PROFILES AND PREVENTIVE STRATEGIES OF NEPHROTOXICITY AMONG ADULT PATIENTS RECEIVING CISPLATIN BASED REGIMENS AT KENYATTA NATIONAL HOSPITAL

BY

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Declaration

I hereby declare that this dissertation is my original work and has not been presented for examination to any other university.

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Dedication

I am grateful to the almighty God for giving me strength and knowledge to carry out this work. This dissertation is dedicated to the memory of my late grandmother Jennifer, brother Protus and sister Molly. God rest their souls in eternal peace.

To my family; dad, Mr Edward Mwai, mom Nancy Mwai, and my siblings for their love, support and understanding throughout my studies.

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Acronyms and Abbreviations

5FU	5 Fluorouracil
AC	Adriamycin, Cisplatin
AKI	Acute Kidney Injury
BEP	Bleomycin, Etoposide, Cisplatin
BSA	Body Surface Area
CDDP	Cis-diaminedichloroplatinum II (Cisplatin)
Cis Vac	Cisplatin, Vincristine, Adriamycin, Cyclophosphamide
CP	Cisplatin, Paclitaxel
ERC	Ethics and Research Committee
FDA	Food Drug Administration
GFR	Glomerular Filtration Rate
ICE	Ifosphamide, Cisplatin, Etoposide
KNH	Kenyatta National Hospital
NAC	N Acetyl Cysteine
PBSCT	Peripheral Blood Stem Cell Transplantation
SPSS	Statistical Package for Social Sciences
UECs	Urea, Electrolytes, Creatinine
UON	University of Nairobi
WHO	World Health Organization

Definition of Terms

Adjuvant therapy: Is the additional cancer treatment after primary treatment to lower the risk of re-emergence. It includes chemotherapy, radiation therapy, hormonal therapy, and targeted biological therapy

Induction: Is the primary therapy given as a definitive treatment of cancer cases. It includes chemotherapy or radiation therapy

Metastasis: Spread of cancer cells from area of origin to other distant sites. Cancer can spread through local invasion, intravasation or through blood and lymphatic spread

Neoadjuvant chemotherapy is the use of chemotherapy alone prior to definitive surgery or radiation therapy. It is given before primary therapy.

Nephrotoxicity: It is the elevation of serum creatinine or blood urea nitrogen, hematuria or proteinuria. It may be due to use of various anti cancer agents.

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. It includes, for example, hydration with Normal Saline, forced diuresis with furosemide, using magnesium sulphate, amifostine, and potassium chloride and stopping the drug in cases of kidney damage.

Abstract

Background: The use of cisplatin in the management of cancer is associated with nephrotoxicity. There is scant literature on the profiles and preventive strategies against renal toxicities in Kenyatta National Hospital.

Study Design, Setting and Methodology: Retrospective cohort study design using simple random sampling was used to find out the renal toxicity profiles among three hundred and sixty seven adult patients in Kenyatta National Hospital, radiotherapy clinic. Preventive strategies employed to prevent development of renal toxicities were also studied.

Results: There was female preponderance at 62.6%. The median age of the study population was 51 years (range 18-91). Cervical cancer (41.5%) was commonest type of cancer where cisplatin based regimen were used. Nephrotoxicity was found to be 58.5% and the profiles of nephrotoxicity increased with the number of cycles. The major risk factors for development of nephrotoxicity were cumulative dose of cisplatin above 200mg/m^2 (66.4%), radio contrast exposure (51.2 %) and electrolyte abnormalities (12.2 %). Most patients experienced grade 2 nephrotoxicity with mean glomerular filtration rate of 59.3 ml/min/1.73m^2 (±20.6). Three-quarters of the patients developed nephrotoxicity during the follow-up on treatment, with the majority (80%) being older than 50 years of age. Electrolyte abnormalities including hypokalaemia (22%) and hypocalcaemia (0.5 %) were also encountered. Preventive strategies against development of nephrotoxicity included postponement of cisplatin dose due to deranged renal function (33.2%), change of cisplatin to carboplatin (3.5%), oral hydration (100%) and intravenous hydration with normal saline (100%). Whereas the change of dose from cisplatin to carboplatin was found not to confer prevention against nephrotoxicity ($p=0.181$), postponing the dose of cisplatin did ($p<0.0001$).

However, the doses of normal saline used did not prevent the development of nephrotoxicity (p=0.486).

Conclusion: Despite the preventive strategies for the development of nephrotoxicity, more than half exhibited nephrotoxic profiles, suggesting that better ways of preventing nephrotoxicity ought to be sought.

CHAPTER ONE: INTRODUCTION

1.1 Epidemiology of Cancer

Cancer is a disease characterized by uncontrolled cell division and these cells have the ability to invade other tissues either by invasion or migrating to distinct sites by metastasis. Global burden of cancer is high and it is growing still larger. Each year more than 11 million people are diagnosed with cancer (1). By 2020, this number is expected to increase to 16 million (2).

According to Global Cancer Network 2012 report, an estimated 14.1 million new cancer cases and 8.2 million cancer-related deaths occurred in 2012, compared with 12.7 million and 7.6 million, respectively, in 2008. Prevalence estimates for 2012 show that there were 32.6 million people alive who had cancer diagnosed in the previous five years (3). More than 60% of world's total new annual cases occur in Africa, Asia, Central and South America. These regions account for 70% of the world's cancer deaths (4).

In addition, cancer causes more than 8 million deaths per year worldwide(5). The most common types of cancers include testicular, ovarian, bladder, cervix, prostate, and breast, head and neck cancers (6).

1.2 Use of Cisplatin in Cancer Management

Cisplatin is a co-ordinate metal complex with significant anti neoplastic activity. It is one of the commonly used chemotherapeutic agents. It can be used alone or with other anticancer agents and it forms the backbone of majority of chemotherapeutic regimens used in many malignancies. The side effects of cisplatin include acute and chronic renal insufficiency, renal magnesium wasting, and electrolyte disturbances like hypomagnesia, hypocalcaemia, hypophosphatemia and

hypokalemia. The magnitude of electrolyte disturbances and renal damage are dose dependent (5).

A study by Yao *et al*, found out that most patients treated with cisplatin have a reversible decrease in glomerular filtration rates (GFR) whereas others do have an irreversible decrease in GFR (7). The frequency and degree of cisplatin induced nephrotoxicity has been shown to be varying in different set ups (8). Preventive strategies to nephrotoxicity is through adequate hydration and electrolyte balance, especially magnesium and potassium replacement (9).

Tiseo *et al* reported that a 24 hour hydration regimen is recommended in patients to prevent nephrotoxicity associated with cisplatin (10). A retrospective study on, short hydration regimen and nephrotoxicity of intermediate to high-dose cisplatin-based chemotherapy for outpatient treatment in lung cancer and mesothelioma reported that the method of hydration with 2L fluid was efficacious (10). Another randomized trial on evaluation of saline, mannitol, and furosemide hydration in acute cisplatin nephrotoxicity reported that hydration with isotonic solution and isotonic solution plus furosemide resulted in less cisplatin- induced nephrotoxicity than compared to hydration with isotonic solution plus mannitol (9).

1.3 Statement of Research Problem

Cisplatin use is limited by its dose limiting nephrotoxicity. Different measures such as fractionation of the dose, slower rate of infusion, forced diuresis with diuretics and hydration are used to counter this side effect(11-14). Hydration with a normal saline solution appears to be the single most important measure. Nevertheless, the amount and duration of hydration is still controversial (10). Due to the concern of renal failure following the use of cisplatin, either the dose of medicine is decreased, or doses are skipped and cycle intervals are prolonged, and as a

result of these, the efficacy is diminished(15).Evaluation of preventive strategies to renal toxicity has not been obtained from retrospective studies in our setting.

1.4 Justification of the study

Cancer is a known leading cause of morbidity and mortality in Kenya and the world at large. Treatment modalities available to manage cancer include radiation therapy, surgical therapy and chemotherapy. The use of cisplatin based regimen, in particular, causes renal dysfunction. Continued use of cisplatin may lead to toxicity and impede optimal use of ancilliary and supportive measures. Therefore, early prediction of predisposition to renal function impairment and taking precautions early are crucial (15).

Evaluation of preventive strategies to nephrotoxicity is important as long term users of cisplatin continue to increase. This is because both acute life threatening adverse effects and long term toxicity on the kidneys impacts negatively on the quality of life of the survivors, and therefore need to be controlled (16).

This study determined the prevalence of use of various preventive measures to nephrotoxicity on patients put on cisplatin based regimen. By analyzing these preventive strategies and the outcome of their use, the study aims at harmonizing the utilization of preventive measures for optimal management of cancer patient.

1.5 Research Questions

1. What is the prevalence of nephrotoxicity in cancer patients treated with cisplatin in KNH?
2. What are the risk factors for nephrotoxicity in cancer patients receiving cisplatin at KNH?
3. What are the profiles of nephrotoxicity in cancer patients treated with cisplatin at KNH?

4. What are the preventive strategies to the development of nephrotoxicity among patients receiving cisplatin based chemotherapeutic agents at KNH?
5. What are the patterns of management of cisplatin induced nephrotoxicity in cancer patients treated in KNH?

1.6 Objectives

1.6.1 General objective of the study

To evaluate the preventive strategies to development of nephrotoxicity in cancer patients treated with cisplatin in KNH.

1.6.2 Specific objectives

1) To determine the prevalence and profile of nephrotoxicity in cancer patients treated with cisplatin based regimens at KNH

2) To identify the risk factors for nephrotoxicity among cancer patients on cisplatin regimen at KNH

3) To find out the agents used to prevent development of nephrotoxicity in patients receiving cisplatin based chemotherapy at KNH

1.7 Study Limitations

The study was retrospectively designed and as such the quality of data in the patient's files directly influenced the information that was abstracted. Serum magnesium measurement, though is a measure of kidney function, is not routinely done at KNH. Therefore, evaluation of hypomagnesaemia was not possible, save for the cases where magnesium levels are measured.

1.8 Significance and anticipated output

The study aimed at finding out the risk factors and preventive measures of nephrotoxicity associated with cisplatin based chemotherapeutic regimens. The result from this study may be used to develop strategies that can be applied in order to minimize renal toxicity due to cisplatin.

2.0 LITERATURE REVIEW

2.1 Cisplatin Use in Cancer Management

Cisplatin is an effective cytotoxic agent that is used as standard treatment of a variety of neoplasms. It is used in the management of various cancers including bladder cancer, cervical cancer, malignant mesothelioma, non small cell lung cancer, and ovarian cancer, squamous cell carcinoma of head and neck cancer and testicular cancer. The incorporation of cisplatin into combination regimens has resulted in high cure rates, for example, of advanced testicular cancer (1).

A study by Valle *et al* revealed that compared with gemcitabine alone, cisplatin plus gemcitabine was associated with a significant survival advantage without the addition of substantial toxicity. Cisplatin plus gemcitabine was found to be an appropriate option for the treatment of patients with advanced biliary cancer(17). Pujol *et al* found that cisplatin-containing regimen yields a higher response rate and probability of survival than does a chemotherapy containing other alkylating agents without a perceptible increase in risk of toxic-death (18).

The use of cisplatin in cancer management is so far immense. However, clinical application is limited because of serious and sometimes irreversible toxicity, including gastrointestinal, neurotoxicity, nephrotoxicity, myelosuppression, and ototoxicity (19).

Forced diuresis pre- and post cisplatin infusion limits nephrotoxicity, and with current supportive medication, GI toxicity is manageable in the majority of patients. However, despite extensive research, no therapeutic intervention of proven benefit has been found to prevent neurotoxicity and ototoxicity. The most commonly used protective measure against renal toxicity is to establish solute dieresis (19).

There is evidence that the therapeutic efficacy of cisplatin increases with increasing dose. However, cisplatin-induced nephrotoxicity has also been shown to be dose-related in both animals and humans, as the kidney is the primary excretory organ for cisplatin (20). Nephrotoxicity of cisplatin is dose related and cumulative. Early recognition of renal injury is needed for the safe and effective use of this agent. In the study of cumulative dose of cisplatin as a risk factor of nephrotoxicity, Caglar *et al* found that the cumulative prior dose of cisplatin is a strong risk factor for the development of nephrotoxicity in patients undergoing high-dose Ifosfamide, Cisplatin, Etoposide (ICE) followed by peripheral blood stem-cell transplantation. Nephrotoxicity may occur with much lower doses of chemotherapeutic agents than the recommended maximum doses (21).

2.2 Mechanism of Cisplatin Toxicity

Cisplatin administration and exposure to kidney cells, especially the proximal tubule, are associated with the activation of inflammatory reactions, and vascular and ischemic injury to the kidney, involving multifactorial and multidimensional processes comprising the activation of signal transduction pathways, leading to the damage and cell death of the renal tubule epithelium (16).

Daugaard *et al*, found that immediately after administration of cisplatin to dogs, renal blood flow and GFR remained unchanged, while proximal re absorption rates decreased significantly. They concluded that cisplatin induced nephrotoxicity is thus initiated by an acute, mainly proximal tubular impairment, preceding alterations in renal hemodynamics. These data were confirmed in a micro puncture study in rats (22). In the high-dose cisplatin group (40 mg/m^2 daily for 5 days) a severe progressive decrease in GFR was observed during treatment and GFR remained decreased for up to 2 years after termination of treatment (22).

Cisplatin nephrotoxicity present in a number of ways. However, the most serious more common presentations are acute kidney injury (AKI) which occurs in 20–30% of patients (23, 24). Other renal manifestation of cisplatin toxicity include hypomagnesaemia , fanconi-like syndrome , distal renal tubular acidosis, hypocalcaemia , renal salt wasting, renal concentrating defect, hyperuricemia, transient proteinuria, erythropoietin deficiency, thrombotic microangiopathy and chronic renal failure (16).

Biotransformation of cisplatin could play an important role in renal toxicity. A decrease in sulphydryl groups in the kidney may be a primary event, and reactive metabolites may be formed. However, the incidence of cisplatin nephrotoxicity has been observed to decrease when patients are prehydrated. The clinical recommendations are to avoid rapid cisplatin infusion rates (over 1 mg/kg per hour) and to induce hydration at least during and after cisplatin administration(20)

2.3 Clinical Characteristics of Cisplatin Nephrotoxicity

Early clinical use of cisplatin results in dose-related cisplatin-induced AKI in 14 to 100% of patients, with the incidence varying with the cumulative dose. The incidence of renal insufficiency in more recent experience using saline hydration and diuresis, is in the range of 20–30% of patients and is revealed by increases in the serum creatinine and blood urea nitrogen concentrations (25).

The urine output is usually preserved (non-oliguric) and the urine may contain glucose and small amounts of protein, indicative of proximal tubular dysfunction. Hypomagnesaemia is also common, particularly after repeated doses of cisplatin, even in the absence of a fall in the GFR. Recovery of renal function usually occurs over a period of 2–4 weeks, though more

protracted courses, as well as lack of recovery are reported. Progressive and permanent nephrotoxicity can result with successive treatment courses despite preventative measures (9, 26) Studies have revealed that the prevalence of cisplatin nephrotoxicity is high, occurring in about one-third of patient undergoing cisplatin treatment (27). Clinically, cisplatin nephrotoxicity is often seen after 10 days of cisplatin administration and is manifested as lower GFR, higher serum creatinine, and reduced serum magnesium and potassium levels (7, 28).

On the other hand, the long-term effects of cisplatin on renal function are not completely understood, but it is believed that cisplatin treatment may lead to subclinical but permanent reduction in GFR (15).

Nephrotoxicity increases with the dose and frequency of administration and cumulative dose of cisplatin .High peak plasma free platinum concentration has been correlated with nephrotoxicity (24), and one study suggested GFR and plasma magnesium concentrations decreased after cisplatin doses of higher than 50 mg/m^2 body surface area, but were unchanged if the dose was below 20 mg/m^2 (16).

Patient variable factors that increase the risk of nephrotoxicity, include female sex, older age, smoking, and hypo albuminemia. In addition, pre-existing renal dysfunction increases the risk for AKI. In the specific case of cisplatin, however, there are limited data on the incidence of nephrotoxicity in populations with chronic kidney disease since many trials exclude patients with renal insufficiency. Diabetes decreases the risk of cisplatin nephrotoxicity in animal models, but clinical studies have not found any impact of diabetes on nephrotoxicity in humans (16).

2.4 Risk Factors for Cisplatin Nephrotoxicity

Risk factors that increase kidney impairment after CDDP(*cis* diamminedichloroplatinum(II) administration include previous or concomitant renal diseases, solitary kidney (nephrectomy),

combined anticancer treatment with Ifosfamide and Methotrexate, concurrent treatment with other nephrotoxic agents such as aminoglycosides and amphotericin B, the cumulative dose of cisplatin (≥ 200 mg/m^2), radiation impacting the kidney (renal radiation dose ≥ 15 Gy), diabetes mellitus, hypertension, dehydration and hypoalbuminaemia (13).

Hypocalcaemia is another common electrolyte disturbance related to cisplatin treatment and hence also a risk factor. It may be caused by various mechanisms, but even the cisplatin-induced hypomagnesaemia itself may lead to hypocalcaemia (29). According to Caglar *et al*, cumulative dose of cisplatin is a strong risk factor for the development of nephrotoxicity in patients who receive high doses of ICE. Nephrotoxicity may occur with much lower doses than the currently recommended maximum doses (21).

A study by Asangansi, Oshin and Akinloye, patient related factors, and drug related factors as well as drug interactions play a role in nephrotoxicity. These include age, sex, race, specific diseases (diabetes mellitus, hypertension, sickle cell disease, multiple myeloma, proteinuric disease, Systemic Lupus Erythromatosus) Sodium-retaining states (cirrhosis, heart failure, and nephrosis) dehydration and volume depletion, acidosis, potassium and magnesium depletion, hyperuricemia, hyperuricosuria, sepsis, shock and renal transplantation (30). Other drug-related factors involved are inherent nephrotoxic potential, dose duration, frequency, and form of administration repeated exposure (29).

Drug interactions involve combined or closely associated use of diagnostic or therapeutic agents with added or synergistic nephrotoxic potential for example, radio contrast agents, aminoglycosides, nonsteroidal anti-inflammatory drugs, cisplatin, angiotensin-converting enzyme inhibitors (30).

2.5 Cytoprotective Therapy to Prevent the Nephrotoxicity of Platinum Derivatives

Intensive hydration simultaneous to cisplatin administration, osmotic diffusion, magnesium supplementation, increasing duration of infusion and dividing the dose of cisplatin within the cycle all decrease the nephrotoxicity of this cytostatic agent (31). Hydration and intravenous mannitol administration reduce the incidence of cisplatin nephrotoxicity by decreasing the exposure of the renal tubular cells to the drug (19).

Cisplatin is less nephrotoxic when administered in a long infusion compared to a bolus. This is because endogenous sulphydryls present in renal tubules neutralize cisplatin at lower concentrations but are less efficient at higher concentrations achieved by a cisplatin bolus (19).

Amifostine (Ethyol) application has been used for reducing cisplatin nephrotoxicity. Its main mechanism of its protective action is the removal of free radicals. Moreover, N-acetylcysteine (NAC) has been considered to be cisplatin-nephroprotective (32). It inhibits apoptosis caused by cisplatin by interfering with caspase signaling. A liposomal formulation of cisplatin, lipoplatin, has been intensely studied over the recent years. It is regarded as equally effective but much less nephrotoxic which has been confirmed in animal studies as well as in clinical trials in adult patients with advanced pancreatic cancer, non-small cell lung carcinoma, head and neck neoplasm and metastatic breast cancer (33).

2.5.1 Evaluation of Renal Function in Patients Receiving Cisplatin Therapy

Grading of nephrotoxicity involves the use of electrolytes, urea and creatinine concentration in plasma. The calculation of GFR grades of renal function according to Skinner *et al* is in a scale of 0 to 4 (29).

Table 1: Grading of Nephrotoxicity

Nephrotoxicity Grade	GFR (ml/min/1.73m^2)
0	>90
1	60-89
2	40-59
3	20-39
4	< 20

Where;

Grade	**Interpretation**
0	No nephrotoxicity
1	Mild nephrotoxicity
2-3	Moderate nephrotoxicity
≥4	Severe nephrotoxicity

2.6 Ways of Minimizing Nephrotoxicity Associated With Use of Cisplatin Compounds

Renal toxicity is reduced, but not completely prevented, by different measures such as fractionation of the dose, slower rate of infusion, enforced diuresis with diuretics and hydration(11-14)

Hydration expands the post-renal volume thereby reducing cisplatin concentration and its contact time with the tubular epithelium. The most used form of hydration is a normal saline solution alone or it may be combined with mannitol or with a diuretic, such as furosemide, to maximize urine flow (28). However, there is no consistent data regarding the specific protective effect of either mannitol or furosemide. In fact, a study of high dose cisplatin (100 mg/m^2) comparing mannitol and furosemide showed no differences in nephrotoxicity (34). Nevertheless, this is not

the crucial issue; since there is strong evidence that hydration with a normal saline solution is the single most important measure in this regard. However, the amount and duration of hydration is still controversial (10).

The FDA cisplatin approval document, for example, recommends the use of a pretreatment hydration regimen with 1 to 2 liters of fluid infused for 8 to 12 hours. Cisplatin has to be diluted in 2 liters of 5% dextrose in $^1/_2$ or $^1/_3$ normal saline solution containing 37.5 g of mannitol and infused over a 6 to 8-hour period. Adequate hydration and urinary output must be maintained during the following 24 hours (15).

However, excretion of most of the cisplatin occurs within the first few hours, and 2 hour after the end of cisplatin infusion, 90% of the plasma platinum is protein bound and therefore, slowly eliminated and less nephrotoxic (16).

A research done by Luzonckzy *et al* came up with recommendations to be followed on administering cisplatin. Renal function should not be evaluated by serum creatinine concentration and should be based on calculated creatinine clearance (for example, by the Cockcroft-Gault equation) and patients to be treated by high-dose cisplatin should be euvolemic and should have saline diuresis (urine NaCl concentration ~1%) of at least 100 ml/hour prior to, during and several days following the administration of cisplatin. Keeping these recommendations ensures prolonged cisplatin treatability of lung cancer patients. Moreover, decreased renal function will not limit the full dose administration of several other cytotoxic agents (35).

2.7 Use of Cisplatin in Cancer Management in KNH

Cisplatin forms the backbone of various cancer treatment protocols in KNH. It is used alone in treatment of cervical cancer at a dose of 50mg/m^2. It is also combined with paclitaxel at a dose of

50-75 mg/m^2 for each cycle of chemotherapy. In esophageal cancer, it is combined with 5-FU given as 80mg/m^2 IV infusion. A higher dose of 150mg/m^2 is used in combination with docetaxel and 5FU in treating esophageal cancer.

For germ cell tumors, cisplatin (100mg/m^2) is combined with etoposide and bleomycin. Doxorubicin and cisplatin at 100mg/m^2 is given as continuous infusion for treating osteosarcoma. For head and neck cancer, it is combined with 5FU at a dose of 100mg/m^2. For ovarian cancer, cisplatin at a dose of 75mg/m^2 is combined with paclitaxel given either on day one or two.

The amount and duration of hydration given before, during and after cisplatin administration varies across different types of cancers. This also varies depending on hydration state of the patient.

2.8 Pre-Treatment/Preventive Measures of Nephrotoxicity in KNH

General preventive measures include using alternative non nephrotoxic drugs whenever possible, correcting risk factors, assessing baseline renal function before initiation of therapy, followed by adjusting the dosage, monitoring renal function and vital signs during therapy and avoiding nephrotoxic drug combinations. Adequate hydration is also important to maintain renal perfusion and to avoid drug-induced renal impairment (36).

In KNH, hydration is maintained by administering at least 2L of Normal Saline during treatment with cisplatin. Prevention still relies on decreases in drug dosage, hydration measures, and active screening for renal abnormalities as part of the usual pre-therapeutic biological work-up in patients treated with anticancer drugs.

The European Society of Clinical Pharmacy Special Interest Group on Cancer Care suggested that hydration should be maintained for at least 3 d after the chemotherapy course, and by IV or oral route when feasible (28).

3.0 METHODOLOGY

3.1 Study Design

The study was a retrospective cohort. All study participants who met inclusion criteria had information extracted from their files using a predesigned data collection sheet (Appendix I).

3.2 Study Area Description

The study was conducted at Kenyatta National Hospital, the largest national referral, teaching and research hospital in East Africa. The hospital has a staff capacity of 6,000, bed capacity of 2000 bed with an average annual out-patient attendance of 600,000 and an average in-patient attendance of 89,000 patients. It receives patients on referral from other hospitals or institutions within or outside Kenya for specialized health care.

It also provides facilities for medical education for the University of Nairobi and Kenya Medical Training College and for research either directly, or through other collaborating health institutions. Data from the medical records department in KNH indicate that there are approximately 50 inpatients and 100 outpatients who are admitted and treated at the oncology wards/clinics weekly. KNH offers comprehensive cancer treatment within the country. Being a public hospital, it offers the lowest cost for these services when compared to the private hospitals. The study was based at the radiotherapy clinic. All cancer patient files are kept at the department during of therapy.

3.3 Study Population

The participants of interest were cancer patients, both male and female, aged 18 years old and above, diagnosed as having cancer and on cisplatin as one of the chemotherapy agent, at KNH.

3.3.1 Inclusion Criteria

The potential participants considered were those that fulfilled the following criteria:

- Cancer patients aged 18 years and above
- Those on cisplatin treatment for at least 2 cycles
- Must have received a form of prevention to nephrotoxicity
- Those with available laboratory renal test results (UECs)

3.3.2 Exclusion Criteria

The following were not considered to participate in the study.

- Those aged below 18 years
- All those to whom cisplatin administration was contraindicated
- Files without the laboratory measurement of urea, electrolytes and creatinine

3.4 Sample Size Determination

In the study by Songul Tezcan *et al*, nephrotoxicity among patients receiving single dose cisplatin of $50mg.m^{-2}$ was found to be 28%-36% (6).

Muthoni *et al* reported a prevalence of nephrotoxicity at 37 % in a local study of assessment of nephrotoxicity profile of pediatric patients at KNH (37). The proportion of 0.37 was used in the estimation of sample size as it represents the prevalence of nephrotoxicity in our setting. Therefore, at 95% confidence interval, the minimum sample size was estimated using Cochran formula (38):

$$N \geq \frac{Z\alpha^2 P(1-P)}{d^2}$$

Where

N= Sample size, estimated.

$Z\alpha$ = 1.96, Z value corresponding to 95% confidence interval

P= Estimated Prevalence of Nephrotoxicity in Kenya = 37% or 0.37

d= Degree of accuracy desired= 0.05

q= 1-P

$$N \geq \frac{(1.96^2)\ (0.37)\ (1-0.37)}{0.05^2}$$

$\geq$ 358 Patients

Therefore, a sample of 367 patients' files were reviewed with an over age of 3% to cater for data losses.

3.5 Sampling Method

Cancer files are kept at radiotherapy clinic. Sampling involved identifying all the 2012 and 2013 cancer files. Then files of patient aged 18 years and above were identified and separated according to treatment types given. Those patients put on cisplatin were separated from those without. Non cisplatin containing files were excluded. A computer generated random numbers was used to pick at random a sample of 367 study files from eligible participants' files.

3.6 Case definition

The cases were defined as those patients who had been prescribed cisplatin as part of chemotherapy. Patient specific data was collected in terms of the type of the regimen given, the total cycles received, pre medications given, other nephrotoxic medications given, if any,

laboratory data in terms of urea, electrolyte and creatinine values and the preventive strategies given.

3.7 Data Collection

The principal investigator was assisted by two trained research assistants to abstract data from files of all eligible patients. The patient's file number was noted down and counter-checked so as to avoid duplication. A data collection tool (Appendix I) was used to collect all the necessary information for this research.

3.8 Training Procedures and Pilot Study

The two research assistants were trained beforehand by the principal investigator on the data collection procedure.

This was done in radiotherapy department at KNH before the actual study to check on the suitability and ease of use of the data collection tool and process. The data was then entered into the appended data collection form to test for its suitability in data collection. Any changes noted were incorporated before the main study began.

3.8.1 Validity

To maintain internal validity, the data collection tool had questions that were to address the objectives of the study. Two research assistants were trained prior to the actual study on how to collect data. External validity was maintained since KNH being a referral hospital attends to patients from all parts of the country; hence the sample was representative of the country. Randomization during sampling of participants' files ensured that the sample selected for the study was representative.

3.9 Delimitations

There was some missing data (serum magnesium) from patient files of the participants. This made analysis of these specific items impossible.

3.10 Data Collection Instrument

A data collection form (Appendix II) was used in data collection. It had both open ended and closed ended set of questions. Data collected included the participants' socio-demographic data, diagnosis, the various drug regimen used (conventional and anticancer drugs) including doses and duration, the number of courses given, reasons for stopping treatment, intravenous fluid therapy given and laboratory test results. This data was filled for each cycle of treatment.

3.11 Variables

Independent variables included patient demographics such as age, gender, and education level, place of residence, employment status and marital status.

Dependent variables included type of anticancer, duration of treatment, fluid therapy, the GFR values and reasons for stopping treatment, if any.

3.12 Quality Assurance Procedures

Data collection forms were pre-tested before use. Modifications were done once inconsistencies or inadequacies were noted from pilot study. Once data collection was completed, entry of data was done which was followed by data cleaning before the actual analysis of data.

3.13 Ethical Considerations

Approval to carry out the research

Permission to carry out the research was sought from the KNH/UoN-ERC before the research was carried out. Approval was given on 15 June 2014 as evidenced by appendix III.

Risks involved

There were no risks involved for the participants since the research involved data abstraction from patient files. Also, data was obtained from the patient files for past treatment.

Confidentiality

The information regarding the patient identity was kept confidential. The patient identification information such as the name was not included in the data collection forms. Study serial numbers was assigned to each participant.

3.14 Data Management and Analysis

Data was collected using data collection tool and entered into a password protected Microsoft Access (version 2010) database and then exported to SPSS version 21.0 for analysis. The hard copy data forms were stored in a lockable cabinet in the Principal Investigator's office during data collection and after analysis. These were moved to a lockable cabinet in the statistician's office during data entry and analysis. Upon completion of data entry, hard copy forms were compared with the entered data to identify errors and corrections made appropriately.

Descriptive statistics was carried out where discrete variables were summarized with frequencies and percentages while continuous variables were summarized using measures of central tendency and dispersion such as mean, median, standard deviation and inter-quartile ranges.

The presence and profile of nephrotoxicity was estimated using simple proportions. Each individual patient was categorized according to nephrotoxicity grade as follows;

Grade 0: No nephrotoxicity, Grade 1: Mild nephrotoxicity, Grade 2&3: Moderate nephrotoxicity, Grade 4: Severe nephrotoxicity.

We then re-categorized the grading; patients in grade 2 and above were assigned to have developed nephrotoxicity while those with a score of 0 or 1 were considered to not have nephrotoxicity.

Simple proportions were used to analyze the preventive strategies against development of nephrotoxicity.

As the main variables of interest, risk factors associated with nephrotoxicity were analyzed using simple proportions. Some of these factors included age, weight, gender, residence, marital status, education level, occupation, co morbidities, and concomitant drugs given. The relationship between nephrotoxicity and preventive strategies was determined using chi square at $p < 0.05$. During multivariate analysis, we adjusted for confounders and effect modifiers in the model to determine independence in the relationship between nephrotoxicity and preventive strategies. This was achieved using binary stepwise backward multinomial logistic regression.

CHAPTER 4: RESULTS

4.1 Introduction

In the section below, we present data from the study involving demographic characteristics and baseline data, the prevalence and profile of nephrotoxicity, the risk factors for nephrotoxicity among cancer patients treated with cisplatin regimen and the agents used to prevent development of nephrotoxicity.

4.2 Demographic Characteristics

A total of 367 patients were studied, out of which the majority, 229 (62.6%) were females. The rest were males.

The median age was 51 years (IQR18-91 years). The mean age was 50 years (±13). The mean weight was 60Kg (±13 Kg). The median height and BSA were 164cm (IQR 114-191cm) and 1.6 kg/m^2 (IQR 1.1-2.3 kg/m^2), respectively (Table 2).

Table 2: Bio-demographic Data

	N	Mean	Median	Min	Max	SD
Age (Years)	367	50	51	18	91	13
Weight(Kg)	358	60	57	30	106	13
Height(Cm)	357	163	164	114	191	9
BSA(Kg/m^2)	356	1.6	1.6	1.1	2.3	0.2

Most participants were aged between 50-60 years with females mostly affected in all age ranges except in the lowest 18 to 30 years where more men than women had cancer (Figure 1).

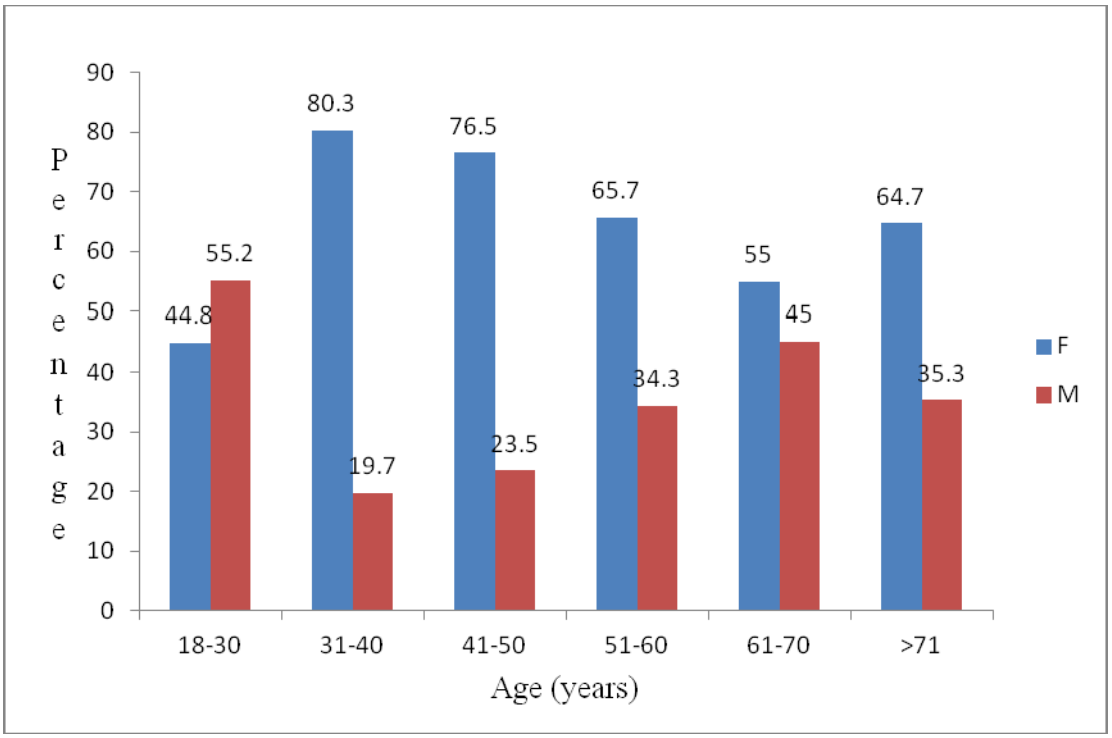

Figure 1: Age and gender distribution of the study participants

4.2.1 Socio-demographic characteristics

Of the 367 patients, 44.3% were residing in urban areas. Majority had secondary education as the highest level of academic attainment at 30% closely followed by primary school, at 26.2%. Sixty seven percent were married, 15% widowed and 13% were single. Sixty three percent of participants were not employed and 27% were employed (Table 3).

Table 3: Socio-demographic characteristics of the study population

		n	%
Residence	Urban	149	44.3
	Rural	187	**55.7**
Highest Academic Achievement	Informal	72	21.0
	Primary	90	26.2
	Secondary	103	**30.0**
	College	78	22.7
Marital status	Married	242	**67.2**
	Single	48	13.3
	Divorced	8	2.2
	Widowed	54	15.0
	Separated	8	2.2
Employment status	Employed	96	27.2
	Not employed	221	**62.6**
	Student	19	5.4
	Retired	17	4.8

4.2.2 Types of cancers

Most cancers treated were cervical cancer at 41.5%, followed by ovarian cancer with a proportion of 12.7%. Others were nasopharyngeal carcinoma (NPC) at 10.6%, esophageal cancer at 6.2% and osteosarcoma at 2.7%. The duration since diagnosis ranged between 4 and 12 months (Table 4).

Table 4: Types of cancers Diagnosed and Mean Duration Since Diagnosis

Type of cancer	N	%	Mean Duration (months)
Cervical	153	41.5	8
Ovarian	47	12.7	11
Nasopharyngeal C a	38	10.6	9
Esophageal	23	6.2	6
Osteosarcoma	10	2.7	4
Breast Cancer	9	2.4	5
Larynx	9	2.4	12
Stomach	9	2.4	6
Adenocarcinoma	7	2.2	12
Post Nasal Space	7	1.9	12
Squamous Cell Ca	4	0.8	8
Lung Cancer	2	0.5	12
Germ cell	1	0.3	4
Other cancers	48	14	9

4.2.3 Co morbidities

Anemia was the most frequent occurring co morbidity at 29% of the study population. This was followed by hypertension at 5% and diabetes at 2% (Figure 2).

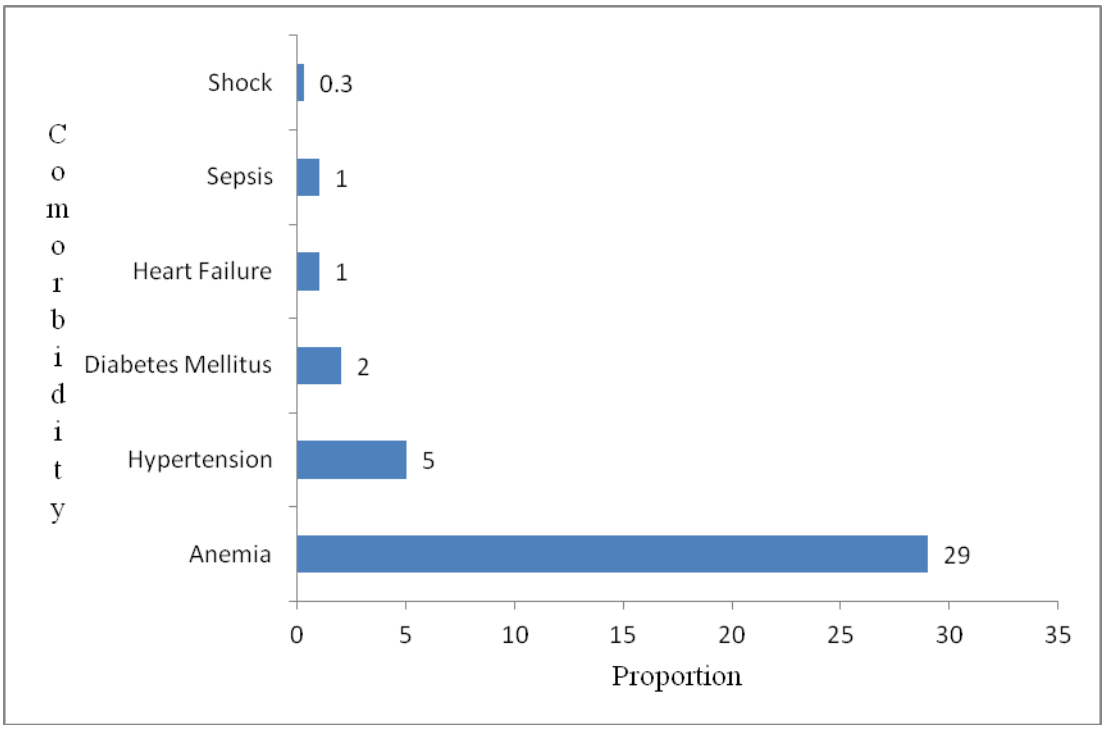

Figure 2: Co morbidities among the study participants

4.3 Prevalence and Profiles of Nephrotoxicity in patients treated with Cisplatin based regimen

4.3.1 Hematological Changes Associated with Nephrotoxicity

Serum urea concentrations increased steadily from 4.8mmol/l to 8.4mmol/l at visit 5 (the fifth course of treatment). Serum creatinine concentrations also increased from 86.4mg/dl to 101.1mg/dl in course 3. There was a general trend of fall in WBC level from an average of 7.7

to 5.3x10^9/L in course 6. Neutrophils reduced from a mean of 4.9 to 4.3x10^9/L and Lymphocytes reduced from 2.2 to 1.8x10^9/L.

Red blood cells reduced from a mean of 4.5 to 4.0 x10^{12}/L in course 6. The hemoglobin reduced from 12.3g/dL to a mean of 11.4 g/dL in course 6. There was a general decline in platelet count from a mean of 371.7 in visit 1 to 278.1x10^3/mm^3 in visit 6 (Table 4).

Table 5: Mean hematological test values at each visit (course of therapy)

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Urea(mg/dL)	4.8	4.5	5.5	6.4	8.4	6.3
Creatinine(mMol/L)	86.4	67.5	101.1	46.8	38.1	103.0
Na(mEq/L)	138.4	138.6	137.5	137.7	137.7	138.1
K(mEq/L)	4.4	4.3	4.2	4.3	4.2	4.3
Mg(mEq/L)	2.5		2	-	-	7
CL(mmol/L)	103	100.4	108.5	100.6	103	101
BUN(mmol/L)	1.9	1.9	1.7	4.3	2.9	1.9
HCO3(mmol/L)	28.6	4	2	-	-	-
WBC(*$10^{9/}$/L)	7.7	6.4	5.9	6	5.7	5.3
N(*$10^{9/}$/L)	4.9	4.3	4.6	4.1	4.1	4.3
L(*$10^{9/}$/L)	2.2	1.9	1.8	2	2.1	1.9
RBC(*$10^{12/}$/L)	4.5	4.4	4.4	4.1	4.2	4
Hb(g/dl)	12.3	11.8	11.8	11.5	11.6	11.4
Platelets(10^3/mm^3)	371.7	361.4	328.4	311.1	291.3	278.1

Key

Na: Sodium, K: Potassium, Mg: Magnesium, CL: Chloride, BUN: Blood Urea Nitrogen, HCO_3: Sodium Bicarbonate, WBC: White Blood Cell count, N: Neutrophils, L: Lymphocytes, RBC: Red Blood Cells, Hb: Hemoglobin.

Table 6: Mean Square Differences in Laboratory Parameters between Cycles from the Baseline N=363*

Parameter	V2	V3	V4	V5	V6
Urea	70.3	85.2	106.4	408.6	82.1
Creatinine	15265.6	13175.6	7298.3	8695.7	9339.2
Na	8589.2	10639.5	11129.3	13068.1	15585.6
K	9.0	11.9	547.6	618.9	16.5
Mg	4132.4	1118.2	1396.6	1396.6	957.5
CL	4132.4	1118.2	1396.6	1396.6	957.5
BUN	1002.8	137.9	93.3	11.1	5.2
HCO_3	33502.9	37222.0	41874.4	41874.4	41874.4
WBC	44.6	833.0	1345.4	1404.6	71.8
N	49.9	1442.9	94.9	49.9	55.9
L	819.6	271.1	289.6	372.4	281.7
RBC	8.2	9.5	11.7	13.3	15.7
Hb	1505.0	2175.6	1472.5	1622.2	1530.4
Platelets	114745.7	69827.2	58332.4	37606.7	23669.0

*Four Participants could not be assessed for GFR because of missing weights and/or age.

The analysis of mean square differences in laboratory parameters indicate an increase in urea, sodium, potassium, bicarbonate, white blood cell count and red blood cell counts. There was, however, decreases in creatinine, magnesium, chloride, blood urea nitrogen, neutrophils, lymphocytes, platelets and hemoglobin levels (Table 6).

Table 7 on page 61, appendix II, summarizes the changes in six laboratory parameters throughout the 6 courses of chemotherapy.

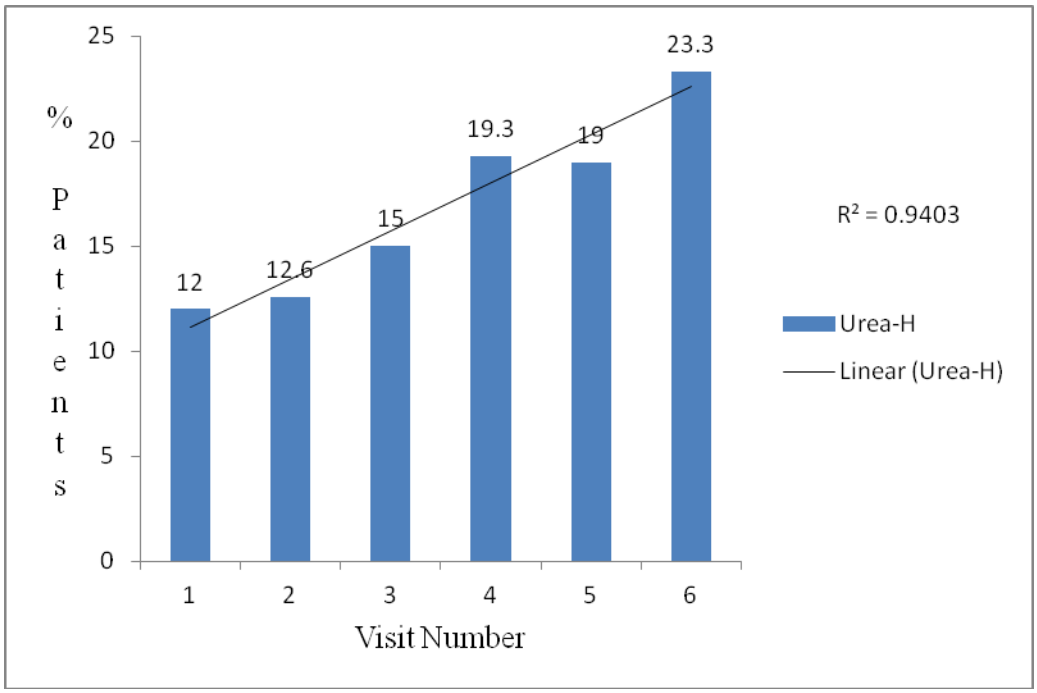

Figure 3: Proportion of Patients with Hyper uricaemia per Visit Cycle

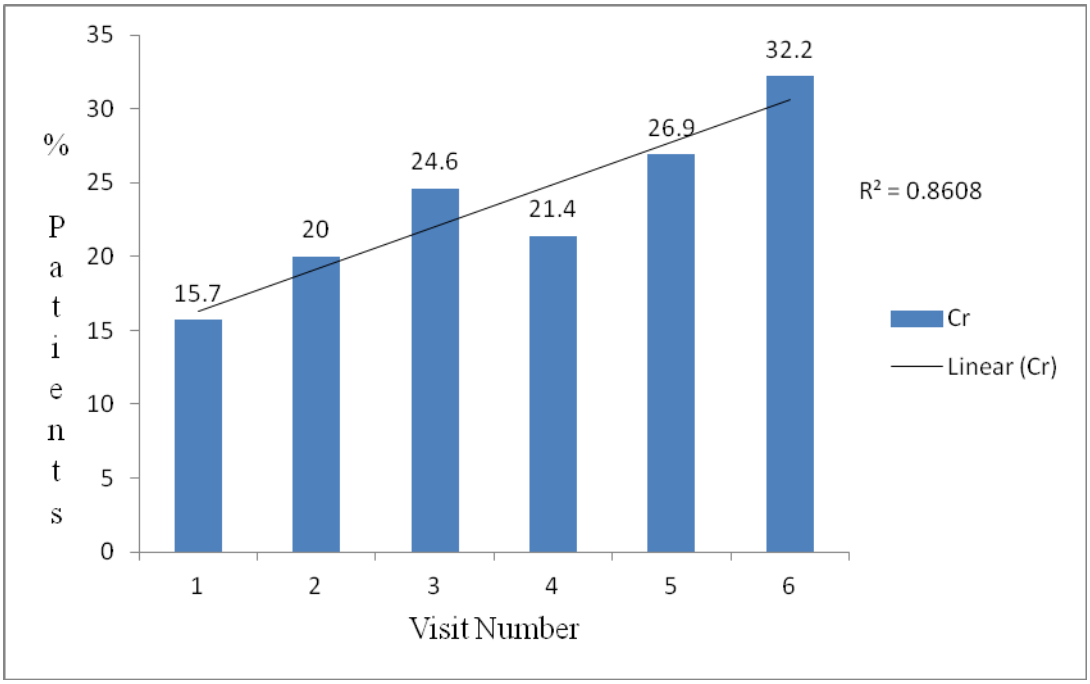

Figure 4: Percentage of patients having elevated Creatinine Concentration per Visit Number

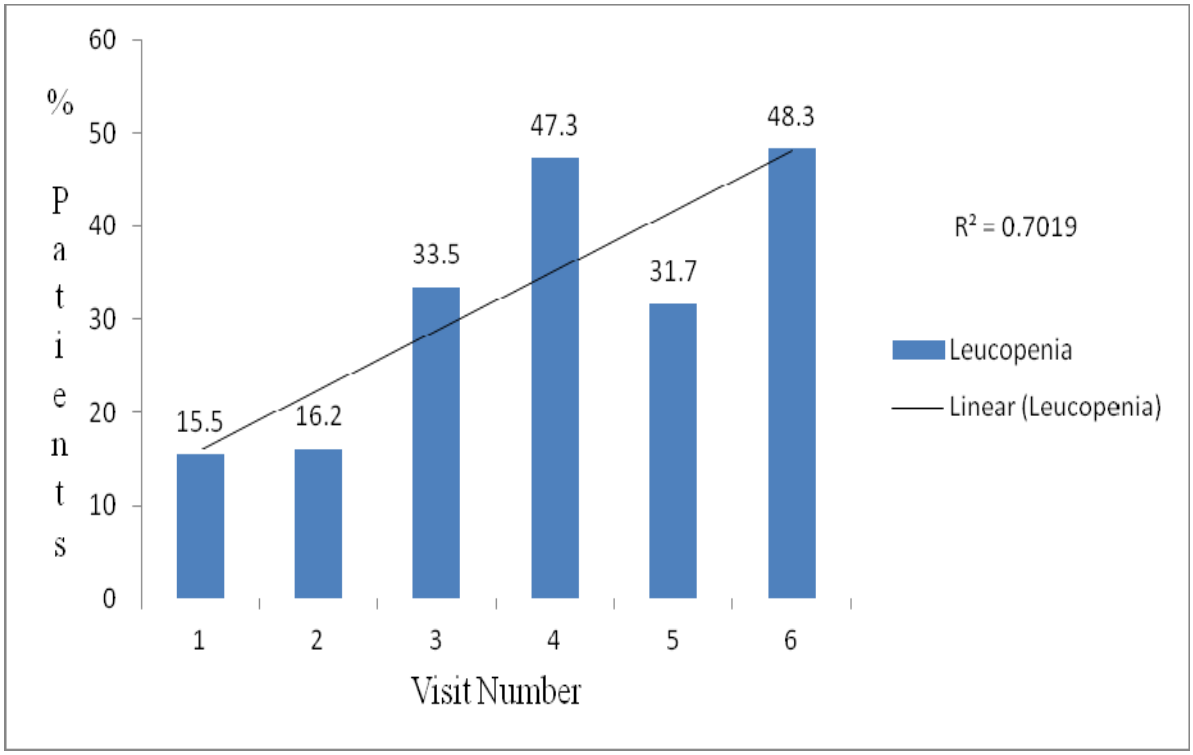

Figure 5: Proportion of patients with Leucopenia per Visit Cycle

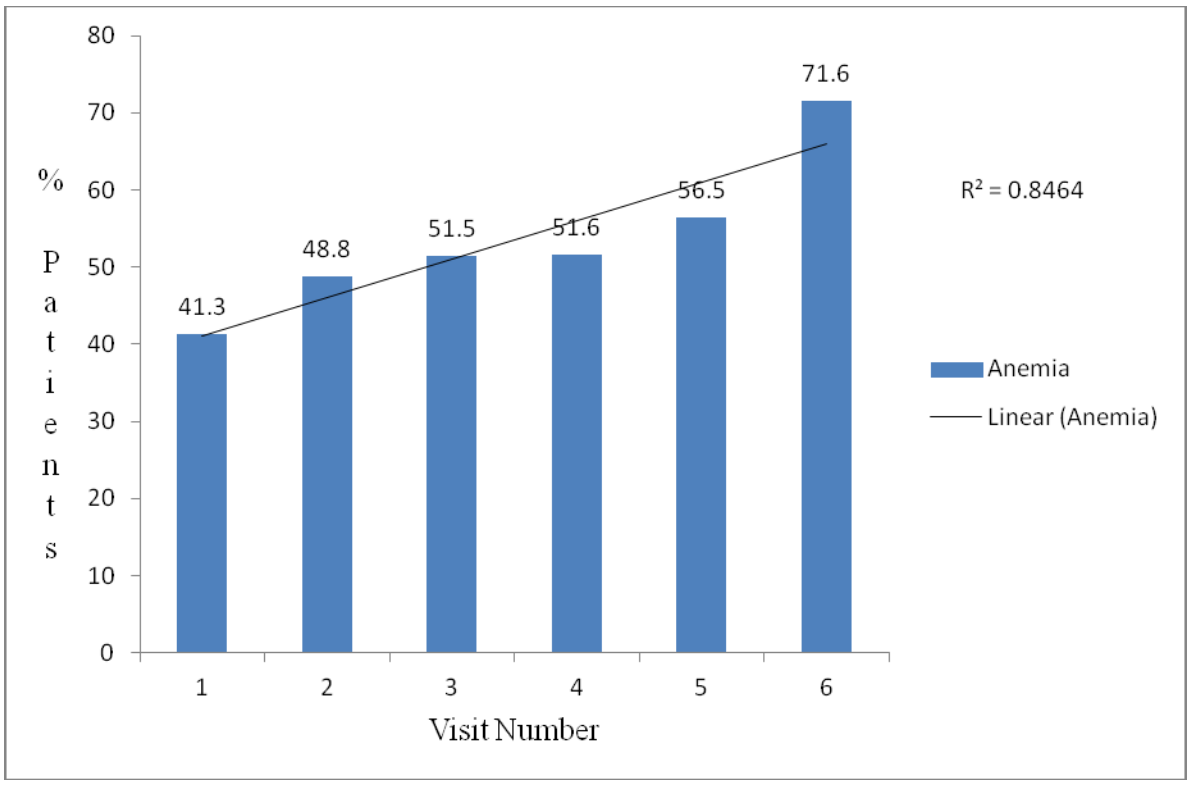

Figure 6: Percentage of patients with Anemia per Visit Number

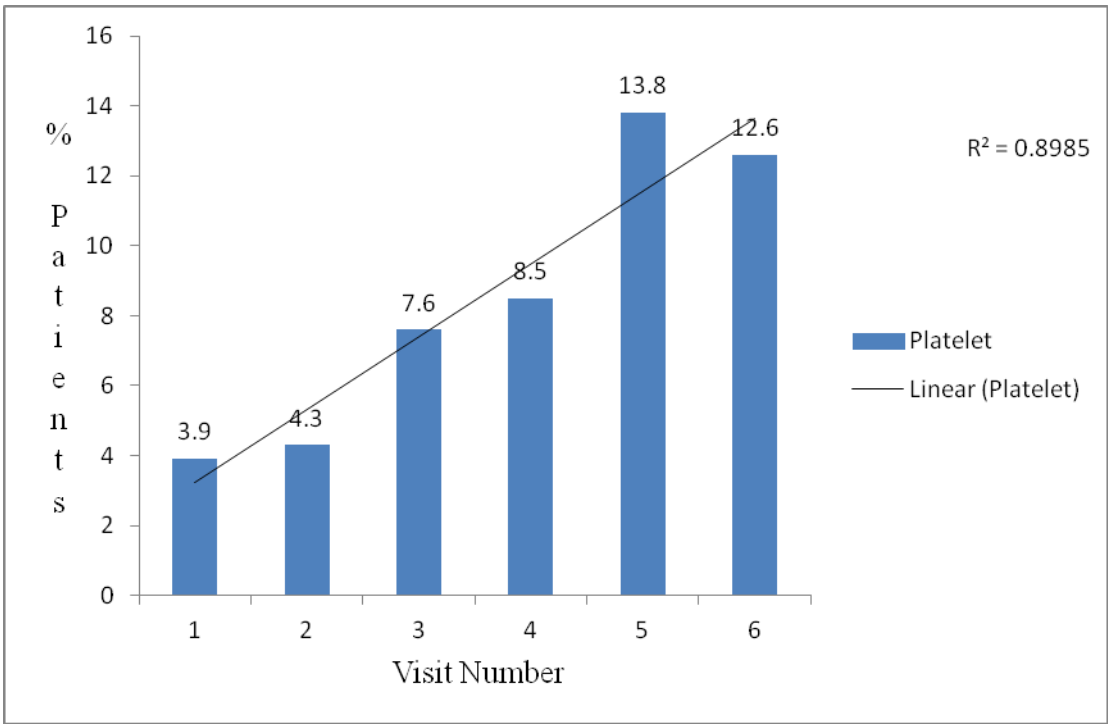

Figure 7: Percentage of patients having Platelet < 150,000/mm^3 per Visit cycle

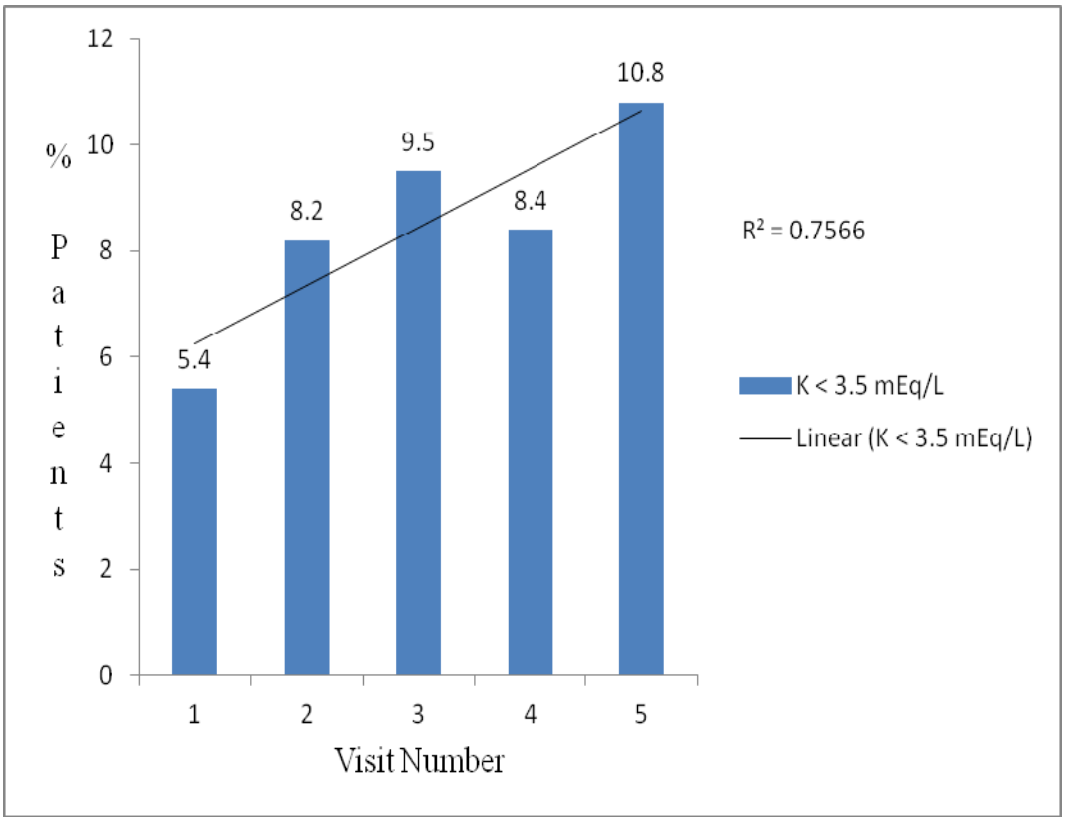

Figure 8: Percentage of patients having potassium < 3.5 mEq/L per Visit cycle

4.3.2 Glomerular Filtration Rates Trends

There was a general fall in mean GFR rates from course 1 through 5 with a slight rise in course 6. The overall GFR achieved was 59.3ml/min/m^2 (±SD 20.6). The 25th percentile GFR was 44.7 and the 75th percentile GFR was 71.1 ml/min/m^2.

Table 8 below shows the trend of glomerular filtration rates (GFR) among the study participants during the course of treatment with cisplatin based regimens.

Table 8: Mean Median, Minimum and Maximum GFR (ml/min/m^2) and Overall GFR for each Cycle

	GFR1	GFR2	GFR3	GFR4	GFR5	GFR6	Overall GFR
Mean GFR(ml/min/1.73m	65.6	59.2	58.1	58.0	54.4	56.1	59.3
Median	61.9	56.4	55.6	55.9	51.4	55.1	55.8
Minimum	4.8	3.9	3.4	12.7	10.7	8.3	22.1
Maximum	429.3	151.9	173.4	180.1	124.1	114.1	157.6
Percentile 25	45.8	43.5	42.2	41.9	37.0	41.8	44.7
Percentile 75	73.9	71.7	69.8	69.0	70.2	66.9	71.1
Standard Deviation	37.1	21.7	23.5	23.6	22.6	21.5	20.6

4.3.3 Grading of Nephrotoxicity

The number of patients with grade 0 and 1 nephrotoxicity declined from visit 1 through visit 6 whereas the number of those suffering nephrotoxicity grades 2-4 increased from visit 1 to visit 6. Overall, 6.5% of the patients developed grade 0 nephrotoxicity, 35% developed grade 1, 43.8% developed grade 2, while 14.7% developed grade 3. Table 8 below shows the grade of nephrotoxicity achieved at each visit.

Table 9: Grading of Nephrotoxicity According to the Estimated GFR

GFR (ml/min/1.73M^2)	Grade0 (>90)		Grade 1 (60-89)		Grade 2 (40-59)		Grade 3 (20-39)		Grade 4 (<20)	
Visits	n	%	n	%	n	%	n	%	n	%
V1	33	11.3	123	42.0	95	32.4	41	14.0	1	0.3
V2	20	7.9	85	33.7	105	41.7	37	14.7	5	2.0
V3	18	8.6	68	32.5	79	37.8	40	19.1	4	1.9
V4	15	8.6	54	30.9	71	40.6	34	19.4	1	0.6
V5	9	7.0	36	28.1	43	33.6	34	26.6	6	4.7
V6	7	8.6	21	25.9	36	44.4	15	18.5	2	2.5
Overall	22	6.5	119	35.0	149	43.8	50	14.7	0	0.0

4.3.4 Proportion of Patients developing Nephrotoxicity at each visit

The number of patients developing some form of nephrotoxicity at each subsequent visit increased over time from a proportion of 46.8% in visit 1 to 65.4% in visit 6 (Table 10).

Table 10: Proportion of Patients developing Nephrotoxicity at each visit

Visit	No Nephrotoxicity n (%)	Nephrotoxicity n (%)	Total n (%)
V1	156 (53.2)	137 (46.8)	293 (100)
V2	105 (41.7)	147 (58.3)	252 (100)
V3	86 (41.1)	123 (58.9)	209 (100)
V4	69 (39.4)	106 (60.6)	175 (100)
V5	45 (35.2)	83 (64.8)	128 (100)
V6	28 (34.6)	53 (65.4)	81 (100)

Table 11: Table of Attrition

n=363*

Visit	Patients Evaluated	Patients not evaluated	Attrition Rate
V1	293	70	19.1
V2	252	111	30.1
V3	209	154	41.9
V4	175	188	51.2
V5	128	235	63.7
V6	81	282	76.8

*Four participants had no weight and/or age recorded and GFR could not be calculated.

Attrition rates increased from 19.1% in visit 1 to 76.8% in visit 6. Some patients lacked creatinine measurement, weight not taken and hence not recorded; others transferred out or died. Missing data on weight and age resulted in four participants not able to be evaluable hence missing from the (Table 10) above.

4.3.5 Nephrotoxicity Grades and Trends

The overall grade of moderate to severe nephrotoxicity was 59.3%. The figure below summarizes the proportion of patients developing nephrotoxicity at each visit.

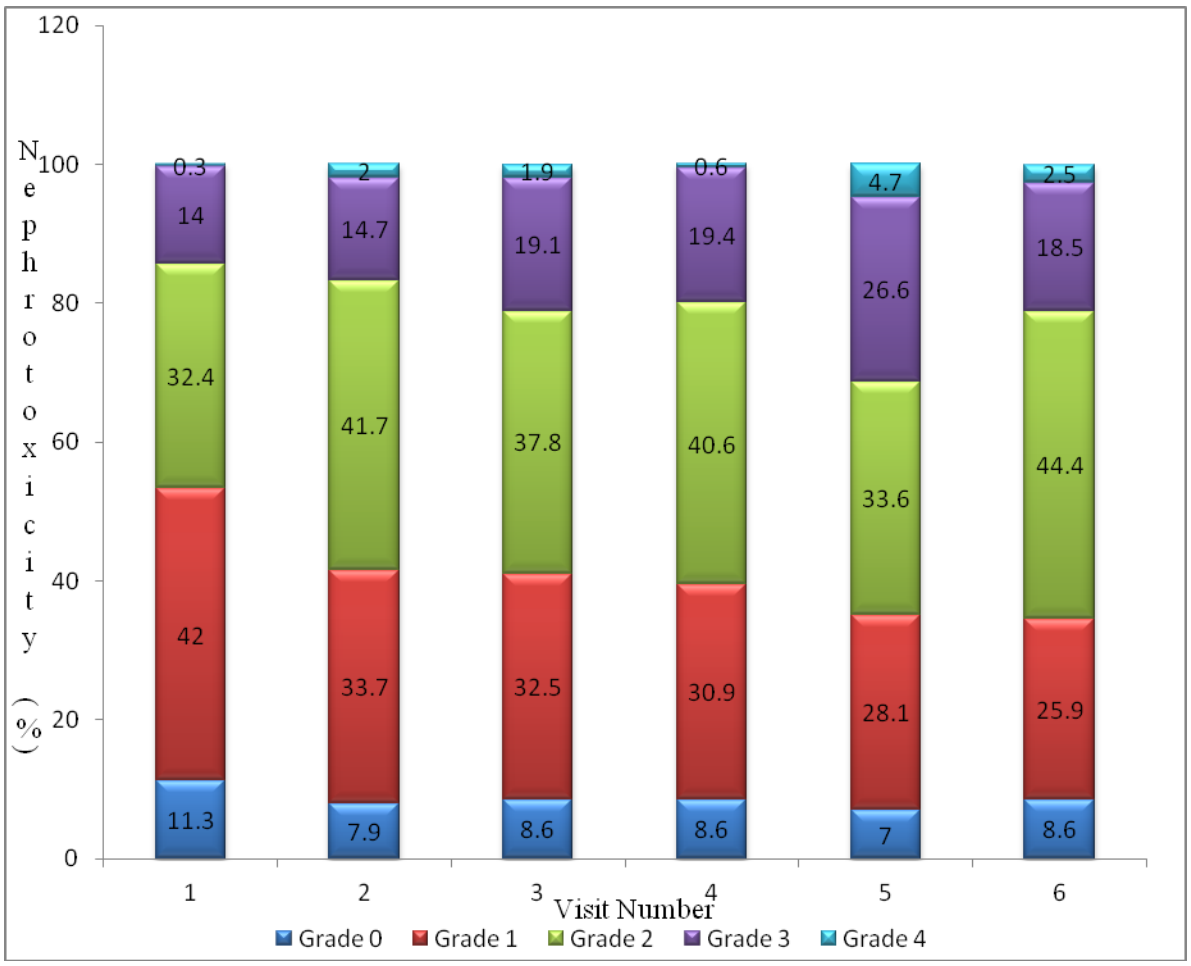

Figure 9: Proportion of patients developing Nephrotoxicity at each visit according to grades

The equation of the trend line in the development of nephrotoxicity through the visit numbers has a coefficient of determination, R^2, of 0.8224 (Figure 10).

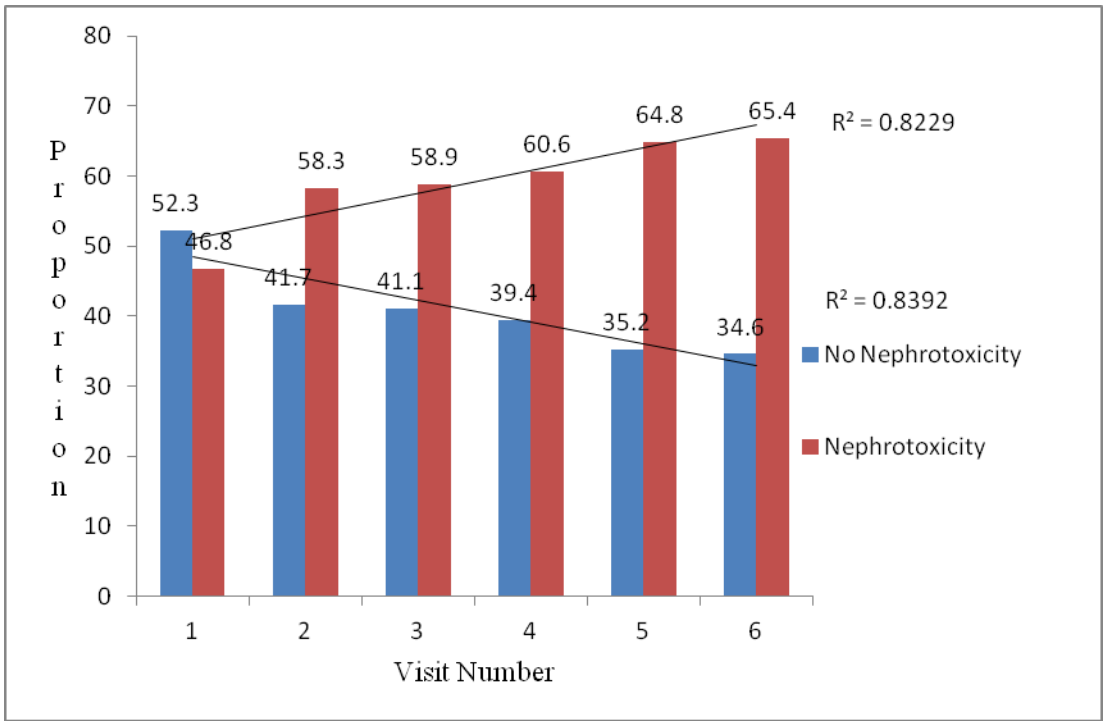

Figure 10: Nephrotoxicity Trends per Visit cycle.

4.3.6 Manifestation of renal toxicity

Anemia was the commonest manifestation of renal toxicity at 57.5% followed by hypokalaemia at 23%. Hypocalcaemia was noted in 0.5% of the patients (Figure 11).

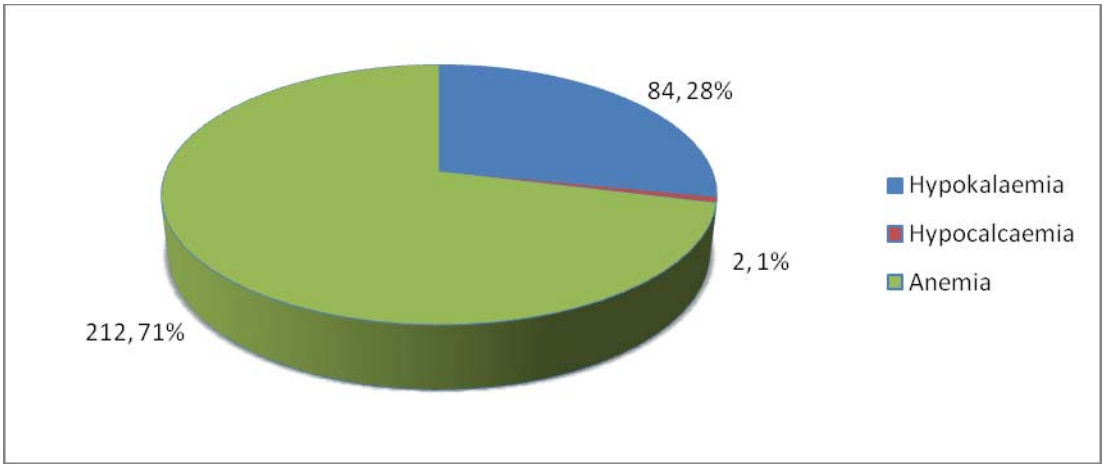

Figure 11: Manifestation of Renal Toxicity

4.4 Strategies used to prevent the development of Nephrotoxicity in patients on Cisplatin Chemotherapy

Table 12: Association between Strategies and Development of Cisplatin Nephrotoxicity

Preventive Strategy	**Nephrotoxicity**				**Chi square**	**P value**
Normal Saline Dose	No Nephrotoxicity		Nephrotoxicity Developed			
	n	(%)	n	(%)		
1L	38	22.5	131	77.5	1.441	0.487
2L	44	26.7	121	73.3		
3L	0	0.0	2	100.0		
Drug Postponed : No	82	36.1%	145	63.9%	47.863	**<0.0001**
:Yes	2	1.8%	111	98.2%		
Regimen changed: No	83	25.3%	245	74.7%	1.792	0.181
:Yes	1	8.3%	11	91.7%		

The dose of normal saline used (p=0.487) and the change of regimen from cisplatin to carboplatin did not seem to confer protection to development of nephrotoxicity (p=0.181). However, postponement of the regimen conferred the protection to the kidneys (p<0.0001).

All patients were given pre and post hydration using normal saline and advised to take up to 2L of water orally. Dose of cisplatin was changed in 3.5% of patients and 33.2 % had dose postponed because of deranged laboratory values (Table 12).

4.5 Risk factors associated with Nephrotoxicity

4.5.1 Risk Factors

Cumulative dose of cisplatin greater than 200mg/m^2 was the commonest risk factor (66.4%) associated with nephrotoxicity. This was followed by radio sensitization at 51.2% and electrolyte abnormalities at 12.2%. The latter included hypokalaemia (22%) and hypocalcaemia (0.5 %).

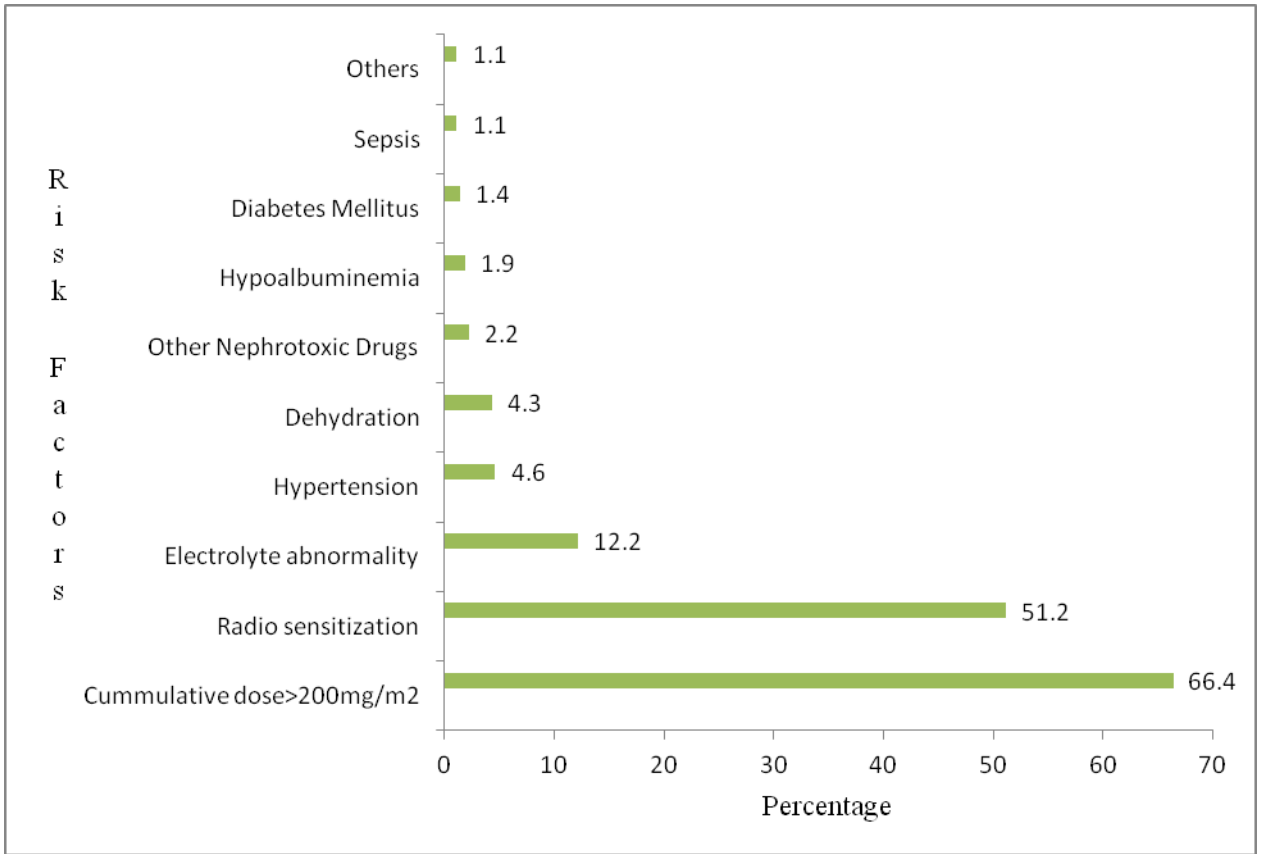

Figure 12: Risk Factors for Nephrotoxicity

4.5.2 Assessment of socio demographic Characteristics associated with Nephrotoxicity

Gender, residence, weight, educational level, and employment status were all found to be statistically significantly associated with nephrotoxicity (**$p < 0.05$**). Marital status was,

however not found to be statistically significantly associated with development of nephrotoxicity (p= 0.166.) (Table13).

Table 13: Association between the risk factors associated with Nephrotoxicity and Socio-demographic characteristic of the study Participants

Characteristic		Nephrotoxicity				Chi square	P value
		No nephrotoxicity		Nephrotoxicity developed			
		N	%	n	%		
Gender	Male	39	30.7	88	69.3	3.927	**0.048**
	Female	45	21.1	168	78.9		
Residence	Urban	42	29.8	99	70.2		
	Rural	33	19.2	139	80.8	4.779	**0.029**
Education level	Informal	8	12.3	57	87.6		
	Primary	14	16.5	71	83.5	14.040	**0.003**
	Secondary	28	28.6	70	71.4		
	College	25	35.7	45	64.3		
Marital status	Married	56	25.3	165	74.7		
	Single	15	33.3	30	66.7	6.482	**0.166**
	Divorced	2	25.0	6	75.0		
	Widowed	6	11.8	45	88.2		
	Separated	2	25.0	6	75.0		
Employment status	Employed	31	34.4	59	65.6		
	Not employed	42	20.6	162	79.4	9.474	**0.024**
	Student	3	16.7	15	83.3		
	Retired	1	7.1	13	92.9		

Logistic regression was carried out on all variables statistically significant on bivariate analysis to remove iteratively all variables not significant at $p < 0.05$. We started with

eight factors including age, weight, gender, height, residence, education level, marital status and employment status. Upon fitting these factors and specifying "backward conditional" method with removal at $p<0.05$, three factors were retained in the final model as seen in Table 14 below.

Table 14: Multivariate analysis on Factors Shown to be Associated with Nephrotoxicity

	Coefficient	S.E. of coefficient	P value	OR	95% C.I. for OR	
					Lower	Upper
Age	0.070	0.012	**<0.0001**	1.073	1.047	1.099
Weight(>58Kg)	-0.073	0.012	**<0.0001**	0.929	0.908	0.952
Gender	0.859	0.295	**0.004**	2.361	1.324	4.211

The analysis showed that older patients were more likely to develop nephrotoxicity [OR 1.07 (95% CI 1.05 – 1.10), $p<0.0001$].

Weight more than 58Kg was associated with lower risk of developing nephrotoxicity [OR 0.93 (95% CI 0.91 – 0.95), $p<0.0001$].

Female patients were at a greater risk of developing nephrotoxicity than their male counterparts [OR 2.36 (95% CI 1.32 – 4.21), $p=0.004$].

CHAPTER 5: DISCUSSION, CONCLUSIONS AND RECOMMENDATIONS

5.0 Discussion

Our study revealed female predominance at 62.6% and the mean age of the study population as 51 years. These findings are in contrast with a similar study done by Agwata *et al* (39) which showed male preponderance. These differences could be attributed to differences in study population and the study period. Agwata *et al* studied cancers in children over a ten year period whereas our study was looking at adult cancers over a two year period.

Nephrotoxicity was more common in females than males. This differs from a study by Nematbakhsh *et al* which found it more common in males than females. However, unlike our study in humans, they investigated this latter study in rats and proposed that it could be due to differences in renal circulation, and the pharmacokinetics of the drug and genetic makeup could be factors contributing (40).

About fifty five per cent of patients were from rural areas. KNH is a national referral centre for management of cancer. Perhaps most of our participants were referrals from rural facilities which do not have capacity to manage their cancers. Education level was found to be strongly associated with the development of nephrotoxicity. Educational status influences income status and hence higher level of socioeconomic status. This may suggest that the lower the socioeconomic status and by extension the educational status, the fewer the screening for cancer status hence the higher prevalence of nephrotoxicity.

We found age to be an independent predictor of nephrotoxicity. This is because elderly patients had a significantly higher incidence of severe nephrotoxicity. This is in

concordance with other similar studies (41). Further, it has been shown that renal function declines with increase in age because the number of active nephrons reduces with advanced age (42).

A majority of cancer type treated was cervical cancer (41.5 %) followed by ovarian cancer (12.7%). Most patients were put on cisplatin therapy as a radio sensitizer for patients undergoing concurrent radiation. Punushapai *et al* have shown that chemo radiotherapy with weekly cisplatin 40 mg/m2 in locally advanced cervical cancer gives good treatment outcomes (43). Suggesting that cisplatin based regimen are more commonly used in cervical cancer for better outcome.

We found out that anemia (29.0%), hypertension (5%), diabetes (2%), heart failure (1 %) and sepsis (1 %) were co morbidities associated with cancer in study patients. A study done by Mathe *et al* found that anemia, hypertension, diabetes and heart failure as the commonest co-morbidities (44). Asangansi *et al* found anemia, hypertension and diabetes (30) while Miller et al found that diabetes was not a common co morbidity (16). A study by Mizumo *et al* found that diabetes mellitus, cardiovascular disease and advanced cancer increased the risk of severe cisplatin induced acute kidney injury and shortens the survival period (45). Other similar studies have found anemia in 29%, neutropenia and thrombocytopenia (46).The commonest complication of most cancers is anemia due to direct effect on hematopoiesis and impaired erythropoiesis(47).

We found the prevalence of nephrotoxicity in our study patients to be 58.5%. This was similar to a study by Vaibhav Sahni *et al* who reported the prevalence of underlying renal dysfunction in patients with cancer to be as high as 60% (48). Blachey *et al* reported that nephrotoxicity may occur in as many as 50% to 75% of patients receiving cisplatin (49).

However, the findings differed with Hartmann et al and Vaibahv Sahni *et al* who found reduction in glomerular filtration rate occurring in 20% to 30% of patients (48). This high prevalence of nephrotoxicity in patients using cisplatin is due to renal tubular injury (46). The prevalence of nephrotoxicity in pediatric cancer patients on chemotherapy at KNH was 37% (37). The possible explanation of the difference in the prevalence is because of different populations studied.

Our study has revealed that nephrotoxicity increased with subsequent cycle of chemotherapy. This was probably due to cumulative renal tubular injury caused by cisplatin (46). Daugard *et al* (22) in their prospective study on Cisplatin nephrotoxicity, experimental and clinical study, found that, there was a severe progressive decline in GFR observed during treatment and GFR remained decreased for up to 2 years after termination of treatment.

In addition some co morbidities such as diabetes and hypertension may increase kidney damage. However, this study has revealed that nephrotoxicity profiles were all reversible following cisplatin postponement in 33.2 % of our population. Studies have shown that nephrotoxic reactions such as leucopenia and thrombocytopenia which are associated with cisplatin therapy are all reversible (42) upon discontinuation of therapy.

There was a trend of decrease in hemoglobin, potassium, white blood cells and platelets and an increase in urea and creatinine with the subsequent courses of cisplatin chemotherapy. This was similar to studies done by Yao et al, Gomez et al and Launey *et al* which all found hypokalaemia and hypomagnesaemia as being the commonest derangements associated with cisplatin administration (7, 27, 28).

Our study findings indicate that the risk factors predisposing to cisplatin nephrotoxicity development included cumulative dose of cisplatin (>200mg/m^2), prior radio sensitization ,electrolyte abnormalities (hypokalaemia, hypocalcaemia, hypomagnesaemia, hyponatremia, hyochloraemia), hypertension, dehydration, hypoalbuminaemia, diabetes and sepsis. These findings are similar to several studies by various authors(20, 21). A study done by Vaughan *et al*, found that a cumulative cisplatin dose ≥500 mg/m^2 was associated with increased risk of nephrotoxicity. Doses of cisplatin in excess of 50 mg/m^2 can cause renal insufficiency (50).

The key to proper prevention of nephrotoxicity has been shown to be the identification of patients at high risk of chemo therapy induced nephrotoxicity, adequate volume infusion, early detection of renal damage, avoidance of concurrent use of other nephrotoxic drugs, serial monitoring of renal function, and electrolyte repletion when necessary(48).

Our study has revealed that the dose of normal saline used was statistically insignificantly associated with development of nephrotoxicity (p=0.487). Studies have shown that despite saline infusion, nephrotoxicity remained frequent in patients receiving cisplatin regimen. However, this was more common among patients also suffering from cardiovascular disease or diabetes mellitus (35). This differed with a study by Tiseo *et al*, who investigated a short hydration regimen and found that normal saline reduces cisplatin nephrotoxicity (10). However, the amount and duration of hydration remains controversial. Our study contrasts with other studies which have shown that Sodium chloride showed protection against nephrotoxicity caused by cisplatin metabolites only at low doses of platinum (51).

The nephrotoxic preventive strategy of drug postponement was done in 1 out of 3 patients because of untoward renal functions of hyperuricaemia and increased creatinine. Cessation or reduction of chemotherapy should be considered for patients who have an elevation of Serum creatinine levels during cisplatin combination chemotherapy (52). In patients who are at high risk for drug toxicity, the dosage should be adapted to renal function, and the use of nephrotoxic therapies avoided whenever possible (28).

About 4% of the participants had cisplatin replaced with carboplatin due to unwanted side effects. Carboplatin is equally effective as cisplatin but has the advantage of being less nephrotoxic. It is associated with a lower risk of developing renal complications than cisplatin, but it should not be routinely used, as it reduces the long-term cure rate of metastatic testicular cancer patients (50).

Three factors, age, female gender and weight were strongly associated with high risk of nephrotoxicity following cisplatin administration ($p=0.001$). Increased age and pre-existing renal disease have been associated with renal toxicities (50). Nephrotoxic risk was higher in those aged over 52 years, weighing less than 58 kg and female gender. A patient older than 52 years, weighs less than 58 kg and is female had a higher likelihood of developing nephrotoxicity following cisplatin exposure.

5.2 Conclusions

Most common type of cancer in the use of cisplatin combination was cervical cancer. Nephrotoxicity was found to be high (58.5%) in our study population and the profiles of nephrotoxicity increased with the number of cycles. The most common preventive strategies to nephrotoxicity were use of normal saline and oral hydration. However, the

dose of normal saline was found to be statistically insignificant towards development of cisplatin nephrotoxicity.

Advanced age above 52 years, female gender and weight less than 58 kg were found to be significantly associated with development of cisplatin nephrotoxicity. Although age and gender risk factors are non- modifiable, weight may be modified by maintaining weight in the normal BMI to avert nephrotoxicity. Nevertheless, recognizing risk factors that increase renal vulnerability to drug-induced kidney disease is the first step in reducing the renal complications of drugs and toxins (53). For the elder patients, care must be exercised in them by reducing the doses of cisplatin (54).

5.3 Recommendations and Future Work

Despite the fact that patients receiving cisplatin based regimens are put on preventive strategies to prevent the development of nephrotoxicity, more than half exhibit nephrotoxic profiles, suggesting that better ways of preventing nephrotoxicity ought to be sought.

5.4 Limitations of the study

The study relied immensely on pre recorded information in the patients' files and therefore incomplete records from the files greatly hindered the study missing drug treatments given, weight and serum creatinine values making it impossible to calculate GFR. We minimized this by ensuring that only the files with as much information as possible were used for the study. Secondly, many patients were lost to follow up because of transfer to get chemotherapy at other hospitals. It was minimized getting as much information in other clinics and the files' registry about them.

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Appendices

Appendix I: Data Collection Form

For The Study "Evaluation of Preventive Strategies Against Development of Nephrotoxicity in Patients Receiving Cisplatin Based Regimen at Kenyatta National Hospital"

Study ID…….. Study Serial Number**…….**

1.0 Participant Socio-demographic Data

Date of data collection: ……

Patient Code Number: ……. Data Collector's initials: …….

1. Age: ……Years
2. Weight:……..…Kg
3. Height: ……M
4. Gender: 0. Male ( ) 1. Female ( )
5. Place of residence: 0. Urban ( ) 1. Rural ( )
6. Highest level of Education

0. Informal ( ) 1. Primary ( ) 2. Secondary ( ) 3. College ( )

7. Marital Status

0. Married ( ) 1. Single ( ) 2. Divorced ( ) 3. Widowed ( ) 4. Separated ( )

8. Employment Status

0. Employed ( ) 1. Not Employed ( ) 2. Student ( ) 3. Retired ( )

2.0 Cancer specific information

What type of cancer was diagnosed? Duration since Diagnosis?

No	Type of cancer	Tick as	Duration since Diagnosis
1	Cervical		
2	Esophageal		
3	Germ cell		
4	Head and Neck		
5	Ovarian		
6	Osteosarcoma		
7	Squamous Cell		
8	Breast Cancer		
9	Lung Cancer		
10	Other (Specify)		

3.0 Conventional Anticancer Medicine prescribed

Name the drug, dose and frequency of the anticancer medications.

No	Drug Name	Dose	Frequency	Duration
1				
2				
3				
4				
5				

6. Has the regimen been changed? Yes ( ) No ( )

7. If Yes, why?

Specify.....

4.0 Specify other co morbidities present in the patient.

1. Cirrhosis □Yes □No
2. Diabetes Mellitus □Yes □No
3. Hypertension □Yes □No
4. Heart Failure □Yes □No

5. Nephrosis □Yes □No
6. Hyperuricaemia □Yes □No
7. Shock □Yes □No
8. Sepsis □Yes □No
9. Anemia □Yes □No
10. Others (Specify)……

……

5.0 Laboratory Test Values Before Chemotherapy

Parameter	1st cycle Date….	2nd cycle Date…….	3rd cycle Date……	4th cycle Date……	5th cycle Date…….	6th cycle Date……
Urea						
Creatinine						
Na						
K						
Mg						
Ca						
Hco3						
Urine K						
Urine Na						
Urine PH						
WBC						
RBC						
Hb						
Platelets						
e/ GFR						

6.0 Describe the Type of Therapy given as Preventive Strategy to Nephrotoxicity

Fluid Therapy Given	1st Cycle		2nd Cycle		3rd Cycle		4th Cycle		5th Cycle		6th Cycle	
	Dose	Duration	Dose	Duration	Dose	Duration	Dose	Duration	Dose	Duration	Dose	Duration
0.9% NaCl												
5%Dextrose												
Mannitol												
MgSO4												
Inj. Furosemide												
KcL												
Advised to drink 2L												
Amifostine												
Combination of												
Dose Reduced												
Drug Withdrawn												
Other(Specify)												

7.0 Risk Factors Associated with Nephrotoxicity

Risk Factor	Tick As Appropriate
Previous Kidney Disease	
Solitary Kidney	
Diabetes Mellitus	
Hypertension	
Dehydration	
Hypoalbuminuria	
Sepsis	
Shock	

Radiocontrast Agent Exposure	
Other Nephrotoxic Anticancer Agents Use	
Cummulative Dose > 200mg/m^2	
Electrolyte Abnormalities	
Us of Other Nephrotoxic Drugs	
Other (Specify)	

8 Outcome of Preventive Strategy

Nephrotoxicity development √ ×

Grade of Nephrotoxicity (As Per Estimated GFR) …….

No Nephrotoxicity √ ×

Other (Specify)…….

9 Renal Manifestation of Renal Toxicity, if any (Tick).

Hypokalaemia [ ]

Hypomagnesaemia [ ]

Hypocalcaemia [ ]

Anemia (Hb < 12g/dl) [ ]

Renal Tubular Acidosis [ ]

Reduced GFR [ ]

Other (Specify)……..

Appendix 2: Table 7: Proportion of low, normal and elevated laboratory parameters per visit.

Parameter	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Urea (mg/dl)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Low	23(6.8)	19(6.6)	14(6.1)	16(8.1)	9(6.3)	4(4)
Normal	276(81.2)	231(80.8)	180(78.9)	143(72.6)	106(74.7)	72(72.7)
High	41(12)	36(12.6)	34(15)	38(19.3)	27(19)	23(23.3)
Total	340	286	228	197	142	99
Creatinine(mg/dl)						
Low	21(6.6)	12(4.4)	12(5.3)	8(4.1)	4(2.8)	5(5.4)
Normal	248(77.7)	219(79.6)	102(70.1)	145(74.4)	102(70.3)	58(62.4)
High	50(15.7)	44(20)	56(24.6)	42(21.5)	39(26.9)	30(32.2)
Total	319	275	228	195	145	93
WBC($x10^9$/L)						
Low	55(15.5)	45(16.2)	71(33.5)	78(47.3)	39(31.7)	42(48.3)
Normal	239(67.5)	202(72.7)	126(59.4)	74(44.8)	76(61.8)	41(47.1)
High	60(17)	31(11.1)	15(7.1)	13(7.9)	8(6.5)	4(4.6)
Total	354	278	212	165	123	87
Hemoglobin(g/dl)						
Low	147(41.3)	138(48.8)	111(51.5)	99(59.3)	19(15.3)	10(11.4)
Normal	198(55.6)	142(50.2)	102(47.4)	68(40.7)	105(84.7)	78(88.6)
High	11(3.1)	3(1)	2(0.1)	0(0)	0(0)	0(0)
Total	356	283	215	167	124	88

Platelets(x10^3/mm^3)						
Low	14(3.9)	12(4.3)	16(7.6)	14(8.5)	17(13.8)	11(12.6)
Normal	264(74)	208(74.3)	158(74.9)	135(82.3)	92(74.8)	67(77)
High	79(22.1)	60(21.4)	37(17.5)	15(9.1)	14(11.4)	9(10.4)
Total	357	280	211	164	123	87
Potassium(mEq/L)						
Low	15(5.4)	21(8.2)	19(9.5)	15(8.4)	14(10.8)	6(7.3)
Normal	230(83)	203(79.6)	158(79)	137(77)	108(83.1)	67(80.8)
High	32(11.6)	31(12.4)	23(11.5)	26(14.6)	8(6.1)	9(10.9)
Total	277	255	200	178	130	83

Appendix 3: Ethical Approval

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KENYATTA NATIONAL HOSPITAL APPROVED 15 JUN 2014 KNH/UoN-ERC P.O.Box 20723-00202

Dear Dr. Odhiambo

RESEARCH PROPOSAL: EVALUATION OF PREVENTIVE STRATEGIES TOWARDS DEVELOPMENTOF NEPHROTOXICITY IN PATIENTS RECEIVING CISPLATIN BASED REGIMEN AT KENYATTA NATIONAL HOSPITAL (P167/03/2014)

This is to inform you that the KNH/UoN-Ethics & Research Committee (KNH/UoN-ERC) has reviewed and **approved** your above proposal. The approval periods are 12th June 2014 to 11th June 2015.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH/UoN ERC before implementation.
c) Death and life threatening problems and severe adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH/UoN ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH/UoN ERC within 72 hours.
e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
f) Clearance for export of biological specimens must be obtained from KNH/UoN-Ethics & Research Committee for each batch of shipment.
g) Submission of an *executive summary* report within 90 days upon completion of the study This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/or plagiarism.

For more details consult the KNH/UoN ERC website **www.uonbi.ac.ke/activities/KNHUoN.**

Protect to Discover

Yours sincerely

PROF. M. L. CHINDIA
SECRETARY, KNH/UON-ERC

c.c. The Principal, College of Health Sciences, UoN
The Deputy Director CS, KNH
The Chairperson, KNH/UoN-ERC
The Assistant Director, Health Information, KNH
The Dean, School of Pharmacy, UoN
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