blood platelets and hemoglobin where compared between the two arms based on followup days. However, the differences between the groups were not statistically significant for blood components in all follow-up days (P >0.05).

4.9. Determinants of cisplatin induced nephrotoxicity

Factors with p-values less than 0.2 in bivariate analysis were entered into logistic analysis regression. All factors were found not associated with CIN when logistic regression was performed (P > 0.05) (Table 4). Furthermore, all factors were not estimated when entered into multilogistic regression analysis.

Table 4: Logistic regression analysis of determinants of CIN

Factor		Odds Ratio (OR)	95%CI, P value
Age (years)	30 - 45	0.9	0.3-3.1, 0.847
	46 - 64	0.9	0.3-2.8, 0.943
	>65	-	-
Sex	Male	-	-
	Female	1.2	0.2-6.9, 0.833
BMI (kg/m^2)	<18.5	0.2	0.0-1.4, 0.105
	18.5 – 24.9	0.4	0.1-1.2, 0.093
	25 – 29.9	1.3	0.4-4.3, 0.724
	≥30	-	-
Alcohol use	Yes	-	-
	No	0.3	0.1-1.1, 0.071
Cigarette smooking	Yes	0.8	0.0-9.5, 0.883
	No	-	-
Traditional medicine use	Yes	0.4	0.0-3.7, 0.424
	No	-	-
Type of cancer	Cervical	1.3	0.1-14.4, 0.0853
	Esophageal	0.7	0.0-18.0, 0.7
	Oral	-	-
	Others	-	-

-: Not Estimated

CHAPTER FIVE: DISCUSSION, CONCLUSION AND RECOMMENDATIONS

5.1 Discussion of results

To the best of our understanding this is the first study to be undertaken in our settings. In the current study we analyzed the preventive effects of intravenous electrolytes (magnesium, potassium and calcium) supplementation on cisplatin-induced nephrotoicity (CIN) in cancer patients who received cisplatin dose of at least 50mg/day. We found that 20.41% (10/49) of patients who received intravenous electrolyte supplementation developed CIN where-as 54% (27/50) was found among those who did not receive intravenous electrolyte supplementation. As a result IV electrolyte supplementation significantly reduced the incidence risk of nephrotoxicity (P= 0.0001).

This study agrees with a clinical study done in India by Arunkumar et al to investigate the relationship between serum electrolyte changes and cisplatin induced nephrotoxicity (24). It was concluded that, frequency and severity of cisplatin nephrotoxicity may be reduced by slow intravenous electrolyte infusions and maintaining the hydration; before, during and immediately after the administration of cisplatin [(24),(13)].

Nephrotoxicity has been shown as a frequent major side effect of cisplatin chemotherapy which manifest with hypomagnesemia, hypocalcemia, hypokalemia and acute decline in CrCl or even chronic renal disfunction [(43),(12),(54),(55),(13)]. Several mechanisms have been proposed for renal disfunction following exposure to cisplatin, including tubular epithelial cell toxicity, vasoconstrictions in the renal microvasculature, oxidative stress, inflammatory responses and electrolyte inbalance [(24),(27),(5)]. Although the limitations of serum creatinine for the early detection and accurate estimation of renal injury are widely known, it is still be used as a marker to detect acute kidney injury (AKI). In AKI, serum creatinine does not accurately reflect the GFR because the patient is not in steady state. Serum creatinine is also influenced by tubular creatinine secretion and by nonrenal factors such as muscle mass, liver function, and nonrenal (gastrointestinal) elimination (56). Furthermore, sepsis reduces production of creatinine which blunts the increase in serum creatinine, thus limiting the early detection of acute kidney injury (56). In this study, Serum creatinine is used clinically to

detect and evaluate acute kidney injury (AKI). This is because several novel biomarkers of kidney injury and function such as Plasmacystatin C and trace protein are still under investigation yet proven to be superior to creatinine (56). As in most cases cisplatin induced renal disfunction is irrevessible thus more effort to prevent this toxicity is mandatory. Different preventive measures of cisplatin nephrotoxicity have been investigated and in many studies they have been shown to be moderately promising [(57),(58),(59),(60)].

To our knowledge, this is the first randomized controlled trial to report the protective effect of magnesium, potassium and calcium given at the dose of 8mEq, 20mmol (1.5g) and 1g respectively and just before the administration of cisplatin-based chemeotherapy. Many studies reported the use of magnesium supplementation alone in a dose of 8 to 60 mEq [(14),(61),(45),(62)], few reported the use of magnesium and potassium [(41),(31)] including administration before and/or after cisplatin.

However the dose, method and findings in this study are consistent with those of a prospective study by Seyed et al (41) where patients received KCL and MgSO4 in isotonic saline during 2-3 hrs before chemotherapy and saw a significant decrease on the incidence of cisplatin induced nephrotoxicity and a retrospective study by Yoshida et al (63) where the median number of administered cycle was four and the analysis indicated that magnesium preloading significantly reduced ciplatin induced nephrotoxicity [odds ratio: 0.262; 95% Confidence Interval: 0.106 – 0.596].

As previously reported [(30),(31)] CIN is generally manifested as an increased in serum creatinine level (SCr) in accordance with Common Terminology Criteria for Adverse Effect (CTCAE) version 4.0. Intravenous electrolyte supplementation when evaluated in the current study on the basis of SCr level was shown to be associated with a reduced renal toxicity induced by cisplatin. The difference in SCr elevation between those in NaCl + Electrolyte arm as compared to those who received NaCl alone was statistically significant (P = 0.0001).

Therefore, our findings are consistent with the results of a prospective study by Oka et al (64) where by patients in the treatment group showed no significant difference between pre and post treatment SCr levels.

The Kaplan Meier survival estimates analysis was conducted to compare the pattern of survival rates over time from the first day of cisplatin administration to the end of the follow up period between the two groups. The pattern of survival between the two groups was found highly significant using the log-rank test ($P = 0.0004$).

The statistical significant found between the two survival curves indicate the benefial effects of electrolyte supplementation in extending the time to development of CIN. In addition the survival curves in both treatment groups revealed that CIN mostly occurs within 10 days following cisplatin administration. This is in line with previous studies as well [(65),(43)].

A number of risk factors for cisplatin nephrotoxicity have been identified including dose and dose frequency, older age, female sex, smoking and pre-existing renal insufficiency [(49),(32),(34),(37)]. In the current study, all factors were found not associated with CIN when logistic regression was performed ($P > 0.05$). Furthermore, all factors were not estimated when entered into multilogistic regression analysis.

This is likely because of the small number of smokers (3.03%) in the sample size and most patients aged between 46 – 64 years, the old aged patients (above 70yrs) were excluded from the study, also the gender was not comparable in the sample size as male participants were very few (6.06%) compared to females (93.94%). In addition a great proportion of patients involved as participants in this study were cervical cancer patients (88.9%) of whom, cisplatin was used in chemoradiation therapy as a radiosensitizer in small doses of $40mg/m^2$.

5.2 Conclusion

Intravenous electrolyte supplementantion is significantly associated with reduced frequency of renal toxicity in cancer patients treated with cisplatin-based regimen. The protective effect of electrolyte infusion can be seen in limitation of serum creatinine level elevation and in extending the time to development of nephrotoxicity. Electrolyte supplementation therefore appears to have a protective mechanism that limits renal tubular injury induced by cisplatin.

This treatment added to the current stratergies may be quite beneficial for reducing the neprotoxicity profile of cisplatin in patients treated with cisplatin based regimen, resulting in increased chemotherapeutic efficacy of cisplatin in clinical practice. This in turn will have a very high impact on the treatment of solid tumors as it well known that cisplatin still remains a drug of choice in a number of solid tumors.

The data from this study provide strong and direct evidence in support of the application of intravenous electrolyte supplementation just before administration of cisplatin as a preventive measure of cisplatin induced nephrotoxicity.

5.3 Study Limitations

Electrolyte status was assessed only at baseline investigations to make sure patients that we studied had electrolytes levels within the recommended ranges. The study therefore was not able to determine the impact of electrolyte supplementation by comparing changes in electrolyte profiles among patients in the two comparison groups or to evaluate the association between hypomagnesemia, hypokalemia or hypocalcemia and cisplatin induced nephrotoxicity.Thus admitting that, further study is required to explore the mechanism of electrolyte derangement in association with decline in kidney function.

Blood Urea Nitrogen (BUN) is a major parameter to access renal function. However no BUN evaluation was done to cancer patients at ORCI making it impossible to calculate important values such as GFR.

Some patient’s characteristics and clinical data such as comobidity and concomitant drugs relied on pre-recorded information in the patient files and therefore incomplete records from the files greatly hindered availability of these data.

5.4 Recommendations

Based on the difference in the incidence risk of CIN among the control group (54%) and the treatment group (20.41%), the absolute reduction in percentage of nephrotoxicity is remarkable and this ability of electrolyte supplementation to protect against the renal toxicity warrants further investigations with larger sample size.

Nevertheless, some patients were put on preventive strategy for nephrotoxicity (treatment group) but still developed CIN, supporting the need for further studies aimed at identifying complete preventive measure against CIN. The improvement of the use of cisplatin in clinical practice will be more beneficial for patients in developing countries as cisplatin is cost-effective compared to other platinum derivatives.

Specific recommendations to ORCI; As part of preventive strategy against cisplatin induced nephrotoxicity; 8 mEq magnesium sulfate, 20 mmol potassium chloride and 1g calcium gluconate should be routinely supplemented during each cycle of Cisplatin based regimen.

A routine laboratory workup of electrolyte profile, CBC, liver and renal function test should be ordered and performed precisely prior chemotherapy especially cisplatin based regimen.

Finally, we strongly recommend a larger randomized controlled trial to evaluate the robustiness of this protocol and to allow for analysis of all the variables identified as predictor factors of CIN.

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APPENDIX I: Consent Form
Participant Information Sheet /Participant Consent form (English version)

INFORMED CONSENT FORM

ID NO | | | |

Research Study Title:

PROTECTIVE EFFECT OF HYDRATION WITH ISOTONIC SALINE, POTASSIUM CHLORIDE, MAGNESIUM SULFATE AND CALCIUM GLUCONATE ON CISPLATIN INDUCED NEPHROTOXICITY AMONG PATIENTS WITH SOLID TUMORS AT ORCI

This is a randomized controlled trial, a type of research study. Your study doctor will explain the randomized controlled trial to you. These kinds of trial include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your doctor. You are being asked to take part in this study because you have cancer and as part of your management, you are going to receive treatment that includes the drug cisplatin.

Why is this study being done?

The purpose of this study is to compare the effects of a new protocol of hydration containing magnesium sulfate, potassium chloride and calcium gluconate with a standard hydration protocol which does not contain magnesium sulfate, potassium chloride and calcium gluconate. These electrolytes are given as a supplement to correct or prevent electrolyte deficiency which is a side effect of cisplatin administration. This study is being done to find out if giving electrolytes supplementation before the administration of cisplatin can reduce the occurrence and the degree of nephrotoxicity (damage to the kidneys) in patients with cancer who are undergoing cisplatin-based chemotherapy. In this study, in addition to your cancer chemotherapy, you will get either the hydration regimen with electrolytes or the hydration regimen without electrolytes to prevent nephrotoxicity**.**

How many people will take part in the study?

About 116 people will take part in this study

Who is carrying out the study?

Institution: Department of Clinical Pharmacy and Pharmacology, School of Pharmacy;
Muhimbili University of Health and Allied Sciences (MUHAS)
P.O.Box 65001, Dar-Es-Salaam. Phone number: 2150302-6

Investigator: Ms Tatu Estomih Lyimo, Pharm.D. , Master of Pharmacy Student in Clinical Pharmacy; MUHAS. Contact 0713094689; email: tatulyimo@gmail.com

Main Supervisor: Prof. Omary Minzi: Department of Clinical Pharmacy and Pharmacology, School of Pharmacy; MUHAS.Contact 0759000115; email: minziobejayesu@gmail.com

Co-supervisors: Dr. Christina Malichewe; Departement of Oncology; MUHAS
Dr. Nazima Dharsee; Ocean Road Cancer Institute
Dr. Jerry Ndumbalo; Ocean Road Cancer Institute

What will happen if I take part in this research study?

Before you begin the study, you will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be decided by your study doctor.

1. History and physical exam and an assessment of your ability to carry out activities of daily living (which will include questions such as whether you are able to feed, bathe, and dress yourself)

2. Blood tests to monitor response to treatment.

3. You will be asked to give information about any other medications that you may be taking

During the study

If the exams, tests and procedures show that you can be in the study, and you choose to take part, you will be randomly assigned into one of two study groups. Random assignment means that you will have an equal chance of being placed in either of the groups. Neither you nor your study doctor will be able to choose the group you will be in. The patients in one study groups will receive the hydration regimen with electrolytes, while the other group will receive the hydration regimen without electrolytes.

After the start of treatment, you will need the following tests and procedures

<u>On day 7 and day 21 after administration of cisplatin</u>

- You will be asked to give information about any medications that you may be taking
- You will be asked about any side effects that you may be experiencing
- Vital signs will be monitored to detect any abnormality.
- Blood and urine tests to measure response of the body to treatment will be performed.

How long will I be in the study?

The treatment will have about 8 cycles for both group 1 and group 2 depending on the type of tumor. However, the study will evaluate only 2 to 3 cycles. The study doctor will ask you to visit the office for follow-up examination and to collect the blood for laboratory analysis at day 7 and day 21 after the start of treatment.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely. The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, researchers don't know all the side effects that may happen. Side effects may be mild or serious. Your health care team may give you medicines to help lessen side effects. But side effects of electrolyte supplements occur rarely at the doses that are administered to patients who undergo cisplatin chemotherapy. This is because low levels of electrolytes in the blood is a frequent complication to chemotherapy with cisplatin affecting up to 90% of patients who do not receive prophylactic electrolytes supplementation(54). Any abnormalities related to treatment such as electrolyte inbalance and/or acute kidney injury will be managed with electrolyte supplementation and dialysis.

Risks and side effects related to the pre-hydration solution containing magnesium sulfate, potassium chloride plus calcium gluconate, most of them are rare and minor include: Sweating, Flushing and Dizziness. Some are rare, but serious includes: difficulty breathing, low pulse rate, bradycardia (abnormally low heart rate) hypotension (abnormally low blood pressure) and depressed reflexes but all these will be managed apropriatetly.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. There is proof that preloading electrolyte supplementation can decrease nephrotoxicity (kidney damage) but strong evidence in our setting is not available yet. We do know that the information from this study will help researchers learn more about electrolyte preloading supplementation as an additional treatment for preventing nephrotoxicity in patient undergoing cisplatin based chemotherapy for cancer. This information could also help health care team to consider adding electrolytes as part of treatment right from the beginning of chemotherapy with cisplatin, to prevent nephrotoxicity.

What other choices do I have if I do not take part in this study?

Your other choice will be to get treatment or care for cancer without being in the study. Talk to your study doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

Information will be kept in a password-protected database. We will do our best to make sure that the personal information in your medical record will be kept private. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution. A copy of the signed Informed Consent form will be given to you.

What can I do if I have a complaint or a concern?

If you have questions about this study, you should contact the office of Director of Research and Publications, Muhimbili University of Health and Allied Sciences, PO Box 65001, Dar es Salaam. Phone number: 2150302-6. Any complaint will be investigated promptly and you will be informed of the outcome.

This information sheet is for you to keep

Participant Consent

I have read the above information sheet and understood it. The nature of the study has been explained to me. I voluntarily agree to participate in the study.

_____ _____ _____ / _____ / ____

Signature of Participant **Name (***First name and Surname)* **Year Month Day**

Address: _____ **Telephone:**

Investigator's statement

I, the undersigned, have explained to the participant the procedures to be followed in the study and the risks and benefits involved.

_____ _____ _____ / _____ / ____

Signature of Person Conducting **Name (***First name and Surname)* **Year Month Day**

Consent Discussion

_____ _____ _____ / _____ / ____

Signature of Investigator **Name (***First name and Surname)* **Year Month Day**

Department of Clinical Pharmacy and Pharmacology, School of Pharmacy; Muhimbili University of Health and Allied Sciences (MUHAS) P.O.Box 65001, Dar-Es-Salaam. Phone number: 2150302-6. Email; tatulyimo@gmail.com

_____ _____ _____ / _____ / ____

Signature of Witness **Name (***First name and Surname)* **Year Month Day**

Relationship of Witness to Research

Participant/investigator_____

Consent form (Kiswahili version)

FOMU YA MAELEZO KUHUSU UTAFITI/FOMU YA IDHINI YA KUSHIRIKI UTAFITI

NAMBA YA UTAMBULISHO: ☐☐☐

Fomu ya utafiti wenye kichwa cha habari:

UWEZO WA MADINI YA ZIADA YA MAGNESIA, POTASIA NA CALCIUM YANAYOTUMIKA KABLA YA KEMOTHERAPI KATIKA KUPUNGUZA MATUKIO NA KIWANGO CHA SUMU YA FIGO KWA WAGONJWA WA KANSAWANAOPEWA DAWA AINA YA PLATINI

UTANGULIZI

Hili ni jaribio la aina ya uchunguzi wa kiutafiti. Daktari wako wa utafiti atakueleza vizuri kuhusu jaribio hili. Jaribio hili hujumuisha tu wale watu wanaochagua kushiriki. Tafadhali tafakari kuhusu kushiriki kwako katika utafiti. Waweza kujadili na marafiki, familia yako au na daktari wako wa binafsi kuhusu uamuzi wako. Unaombwa kushiriki utafiti kwa maana unaugua saratani, na kama mojawapo ya matibabu yako, utapewa tiba ya saratani yaani kemotherapi inayojumuisha dawa ya aina ya platini.

KWA NINI UTAFITI UNAFANYWA?

Madhumuni ya utafiti ni kulinganisha athari (iwapo ni kubwa au chache ama sawia) za mfumo mpya wa uvuvio (hydration) wenye madini ya magnesia, patasium na calcium na mfumo kawaida wa uvuvio usio na madini haya. Madini haya hutolewa kama kiambatisho kurekebisha au kuzuia ukosefu wa madini ambao ni athari itokanayo na upewaji wa kemotherapi iliyo na Platini. Uchunguzi unafanywa kubaini ikiwa upewaji wa kiambatisho cha madini kabla ya kemotherapi yenye platini huweza kupunguza matukio na kiwango cha sumu ya figo (nephrotoxicity) kwa wagonjwa wenye saratani walio katika kemotherapi iliyo na Platini. Katika utafiti huu,utapata pamoja na kemotherapi, utaratibu wa matibabu ya uvuvio(hydration) yaliyo na madini ya magnesia, potassium na calcium au yasiyo na madini haya ili kuzuia sumu ya figo(nephrotoxicity).

NI WATU WANGAPI WATASHIRIKI UTAFITI?

Takriban watu mia moja kumi na sita watashiriki katika utafiti huu.

NANI ANAENDESHA UTAFITI?

Chuo: Idara Ya Famasia Na Mazoezi Ya Ufamasia, Kitivo Cha Ufamasia; Chuo Kikuu Cha afya cha Muhimbili

Mtafiti: **Tatu Estomih Lyimo**, Shahada ya Famasia, Mwanafunzi Wa Uzamivu Katika matumizi ya Dawa kwenye Matibabu, Chuo Kikuu Cha afya cha Muhimbili. Simu: 0713094689; Barua Pepe:tatulyimo@gmail.com

Msimamizi: **Profesa Omary Minzi**: Idara Ya Famasia Na Mazoezi Ya Ufamasia. Kitivo Cha Ufamasia; Chuo Kikuu cha Muhimbili. Pamoja na:

Dkt. Christina Malichewe: Idara Ya Matibabu ya Saratani; Chuo Kikuu cha Muhimbili

Dkt. Nazima Dharsee: Kituo Cha Matibabu Ya Saratani, Hospitali ya Ocean Road

Dkt. Jerry Ndumbalo: Kituo Cha Matibabu Ya Saratani, Hospitali ya Ocean Road

JE NITAFANYIWA NINI IWAPO NITASHIRIKI UTAFITI?

Kabla ya utafiti, unahitaji kuwa na yafuatayo: Utafanyiwa uchunguzi, majaribio na taratibu ili kujua iwapo unafaa kushiriki utafiti. Uchunguzi huu, majaribio na taratibu ni huduma za kawaida za saratani na huwa zinafanywa hata kama hutajiunga kushiriki utafiti. Iwapo umekuwa na huduma hizi hivi karibuni basi si lazima zirudiwe. Hili litategemea na daktari wako wa utafiti.

1. Historia na uchunguzi wa kimwili, na tathmini ya uwezo wako kushiriki shughuli za kila siku (maswala kama; iwapo unaweza kujilisha,kuoga na kuvaa nguo).
2. Uchunguzi wa kimaabara wa damu na mkojo utafanyika ili kupima Maendeleo ya dawa katika matibabu.
3. Utaulizwa kutoa habari kuhusu matibabu yoyote uliyo nayo sasa.

WAKATI WA UTAFITI

Katika uchunguzi, majaribio na taratibu, ikaonyesha kwamba una sifa stahiki za kushiriki na umekubali kushiriki, utanasibishwa katika makundi. Kunasibishwa ina maana kuwa utawekwa katika kundi kupitia bahati nasibu. Mchanganuo wa namba utatumiwa kukuweka katika mojawapo ya vikundi. Sio wewe wala daktari mtaamua kundi lako. Utakuwa na nafasi sawa ya kuwekwa

katika vikundi baada ya kunasibishwa. Siku ya kwanza kabla ya matibabu, makundi yote mawili yatafanyiwa uchunguzi wa awali wa damu dhidi ya sumu ya misuli inayopatikana kwenye damu (serum creatinine) pamoja na kiasi cha madini yaliyopo kwenye damu.

Baada ya kuanza matibabu, utahitajika kufuatiliwa afya yako kwa karibu ikiwa ni pamoja na uchunguzi wa kimaabara kama ifuatavyo: Siku ya 7 na siku ya 21 baada ya kupewa dawa zenye mjumuisho wa chembe za platini (cisplatin). Utapokuja:

- Utaulizwa kutoa taarifa kuhusu matibabu yoyote uliyo nayo wakati huo.

- Utaulizwa kuhusu athari/maudhi madogomadogo ya dawa unayopata.

- Dalili za mapigo ya moyo, nyuzi joto mwilini, mkimbio wa damu na kiwango cha kupumua zitaangaliwa ili kutambua kama kuna uharibifu wowote.

- Uchunguzi wa damu kupima kiwango cha sumu itokayo kwenye misuli (creatinine) na vimelea vya nishati/madini mwilini (electrolytes) ili kutathmini maendeleo ya dawa katika matibabu.

NI KWA MUDA GANI NITASHIRIKI UTAFITI HUU?

Matibabu yatachukua wastani wa mizunguko minane kutegemea na aina ya tatizo ulilonalo. Hata hivyo utafiti huu utatumia mizunguko 2 hadi 3 tu. Wakati wa matibabu haya, daktari atakutaka kuja hospitali kuchukua vipimo vya damu na mkojo kwa minajili ya jaribio la ufuatiliaji wa maendeleo ya dawa. Hii itakuwa siku ya saba na kisha siku ya ishirini na moja baada ya mwanzo wa matibabu katika kila mzunguko.

JE NAWEZA KUJIONDOA KATIKA UTAFITI?

Naam, waweza kuamua kujiondoa wakati wowote. Mwambie daktari wa utafiti ikiwa una fikra za kujiondoa au kuacha. Atakueleza jinsi ya kujiondoa kwa usalama. Daktari wa utafiti anaweza kukusimamisha ushiriki wakati wowote iwapo anaamini ni kwa minajili ya manufaa yako, ikiwa huzingatii sheria au ikiwa utafiti umesimamishwa.

NI ATHARI AU HATARI ZIPI NITARAJIE NIKISHIRIKI UTAFITI?

Unaweza kupata maudhi madogomadogo (side effects) ukishiriki utafiti huu. Kila mmoja anayeshiriki ataangaliwa kwa ukuaribu na kwa makini endapo kuna athari zozote. Hata hivyo watafiti hawafahamu aina zote za athari zinazoweza kuibuka. Athari zinaweza kuwa ni kidogo au kubwa. Ikibainika, wahudumu wa afya wanaweza kukupa dawa ili kupunguza au kuondoa athari hizo.

Hata hivyo athari za madini haya ni nadra kujitokeza katika vipimo vilivyokubalika kupewa wagonjwa wanaoelekezwa katika kemotherapi yenye chembe za platini. Sababu ni kuwa, upungufu wa madini haya ni tatizo la kila mara kwa tiba ya saratani iliyo na platini, upungufu huu huathiri asilimia tisini (90%) ya wagonjwa wasipopewa kizuizi ambatanisho cha madini ya ziada. Madhara madogomadogo (side effects) au athari zinazoweza kutokea kwa wagonjwa wanaopewa kiambatanisho hiki cha madini ya ziada ya magnesia, calcium na potassium ni kama yafuatayo:

Jasho, Joto, Kizunguzungu (madhara madogomadogo) na Kupumua kwa shida, Mapigo duni ya mishipa, Mapigo hafifu ya moyo, Mkimbio wa damu batili (madhara hatari yanayotokea kwa nadra). Kwa habari zaidi kuhusu hatari na athari hizi, uliza daktari wako wa utafiti huu.

JE KUNA FAIDA GANI ZA KUSHIRIKI UTAFITI?

Kushiriki kwako kunaweza kuboresha au kutoboresha hali yako ya afya. Thibitisho lipo kwamba utumiaji mapema wa madini ya magnesia, calcium na potasium huweza kupunguza tukio la sumu ya figo lakini uthibitisho huu bado haujafanyika katika mfumo wa nchi yetu. Data kutokana na huu utafiti zitawezesha watafiti kujua mengi kuhusu kiambatanisho cha madini haya kama kinga dhidi ya sumu ya figo kwa wagonjwa walio katika matibabu ya kemotherapi iliyo na dawa aina ya Platini. Pia madaktari wetu watapata kufahamu umuhimu wa kuongeza tiba hii kwenye utaratibu wa matibabu ya saratani yanayohusisha matumizi ya dawa ya platini.

NI CHAGUO LIPI LINGINE NINALO KAMA SITOSHIRIKI UTAFITI?

Uteuzi wako mwingine ni kama:

Kupata tiba ama huduma za saratani pasi na kushiriki zoezi la utafiti. Ongea na daktari wa utafiti kuhusu hiari zako kabla ya uamuzi wa kushiriki zoezi la utafiti.

JE TAARIFA KUHUSU AFYA YANGU ITAHIFADHIWA KWA SIRI?

Habari zote za kitafiti zitahifadhiwa katika kompyuta iliyo na nambari ya siri (password). Tutahakikisha taarifa za kibinafsi katika rekodi zako za matibabu zimewekwa kwa siri. Taarifa hizi zitatumika kwa madhumuni yaliyokusudiwa tu kwa kuzingatia maelekezo ya Kamati ya Maadili na Utafiti ya Hospitali na Chuo Kikuu cha Afya cha Muhimbili. Iwapo taarifa ya utafiti huu imechapishwa au kuwasilishwa mbele ya makongamano ya kisayansi basi jina lako na ujumbe mwingine wa kibinafsi havitatumika.

HAKI ZANGU NI ZIPI IKIWA NITASHIRIKI KATIKA UTAFITI?

Kushiriki utafiti ni chaguo lako. Una uamuzi wa ama kushiriki au kutoshiriki. Ukiamua kushiriki pia waweza kujiondoa wakati wowote. Mbali na uamuzi unaochukua, hakutakuwa na adhabu yoyote kwako na hutapoteza mojawapo ya faida za kawaida za matibabu unazostahili kupata.
Kujiondoa katika utafiti hautaathiri huduma zako za kimatibabu.

NITAFANYA NINI IKIWA NINA MALALAMIKO?

Malalamishi yoyote kuhusu utafiti huu, yaelekezwe kupitia anwani ifuatayo:
Mkurugenzi wa utafiti
Chuo kikuu cha Afya Cha Muhimbili (MUHAS)
Sanduku la posta: 65001, Dar es Salaam. Namba ya simu: 2150302-6.
Lalamishi lolote litachunguzwa kwa haraka na utaarifiwa kuhusu uamuzi**.**

Kartasi hii ya taarifa ni yako kuihifadhi/kuiweka.

IDHINI YA MSHIRIKI UTAFITI.

Nimesoma na kuelewa maelezo ya idhini yaliyopo hapo juu. Mfumo na sura ya utafiti imeelezwa kwangu ipasavyo. Kwa hivyo nakubali kujitolea na kushiriki utafiti kwa hiari bila kushurutishwa.

_____ _____ / _____ /____

Sahihi ya mshiriki utafiti (*Jina la kwanza na la familia***) mwaka mwezisiku**

Anwani: _____ Simu: _____

TAARIFA YA MTAFITI

Mimi mwenye sahihi hapo chini, nimemweleza mshiriki katika utafiti kuhusu mbinu ambazo zitafuatwa katika uchunguzi na hata athari na manufaa husika.

_____ / _____ / ____

Sahihi ya msimamizi wa (*Jina la kwanza na la familia***) Mwaka Mwezi Siku**

mazungumzo ya idhini.

_____ _____ / _____ / ____

Sahihi ya Mtafiti (*Jina la kwanza na la familia***) Mwaka Mwezi Siku**

Idara ya Famakolojia, Shule Cha Famasia, Chuo Kikuu Cha Afya cha Muhimbili S.L.P 65001, Dar-Es-Salaam. Nmba ya simu: 2150302-6. Barua pepe; tatulyimo@gmail.com

_____ _____ / _____ / _____

Sahihi Ya Shahidi (*Jina la kwanza na la familia***) Mwaka Mwezi Siku**

Uhusiano wa shahidi na mshiriki/mchunguzi:_____

APPENDIX II:Case Report Form

STUDY TITLE: PROTECTIVE EFFECT OF HYDRATION WITH ISOTONIC SALINE, POTASSIUM CHLORIDE, MAGNESIUM SULFATE AND CALCIUM GLUCONATE ON CISPLATIN INDUCED NEPHROTOXICITY AMONG PATIENTS WITH SOLID TUMORS AT ORCI

1. SITE INFORMATION

Name of Data Entry Clerk(**required**):	
Enrollment Date (**required**) (DD-MM-YYYY):	
Consent Method (**required**) ☐Self ☐Parent ☐Other guardian (specify): ☐No consent (STOP)	Enrollment Site ☐NHIF ☐OPD ☐IPD

2. PARTICIPANT INFORMATION

Participant ID No:				
Gender: ☐M ☐F	*Note: if exact date is not known, birth year is sufficient*			Age (Years):
	Birth Day (DD):	Birth Month (MM):	Birth Year (YYYY):	
Body weight……..kg		Body height……..cm		
Calculated Body Surface Area **(BSA)**……..m^2				

Calculated Body Mass Index **(BMI)**……. Estimated Glomerular Filtration rate (**eGFR**)……..
Are you taking alcohol? ☐Yes ☐No **If yes**, Approximate amount…… glass/day or …….beer/day **For how long?** Specify……..
Are you smoking cigarette? ☐Yes ☐No **If yes,** Approximate amount……packs/day **For how long?** Specify……..

3. MEDICAL & MEDICATION HISTORY

1. **Do you have any of the following chronic medical conditions?** (*read options in the table and also asses medical history in the patient file***)**
   If yes, write the duration of the condition.

S/N	Medical condition	Yes	No	If yes Duration (month)
1	Hypertension			
2	Diabetes			
3	Liver disease eg hepatitis			
4	Kidney disease eg kidney stones			
5	Peptic ulcer disease			
6	Chronic diarrhea			
7	allergy			
8	Others (specify)			

2. **Have you taken any of the following medicines for the last two weeks?** ☐Yes ☐No
   (*also asses medication history in the patient file***)**

   If yes, Name the drug, dose, frequency and duration of medications.

S/N	Type of Drug	Name of drug	Dose	Frequency	Duration
	NSAIDs				
	Aminoglycosides				
	ACEIs or ARBs				
	Sulfonamides				

	Others (specify)				

3. **Have you been exposed to CT or MRI scan (contrast media) for the last two weeks?** ☐Yes ☐No (*also asses patient file*)
4. **Have you taken any traditional medication for the last two weeks?** ☐Yes ☐No

If yes, specify: _____

5. CLINICAL ASSESSMENT INFORMATION

Table 1: Vital Signs

Measure vital signs for each participant in every visits and record in the table.

Vital signs	Day 0 At baseline	Day7	Day14	Day 21	Day 28
Body Temperature					
Blood pressure					
Heart beats					
Respiratory Rates					

Table 2: Type of cancer diagnosed

What type(s) of cancer was diagnosed? Tick or write the type of cancer diagnosed.

S/N	Type of cancer	Tick
1	Carcinoma	
2	Sarcoma	
3	Myeloma	

4	Hodgkin lymphoma	
5	Non-Hodgkin lymphoma	
7	Others (specify)	

Table 3: Conventional Anticancer Medicine prescribed

What type of anticancer regimen prescribed? Name the drug, dose, frequency and duration of the anticancer medications.

S/N	Drug name	Dose	Frequency	Duration

Table 4: Adverse Events

Is there any adverse event reported? Assess and record any adverse event reported during the study period.

Day	Type of Adverse Event	Time of onset	Duration	Severity	Medication given
Day7					
Day14					
Day 21					
Day 28					

LABORATORY MEASUREMENTS

Measure and record all parameters for each participant at baseline and at every visit.

		Day 0 At base line	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42
Serum creatinine								
BUN								
Electrolyte profile	Potasium							
	Magnesium							
	Calcium							
	Sodium							
CBC	WBC							
	Neutrophils							
	Lymphocyte							
	Plataletes							
	Hemoglobin							
Urinalysis: proteinuria								
Urinary Pregnant Test (UPT) - female participants only.								

APPENDIX III: Ethical Clearance

MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES
OFFICE OF THE DIRECTOR OF POSTGRADUATE STUDIES

P.O. Box 65001
DAR ES SALAAM
TANZANIA
Web: www.muhas.ac.tz

Tel G/Line: +255-22-2150302/6 Ext. 1015
Direct Line: +255-22-2151378
Telefax: +255-22-2150465
E-mail: dpgs@muhas.ac.tz

Ref. No. DA.287/298/01A/

23th April, 2018

Ms. Tatu Lyimo
MPharm. Hospital and Clinical Hospital
MUHAS.

RE: APPROVAL OF ETHICAL CLEARANCE FOR A STUDY TITLED: "PROTECTIVE EFFECT OF HYDRATION WITH ISOTONIC SALINE, POTASSIUM CHLORIDE, MAGNESIUM SULFATE AND CALCIUM GLOCONATE ON CISPLATIN INDUCED NEPHROTOXICITY AMONG PATIENTS WITH SOLID TUMOURS AT ORCI"

Reference is made to the above heading.

I am pleased to inform you that, the Chairman has, on behalf of the Senate, approved ethical clearance for the above-mentioned study. Hence you may proceed with the planned study.

The ethical clearance is valid for one year only, from 19ath April, 2018 to 18th April, 2019. In case you do not complete data analysis and dissertation report writing by 18th April, 2019, you will have to apply for renewal of ethical clearance prior to the expiry date.

24.04.2018

Dr. E. Mbugi
ACTING: DIRECTOR OF POSTGRADUATE STUDIES

cc: Director of Research and Publications
cc: Dean, School of Pharmacy

THE UNITED REPUBLIC OF TANZANIA

National Institute for Medical Research
3 Barack Obama Drive
P.O. Box 9653
11101 Dar es Salaam
Tel: 255 22 2121400
Fax: 255 22 2121360
E-mail: ethics@nimr.or.tz

Ministry of Health, Community Development, Gender, Elderly & Children
University of Dodoma, Faculty of Arts and Social Sciences
Building No. 11
P.O. Box 743
40478 Dodoma

NIMR/HQ/R.8a/Vol. IX/2805

22nd June 2018

Ms Tatu E. Lyimo
Muhimbili University of Health and Allied Sciences
School of Pharmacy
Department of Clinical Pharmacy and Pharmacology
P.O. Box 65001
Morogoro

RE: ETHICAL CLEARANCE CERTIFICATE FOR CONDUCTING MEDICAL RESEARCH IN TANZANIA

This is to certify that the research entitled: Protective effect of hydration with isotonic saline, potassium chloride, magnesium sulfate and calcium, gluconate on cisplatin induced nephrotoxicity among patients with solid tumors at ORCI (Lyimo TE *et al.*) has been granted ethical clearance to be conducted in Tanzania.

The Principal Investigator of the study must ensure that the following conditions are fulfilled:

1. Progress report is submitted to the Ministry of Health, Community Development, Gender, Elderly & Children and the National Institute for Medical Research, Regional and District Medical Officers after every six months.
2. Permission to publish the results is obtained from National Institute for Medical Research.
3. Copies of final publications are made available to the Ministry of Health, Community Development, Gender, Elderly & Children and the National Institute for Medical Research.
4. Any researcher, who contravenes or fails to comply with these conditions, shall be guilty of an offence and shall be liable on conviction to a fine as per NIMR Act No. 23 of 1979, PART III Section 10(2).
5. Site: Dar es Salaam region in Tanzania.

Approval is valid for one year: 22nd June 2018 to 21st June 2019.

Name: Prof. Yunus Daud Mgaya

Signature
CHAIRPERSON
MEDICAL RESEARCH
COORDINATING COMMITTEE

Name: Prof. Muhammad Bakari Kambi

Signature
CHIEF MEDICAL OFFICER
MINISTRY OF HEALTH, COMMUNITY DEVELOPMENT, GENDER, ELDERLY & CHILDREN

CC: RMO of Dar es Salaam region
DMO/DED of Ilala district

ORCI OCEAN ROAD CANCER INSTITUTE

Box 3592, Dar es Salaam, Tanzania
Tel. 2127597, Fax: 255-22-2118704
On Reply Please quote

SERVICE — TREATMENT
RESEARCH — DETECTION
TEACHING — PREVENTION

Our Ref: 10/VOL.18

Date: 14th January 2019

INSTITUTIONAL ACADEMICS, RESEARCH, PUBLICATIONS AND ETHICS COMMITTEE (IARPEC)

Tatu Lyimo
Candidate: MPharm, Hospital and Clinical Pharmacy
School of Pharmacy
MUHAS

Re: Authorization to undertake a study on 'Protective effect of hydration with isotonic saline, potassium chloride, magnesium sulfate and calcium gluconate on cisplatin-induced nephrotoxicity among patients with solid tumors at ORCI'

We acknowledge receipt of your request for authorization to conduct the above named intervention study that has already received ethical clearance from the Office of Postgraduate Studies, MUHAS, as well as Medical Research Coordinating Committee, NIMR (copies attached in file)

This is to inform you that the Institutional Academics, Research, Publications and Ethics Committee has granted you authorization for the implementation of the above mentioned study within the validity period of the ethical clearance issued. Upon successful completion of the study, you are obliged to submit a copy of the final document of this research project to the IARPEC.

Sincerely,

Nazima Dharsee MD, MMed, MSc
Director, Academic and Research Unit
Ocean Road Cancer Institute