ASSESSMENT OF GLOMERULAR FILTRATION RATE PROFILES OF PAEDIATRIC PATIENTS ON CANCER CHEMOTHERAPY AT THE KENYATTA NATIONAL HOSPITAL

A thesis submitted in partial fulfillment for the requirements of Degree of Master of Medicine in Paediatrics (MMedPaediatrics), University of Nairobi

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DECLARATION

This thesis is my original work and has not been presented for the award of a degree in any other university

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DEDICATION

I DEDICATE THIS WORK TO MY LOVING PARENTS AND SIBLINGS WHO SHOWERED ME WITH THEIR LOVE AND GAVE ME THEIR UNWAVERING SUPPORT AS I DID THIS WORK.

ABBREVIATIONS

ALL	Acute Lymphoid Leukemia
AML	Acute Myeloid Leukemia
ATN	Acute tubular necrosis
ATP	Adenosine Tri-Phosphate
BUN	Blood Urea Nitrogen
CD	Cumulative Dose
CHEM	Chemotherapy
CHOPP	Cyclophosphamide, Adriamycin, Vincristine, Prednisone, Procarbazine
CrCl	Creatinine Clearance
CKD	Chronic Kidney Disease
DNA	Dioxyribonucleic acid
EDTA	Edetate calcium disodium
GFR	Glomerular filtration rate
HCT	Hematopoietic cell transplantation
HD	Hodgkin's disease
K/DOQI	National Kidney Foundation/Dialysis Outcomes Quality Initiative
IL	Interleukin
INF	Interferon
MDRD	Modification of Diet in Renal Disease
MGCTs	Malignant Germ-Cell Tumors
MTX	Methotrexate
NEFA	Non-Esterified Fatty Acids
NHL	Non-Hodgkin's Lymphoma
PCr	Plasma creatinine
RAD	Radiation
SCr	Serum Creatinine
TNF	Tumor Necrosis Factor
VAC —Cis	Vincristine, Adriamycin, Cyclophosphamide & Cisplatin

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ABSTRACT

Background: An accurate estimation of renal function in children is important in optimizing the dose of many drugs used in paediatric oncology, and allows clinical monitoring of the nephrotoxic effects of cytotoxic agents such as cisplatin. Assessment of the glomerular filtration rate (GFR) is widely accepted as the best index of renal function in patients.

Objective: To determine the glomerular filtration rate profiles of paediatric oncology patients on cancer chemotherapy at the Kenyatta National Hospital.

Secondary objective was to assess the changes in glomerular filtration rates that have occurred over at least 6 months following cancer chemotherapy.

Study design: Cross sectional survey

Setting: Kenyatta National Hospital General Paediatric wards, including Paediatric Oncology and Paediatric Ophthalmology ward.

Study population: Paediatric patients who had an established diagnosis of cancer and had been on chemotherapy for at least 6 months

Study method: Chart reviews of oncology patients in general paediatric wards, ophthalmology ward and hematology clinic were done.A total of 115 patients aged upto 12 years who had an established diagnosis of cancer and had been on cancer chemotherapy for at least 6 months were recruited from the wards. Biodata and pre-treatment creatinine measurements were recorded. Creatinine clearance was calculated from measured serum creatinine using the Schwartz formula. Estimated glomerular filtration rates were tabulated.

Results: Out of the 115 children enrolled in the study 43 had abnormal kidney function. This gave a prevalence of 37% (95%CI 28-46).The other 72 children had normal kidney function. Patients aged less than 5yrs and those with solid tumors had a hiher likelihood of having an abnormal GFR compared to their older counterparts and those with lymphomas and leukemias

Conclusions: Monitoring of GFR should be done regulary as decline occurs as one continues on chemotherapy especially for the ones below 5yrs and those with solid malignancies

CHAPTER 1

INTRODUCTION

Renal failure remains an important complication of cancer and its treatment and this is often multifactorial in origin (1-3). Measurement of renal function may be important in monitoring the nephrotoxic effects of drugs such as cisplatin and ifosfamide(4).

Several factors can potentiate renal dysfunction and contribute to the nephrotoxic potential of antineoplastic drugs. It is necessary to exclude all other causes of renal dysfunction (pre-renal, obstructive, iatrogenic or cancer-related) (**Table 1**). These include: Intravascular volume depletion, either due to external losses or fluid sequestration (as in ascites or edema). This is one of the most common factors contributing to the nephrotoxic potential of antineoplastic drugs. The concomitant use of non chemotherapeutic nephrotoxic drugs (e.g. aminoglycoside antibiotics, nonsteroidal anti-inflammatory drugs) or radiographic ionic contrast media in patients with or without preexisting renal dysfunction (5).

Assessment of the toxicity caused by chemotherapy in children with cancer has become more important as the number of long-term survivors has continued to increase. It is vital to monitor both acute life-threatening adverse effects and long-term toxicity that may impair the child's development and cause permanent morbidity (6).

CHAPTER 2

2.1 LITERATURE REVIEW: This will cover background information on malignancies, treatment of malignancies, risk factors for nephrotoxicity and nephrotoxic effects of individual chemotherapeutic drugs.

2.1.1 Background

Thirteen percent of the annual deaths worldwide are cancer-related and 70% of these are in the low- and middle-income countries (7).Worldwide, the annual number of new cases of childhood cancer exceeds 200,000 and more than 80% of these are from the developing world (8). The incidence of childhood cancer in most populations in the world ranges from 75 to 150 per million children per year (9, 10).

It is estimated that the annual frequency of childhood cancers at Kenyatta National

Hospital (KNH) is 125 cases per year. A review of some childhood cancers at KNH by Macharia in 1996 (11) found hospital based prevalence to be 1.27%. The pattern of pediatric solid malignant tumors in western Kenya: an analysis based on histopathologic study by Makata Et al the total number of cancer patients registered by the western Kenya laboratories during the study period of 16 years was 7,148 and of these, 676 cases were children less than15 years old. Childhood tumors therefore constituted 9.5% of all malignancies (10).

The pattern of malignancies among indigenous Zambian children is described. The study, based upon an analysis of histopathology, autopsy and haematology records for a 10-year period (1980-1989), reveals a total of 525 neoplasms with peak prevalence in the 5-9 year age group (10).

2.1.2 Treatment of childhood malignancies

The most common approach to cancer treatment is by combination therapy in which various modalities of surgery, radiotherapy and chemotherapy are used to eradicate both the primary neoplasm and metastatic lesions. (13). At Kenyatta National Hospital, a multimodal approach is used for the treatment of the various paediatric cancers. The most widely used modality in pediatric cancer therapy is chemotherapy (14, 15). Most of the cytotoxic drugs for childhood cancer are selected from several classes of agents, including alkylating agents, antimetabolites, antibiotics, hormones, plant alkaloids, and topoisomerase inhibitors. Therapy nearly always involves combinations of drugs, such as VAC (vincristine, doxorubicin or dactinomycin and cyclophosphamide) and CHOP (cyclophosphamide, doxorubicin , vincristine and prednisone) (**Table 2**).

The increased metabolic and cell cycle activity of malignant cells make them more susceptible to the cytotoxic effects of anticancer drugs. During treatment cytotoxic chemotherapeutic drugs exert their effect by inhibiting cell proliferation. All proliferating cells, whether normal or malignant go through a series of phases: Synthesis of DNA (S phase), Mitosis (M phase) and rest (G 1 Phase). Non cycling cells are quiescent in the G O Phase [16]. Cell cycle non-specific anticancer drugs are known to kill cells regardless of their phase, an example are the alkylating agents. Cell cycle specific anticancer drugs are known to kill only cells that are actively cycling. Ideally these actions should be

limited to cancer cells but unfortunately the effects extend to normal cells hence producing unwanted side effects and toxicities.

2.1.3 Chemotherapy and renal insufficiency

Nephrotoxicity is an inherent adverse effect of certain anticancer drugs (17). Renal dysfunction can be categorised as prerenal uremia, intrinsic damage or post renal uremia according to the underlying pathophysiological process. Renal hypoperfusion promulgates prerenal uremia. Intrinsic renal damage results from prolonged hypoperfusion, exposure to exogenous or endogenous nephrotoxins, renotubular precipitation of xenobiotics or endogenous compounds, renovascular obstruction, glomerular disease, renal microvascular damage or disease, and tubulointerstitial damage or disease. Post renal uremia is a consequence of clinically significant urinary tract obstruction. (17).

Mechanisms of chemotherapy-induced renal dysfunction generally include damage to vasculature or structures of the kidneys, hemolytic uremic syndrome and prerenal perfusion deficits. Patients with cancer are frequently at risk of renal impairment secondary to disease-related and iatrogenic causes (17) (**Table 1**).

Chemotherapy can cause nephrotoxicity, and renal impairment can result in altered excretion and metabolism of chemotherapeutic agents, resulting in increased systemic toxicity. A variety of renal disease and electrolyte disorders can result from the treatment of malignant disease. (see table 2).Chemotherapeutic agents can affect the glomerulus, tubules, interstitium or the renal microvasculature, with clinical manifestations that range from an asymptomatic elevation of serum creatinine to acute renal failure requiring dialysis. The kidneys are the major elimination pathways for many antineoplastic drugs and their metabolites, further enhancing their potential for nephrotoxicity. Delayed drug excretion can result in increased systemic toxicity and is a major concern in patients with renal impairment. Many drugs require dose adjustment when administered in the setting of renal insufficiency. (**Table 2**).

Table 1: Causes of renal failure in a cancer patient

Prerenal

extracellular fluid depletion (poor intake, vomiting, diarrhea, hypercalcemia)

hepatorenal syndrome (veno-occlusive disease, hepatic resection)

drugs (calcineurin inhibitors, nonsteroidals)

Intrinsic

Glomerular

membranous nephropathy

amyloidosis (multiple myeloma)

pamidronate-associated collapsing glomerulopathy (incidence unknown)

light-chain deposition disease

Tubulointerstitial

acute tubular necrosis (toxic/ischemic)

lymphomatous infiltration of the kidney

light-chain deposition disease

drugs (cisplatin, ifosfamide)

intravenous contrast

cast nephropathy (multiple myeloma)

Vascular

thrombotic-thrombocytopenic purpura/hemolytic- uremic syndrome (post-HCT, gemcitabine, mitomycin C)

tumor infiltration (renal cell carcinoma with renal vein thrombosis)

Postrenal

intratubular obstruction

uric acid nephropathy

Methotrexate

cast nephropathy (multiple myeloma)

extrarenal obstruction

bladder outlet, ureteral (primary disease, retroperitoneal lymphadenopathy, retroperitoneal fibrosis)

Table 2; Dose adjustments according to GFR for chemotherapeutic agents in renal failure

Drug	>50 mL/min	10-50 mL/min	<10 mL/min
Azathioprine	100 percent	100 percent	50-75 percent
Bleomycin	100 percent	75 percent	50 percent
Carboplatin	AUC-based dose determined by the Calvert formula		
Cisplatin	100 percent	Avoid	Avoid
Cyclophosphamide	100 percent	100 percent	75 percent
Cytarabine (high dose)	100 percent	50 percent	25-50 percent
Etoposide	100 percent	75 percent	50 percent
Hydroxyurea	100 percent	50 percent	20 percent
Ifosfamide	25 to 50 percent reduction for Scr 2.1-3.0 mg/dL; withhold for Scr >3 mg/dL		
Lomustine (CCNU) Streptozocin	100 percent	75 percent	50 percent
Melphalan	50 percent dose reduction for BUN >30 mg/dL or Scr >1.5 mg/dL		
	Withhold therapy for CrCl < 40 mL/min or Scr >2 mg/dL		
Methotrexate	100 percent	50 percent	Avoid
Mitomycin	100 percent	100 percent	75 percent
Topotecan	100 percent	CrCl 20-39 mL/min: reduce dose to 0.75 mg/m2	CrCl <20: recommendations not available

2.1.4 Risk factors for nephrotoxicity

Several factors can potentiate renal dysfunction and contribute to the nephrotoxic potential of antineoplastic drugs. For example, intravascular volume depletion, either due to external losses or fluid sequestration (as in ascites or edema) is one of the most common factors contributing to the nephrotoxic potential of antineoplastic drugs. Similarly the concomitant use of non-chemotherapeutic nephrotoxic drugs (e.g., aminoglycoside antibiotics, nonsteroidal anti-inflammatory drugs) or radiographic ionic contrast media in patients with or without preexisting renal dysfunction is a major risk factor. Urinary tract obstruction secondary to underlying tumor may also be an additional factor to renal toxicity. Intrinsic renal disease that is idiopathic, related to other comorbidities, or to the cancer itself. (17, 18). (**Table 1**)

2.1.5 Individual drugs

2.1.5.1 Platinum compounds

Cisplatin is a potent and valuable chemotherapy agent used to treat a broad spectrum of malignancies (19, 20). Renal tubular dysfunction and a cumulative impairment in renal function following cisplatin administration as manifested by a decline in the glomerular filtration rate (GFR), can be dose limiting

Pathogenesis-Multiple mechanisms contribute to renal dysfunction following exposure to cisplatin. These include cellular toxicity, vasoconstriction in the renal microvasculature, and proinflammatory effects.

Cellular toxicity — Cisplatin is a potent cellular toxin, particularly in a low chloride environment. In the interior of cells, chloride atoms in cisplatin are replaced by water molecules. This hydrolysis product is believed to be the active species, reacting with glutathione in the cytoplasm and DNA in the nucleus (20). In tumors and other dividing cells, cisplatin-DNA intrastrand crosslink result in cytotoxicity (21). These molecular events are thought to be responsible for arresting cancer cell proliferation. Via this mechanism, cisplatin-induced renal toxicity is a common side effect. This principally occurs because the kidney accumulates and retains platinum to a greater degree than other organs and is the principal route for cisplatin excretion (22, 23).

Vasoconstriction — vasoconstriction in the renal microvasculature appears to contribute to decreased renal blood flow soon after cisplatin injection. This leads to a decrease in glomerular and medullary blood flow and subsequently leading to marked medullary ischemia and tubular necrosis in the medullary thick ascending limb of the loop of Henle. (24, 25).Rise in plasma creatinine levels and electrolyte disturbances follow.

Proinflammatory effects — cisplatin increases the expression of proinflammatory cytokines, such as tumor necrosis factor alpha (TNF-alpha), interleukin-6 (IL-6), interferon-gamma (IFN-gamma) and caspases, which promote the differentiation, maturation and activation of neutrophils, T cells and other components of the cellular inflammatory response. (26). These cytokines lead to increased expression of endothelial cell adhesion molecules and subsequent infiltration of leukocytes and T cells in kidney tissue.

Effects on the proximal tubule - The proximal tubule cells are selectively injured by cisplatin, as manifested by both necrosis and apoptosis, even though nonproliferating cells are generally less sensitive to the toxicity of agents that damage DNA (27).

Other cellular effects that have been proposed as the cause of cisplatin-induced nephrotoxicity include the following: inhibition of mitochondrial F1F0-ATPase and reduction of mitochondrial oxidative phosphorylation and membrane potential, which are two intracellular events that precede cytochrome C release and apoptotic cell death (28, 29). Induction of hyperlipidemia and the accumulation of triglyceride and non-esterified fatty acids (NEFA) in kidney tissue, perhaps due to inhibition of fatty acid oxidation in the proximal tubule (29, 30). Significant reduction in mRNA levels and enzyme activity of mitochondrial medium chain acyl-CoA dehydrogenase (MCAD) by possible direct inhibition of peroxisome proliferator-activated receptor-alpha (PPAR-alpha) activity in renal epithelial cells (31, 32). This may decrease the expression of PPAR-regulated genes, including those encoding potentially protective fatty acid binding proteins (33)

Carboplatin is significantly less nephrotoxic than cisplatin (2, 34). This increase in safety may reflect the enhanced stability of carboplatin, which has carboxylate and cyclobutane moieties in the cis position, rather than chloride (34). Hypomagnesaemia appears to be the most common manifestation of nephrotoxicity, although it occurs less often than with cisplatin (35, 36) .Acute renal failure has been reported, particularly in patients

previously treated with several courses of cisplatin (34). Direct tubular injury leading to acute tubular necrosis is the primary mechanism. A less common renal side effect is renal salt wasting (37, 38).

Kidney damage is the major dose-limiting side effect of cisplatin; treatment protocols may reduce or omit this medication when pre-treatment GFR is less than 60 ml/min/1.73 m^2. Most children receiving cisplatin have some acute loss of renal function, with considerable individual variation in severity (39).

A 20 to 40% reduction of glomerular filtration rate (GFR) following treatment with cisplatin is common. Reduction of mean GFR from 109 ml/min to 68 ml/min following three 21 day cycles of cisplatin 200 mg/m^2 (40 mg/m^2/day for 5 days) is reported(40).

Womer et al. (41) found a mean 8% decrease in GFR rate per 100 mg/m^2 dose received. The magnitude of GFR decline directly correlates with peak serum or urine platinum concentrations and cisplatin infusion rates (42).

The outlook for long-term recovery or stability of renal function is generally favorable, although data are somewhat limited. Mean GFR significantly increased from immediately post-treatment compared to 1 year later (92 ± 8 vs. 104 ± 10 ml/min/1.73 m^2) (43). Of children with reduced GFR at the end of treatment, 92% showed at least some improvement with 46% attaining normal GFR when reassessed at 2½ years (44)Furthermore, 80% of those with normal end-of-treatment GFR maintained their normal GFR over the course of follow-up.

Dose-related nephrotoxicity of carboplatin in children was evaluated in a study which investigated changes and the time course of these changes in renal function in children following treatment with carboplatin, and identified risk factors for nephrotoxicity. Glomerular and proximal renal tubular functions were investigated before and up to 2 years after treatment in 23 children who received carboplatin. The main findings were reduced glomerular filtration rate (GFR), and increased renal tubular loss of magnesium, manifested by low serum magnesium (S Mg). The mean fall in GFR was 22 ml min^{-1} 1.73 m^{-2} , and in S Mg it was 0.17 mmol l^{-1} (45).

Measurement of creatinine clearance at 6 month intervals in 15 patients with testicular cancer receiving 3 or more cycles of cisplatin 100 mg/m^2 (20 mg/m^2/day for 5 days) repeated every 21 days revealed a reduction in mean creatinine clearance from 112

ml/min to 68 ml/min during the initial 6 month period following initiation of treatment (46).

Use of cisplatin concurrently with other nephrotoxic agents, particularly ifosfamide, increases the risk of renal injury (47).

2.1.5.2 Alkylating agents

Cyclophosphamide the main urologic toxicity of cyclophosphamide is hemorrhagic cystitis. Hemorrhagic cystitis is subsequent to urinary excretion of reactive metabolites capable of binding sulfhydryl constituents within proteins of bladder epithelium. Mesna and vigorous saline-based hydration are administered concurrently to reduce the incidence and severity of hemorrhagic cystitis.

The primary renal effect of cyclophosphamide is hyponatremia, which is due to an increased effect of antidiuretic hormone (ADH), impairing the kidney's ability to excrete water (48, 49, 50).

Ifosfamide similar to cyclophosphamide is metabolically activated to become an alkylating moiety with activity against a wide array of tumor types. Used primarily for the treatment of certain solid tumors.

The predominant toxicity of ifosfamide on the urinary tract is hemorrhagic cystitis. However, nephrotoxicity is more likely with ifosfamide than with cyclophosphamide. Renal dysfunction can occur with ifosfamide treatment, particularly with long term and repeated administration. Although the exact underlying mechanism has not been elucidated, ifosfamide-induced nephrotoxicity is probably caused by reactive metabolites. The most common manifestation of ifosfamide-induced nephrotoxicity is proximal tubular dysfunction, and less often, decreased GFR (51-61).

Signs of tubular dysfunction: Metabolic acidosis with a normal anion gap (hyperchloremic acidosis) due to type 1 (distal) or type 2 (proximal) renal tubular acidosis. Hypophosphatemia induced by decreased proximal phosphate reabsorption, which can lead to rickets in children. Renal glucosuria, aminoaciduria, and a marked increase in ß2-microglobulin excretion, all from generalized proximal dysfunction. Polyuria due to nephrogenic diabetes insipidus. Hypokalemia, which may be severe, resulting from increased urinary potassium losses.

Ifosfamide can have serious adverse effects on the kidney despite concurrent use of the uroprotectant mesna. During therapy, acute renal tubular dysfunction often resolves prior to the next course; however, permanent and potentially progressive kidney damage may also occur (59).

A reduction in GFR (defined by serum creatinine levels at or above three times normal) occurred in 25% of patients treated with high dose ifosfamide (14 g/m^2) (60) .Following administration of more conventional doses, progressive renal insufficiency occurred in 17-50% of ifosfamide-treated youngsters (62). A statistically significant fall in mean GFR of 35 ml/min/1.73 m^2 was observed after completion of therapy (62). Although the median GFR at 1 year was no different than that at 10 years follow-up, there are marked differences in the course of individual children (59).

A number of risk factors for chronic ifosfamide nephrotoxicity have been proposed. These include cumulative dose (>60 to 100 g/m^2) (53, 54, 57, 61, 62), age <3 to 5 years (57, 61), concurrent or previous platinum therapy (57, 63), renal irradiation (54) and unilateral nephrectomy (54) or hydronephrosis (52). GFR was below normal in 42% (n = 24) of children with osteosarcoma who were studied a median of 9 months after completion of therapy that included both ifosfamide and cisplatin (64) Subclinical magnesium wasting was present in 25%. More severe renal toxicity occurred in children who had a reduction in renal mass at the time of chemotherapy (65.)The most important predictive risk factor for toxicity appears to be the cumulative dose of ifosfamide.

Evaluation of 174 paediatric patients (median age 8.7 years, range 0.4 to 21 years) receiving treatment with monthly ifosfamide (median cumulative dose 45.5 g/m^2, range 12.4 to 76.6 g/m^2) revealed that the median age of patients developing severe drug-induced nephrotoxicity was 2.2 years compared with 7.0, 8.2 and 10.5 years for patients experiencing moderate, mild and no nephrotoxicity, respectively (57).

2.1.5.3Antimetabolites:

Methotrexate, the dihydrofolate reductase inhibitor is a widely used anticancer drug. Methotrexate dosages are classified as conventional dose (15 to 50 mg/m^2), intermediate dose (50 to 1000 mg/m^2), or high dose (1 to 12 g/m^2) therapy. Leucopenia is the dose-limiting adverse effect of methotrexate.

Methotrexate can produce a transient decrease in GFR, with complete recovery within six to eight hours of discontinuing the drug. The mechanism responsible for this functional renal impairment involves afferent arteriolar constriction or mesangial cell constriction that produces reduced glomerular capillary surface area, diminished glomerular capillary perfusion and pressure (66) leads to precipitation of the drug and metabolites within the renal tubular lumen.

Methotrexate at doses less than 0.5 to 1.0 g/m2 is usually not associated with renal toxicity, unless underlying renal dysfunction is present. In contrast, high-dose intravenous methotrexate (1 to 15 g/m2) can precipitate in the tubules and induce tubular injury; at particular risk are patients who are volume depleted and those who excrete acidic urine. Maintenance of adequate urinary output and alkalinization will lessen the probability of methotrexate precipitation.

However long term administration of conventional dose of methotrexate have been shown to be nephrotoxic (67-69) .

High-dose MTX (HDMTX), in which doses in the range of 1,000-33,000 mg/m^2 are used in combination with leucovorin, is associated with acute renal dysfunction in 0-12.4% of patients, for an overall incidence rate of 1.8% (70). MTX-induced renal dysfunction results in delayed elimination of the drug and its metabolites. Most studies assess acute changes in renal function associated with MTX by measurement of plasma creatinine with various definitions of renal dysfunction. However, a single center study of children who were given HDMTX for ALL noted a significant decline in GFR as measured by inulin clearance over the 3 days after administration of HDMTX (71). Mean GFR returned to baseline by 7 days post-treatment. Only 2 of the 58 patients had clinical evidence of renal dysfunction with a doubling of their baseline serum creatinine levels. MTX related nephrotoxicity appears to be entirely reversible, with a median time to recovery of renal function of 16 days (range 4-48 days) (70). Furthermore, subsequent doses of HDMTX have been successfully given to patients who previously experienced renal dysfunction without recurrence of acute renal failure.

Fossa ET Al evaluated prospectively renal function in 85patients with malignant germ-cell tumors (MGCTs) >10 years after retroperitoneal lymph node dissection alone (RPLND), radiotherapy alone (RAD) or different schedules of cisplatin-based

chemotherapy with or without surgery/radiotherapy (CHEM).Found that Twenty-five patients displayed long-term impaired renal function, 23 of them from the RAD or CHEM group and two patients from the lymphnode dissection group.In the RAD group, renal function decreased by 8%, whereas a 14%reduction of renal function was observed in the CHEM group (72), renal function from the lymphnode dissection group wasn't affected

CHAPTER 3

3.1 STUDY JUSTIFICATION

Cancer in children is a leading cause of morbidity and mortality. Cancer patients are exposed to various modalities of treatment which place them at risk of multiple adverse effects. Renal dysfunction is a problematic effect that can hinder continued administration of anticancer treatment, in addition to impeding the optimal use of ancillary and supportive medications and measures.

Cancer chemotherapeutic agents have been implicated as causing nephrotoxicity especially cisplatin yet it is the drug mainly used as the backbone of treatment regimes of many malignancies.

Assessment of the toxicity caused by chemotherapy in children with cancer has become more important as the number of long-term survivors has continued to increase. It is vital to monitor both acute life-threatening adverse effects and long-term toxicity that may impair the child's development and cause permanent morbidity.

A knowledge gap concerning renal function in patients on cancer chemotherapy exists in our setting .The study will define the prevalence of abnormal glomerular filtration rates in paediatric oncology patients on chemotherapy.

3.2 STUDY UTILITY

The following are study utilities: 1. Regular monitoring GFR calculations should be done as decline occurs in renal function as patients continue on cancer chemotherapy.

2. Potential for early intervention will be created e.g dose adjustments and early referral to nephrologist.

3. The results of the study may be used as baseline for other follow-up prospective studies for evaluation of renal function in children with malignancies.

3.3 STUDY QUESTION: For purposes of this work the study question was, "What are the glomerular filtration rates in children receiving cancer chemotherapy at the Kenyatta National Hospital?"

3.4 OBJECTIVES

3.4.1Primary: To determine glomerular filtration rates following at least 6 months of cancer chemotherapy at Kenyatta National Hospital.

3.4.2 Secondary: To retrospectively evaluate the change in GFR that has occurred following at least 6 months of treatment with cancer chemotherapy.

3.5 MATERIALS AND METHODS

3.5.1 Study design; Cross sectional survey

3.5.2 Time period: 6 months from May to October 2010

3.5.3 Sample size calculation

A sample size of 114 was determined using Daniel's Formula for Sample Size Determination in Prevalence studies:

$$n = \frac{z^2 p(1-p)}{d^2} = \frac{1.96^2 \times 0.92 \times 0.08}{0.05^2} = 114$$

- n = Sample Size
- z = Normal Standard Deviation taken with a 95% Confidence Interval; set at 1.96.
- p = Expected Prevalence of deranged glomerular filtration rate for patients following long term chemotherapy .Nephrotoxicity Induced by Cancer Chemotherapy With Special Emphasis on Cisplatin Toxicity F. Ries. MD, and J. Klastersky(2)
- d = Precision level taken as 5%.(5% is used as the standard for it allows for a minimal error, less than 5% would make the study too sensitve while more than 5 % would be a huge error)

3.5.4 Setting

The study was done at the Kenyatta National Hospital General Paediatrics wards, Paediatric Ophthalmology ward, the Paediatric Oncology ward and Hemato-oncology clinic. KNH is a teaching hospital for the University of Nairobi and is also the major referral hospital for all paediatric cancer patients in Kenya.

3.5.5 Patients: Oncology patients less than 12 years of age with a confirmed diagnosis of cancer.

3.5.5.1 *Inclusion criteria*

- Paediatric oncology patients aged less than 12yrs who have a confirmed histologic diagnosis of cancer and have been on chemotherapy for at least 6 months.
- Those who give consent to be part of the study

3.5.5.2 *Exclusion criteria*;

- Those with a diagnosis of cancer but hadn't been on chemotherapy for a period of more than 6 months

3.6 PROCEDURE AND DATA MANAGEMENT

Paediatric patients who met the above inclusion criteria and had already been on treatment for at least 6 months were identified from paediatric wards, ophthalmology ward, paediatric oncology and the hematology clinic.This was done until I achieved the minimum sample of 114. They were enrolled into the study following consent/accent. Blood samples were taken and sent to the renal laboratory in the renal unit at the Kenyatta National Hospital for analysis. Their files were retrieved and all biodata and disease specifics for each patient were recorded. This included the age, weight, height, body surface area diagnosis, treatment regime and duration of treatment .

Files were studied and previous creatinine levels and the dates they were done were recorded.

Calculation of the GFR was done and tabulated for all results. Different malignancies, chemotherapeutic agents and age groups, cumulative doses of drugs were variables from

which statistically correct conclusions were drawn. Data was entered in a preformatted data sheet.

All patient data did not bear the name of the patient but rather a serial number. Data forms were kept in a secure lockable cabinet only accessible by the study investigator and the statistician. Data was entered into a password protected Ms Access database prepared by the statistician.

3.6.1 Estimation of GFR

The incidence of decreased GFR after exposure to any nephrotoxic agent is affected by the method used to measure GFR (73). GFR is typically measured by clearance techniques that estimate GFR by measuring the clearance of a substrate which is excreted primarily by glomerular filtration (73)

The glomerular filtration rate (GFR) is equal to the sum of the filtration rates in all of the functioning nephrons. It thus provides an approximation of the number of functioning nephrons. A reduction in GFR implies a decrease in the number of functioning nephrons due to underlying disease/injury, which may or may not be reversible.

Estimation equations based upon a stable serum creatinine concentration also correlate with the measured GFR. They are now the most common method used in routine clinical practice due primarily to convenience.

Creatinine, an endogenous marker, is most commonly used to estimate GFR as it does not require an intravenous infusion. Although the GFR can be determined from a timed urine collection for creatinine clearance, the collection is often inconvenient for families and inaccurate due to missed samples, episodes of incontinence, or voiding problems.

In children, an alternative to timed urine collection is estimating GFR by using either the Schwartz or Counahan-Barratt formula, which is based upon serum creatinine, age, height, and in adolescents, the gender of the patient (74-76). Studies describing the accuracy of the estimate show that approximately 75% of Schwartz formula estimates of GFR are within 30% of the measured GFR by inulin clearance.

The estimated GFR(eGFR)was determined from the Schwartz formula as follows:

$$eGFR = \frac{k*Height}{\text{serum creatinine}}$$

Height represents the body height measured in centimeters, and Screat is the serum creatinine. The constant k is directly proportional to the muscle component of body, and varies with age. The value for k is 0.33 in premature infants, 0.45 for term infants through the first year of life, 0.55 in children and adolescent girls, and 0.7 in adolescent boys (74-76).

Formula allows for estimation of kidney function, and even serum creatinine levels <1.0 mg/dL can be associated with substantially impaired kidney function in small children and adults who have low muscle mass or malnutrition.

The methods currently used to calculate GFR in adults Cockcroft-Gault equation and MDRD generally overestimate GFR in children compared to measured values (78).

MDRD

GFR (mL/min/1.73 m^2) = **186** x $(S_{cr})^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if female) x (1.212 if African) (conventional units)

The equation does not require weight because the results are reported normalized to 1.73 m^2 body surface area, which is an accepted average adult surface area

Cockcroft-Gault GFR = (140-age) * (Wt in kg) * (0.85 if female) / (72 * Cr)

The MDRD equation estimates GFR adjusted for body surface area. The equation includes a term for age to account for the fact that younger people have a higher GFR than older people at the same level of serum creatinine. This is due to higher average muscle mass and creatinine generation rate in younger people (79)

GFR estimates from the MDRD equation can therefore be applied to determine level of kidney function, regardless of a patient's size but the MDRD equation has not been validated in children (age <18 years). The Cockcroft and Gault equation estimates creatinine clearance and is not adjusted for body surface area. (79,80)

In summary, any estimation of GFR based upon either a 24-hour urine collection or from the serum creatinine concentration has limitations and may be inaccurate in some patients. (77,78). It is important to obtain the most accurate assessment of kidney function possible given the importance of both the potential risk of increased drug toxicity in a patient with reduced GFR as well as the potential benefit to be derived from appropriately dosed therapy.

Table 3:NORMAL GFR IN CHILDREN AND YOUNG ADULTS

gender)	Schwartz equation	Mean GFR ± SD mL/min/1.73m2
k (males and females)	GFR=0.33x(Length/SCr) in Preterm	40.6±14.8
	GFR=0.45x(Length/SCr) in Term	
eeks (males and females)	GFR=0.45x(Length/SCr)	65.8±24.8
eks (males and females)	GFR=0.45x(Length/SCr)	95.7±21.7
years (males and females)	GFR=0.55x(Length/SCr)	133.0±27.0
years (males)	GFR=0.70x(Length/SCr)	140.0±30.0

3.6.2Quality control measures for creatinine

3.6.2.1 External control: The renal laboratory is registered with a Quality control program "Huqas".The program sends the laboratory a sample for analysis 3 times a year. The laboratory will run the sample and send them the results. Analysis is then carried out by Huqas and feedback is given to the laboratory.

3.6.2.2 Internal control: The laboratory purchases a commercial control material from the company where they get their equipment. This control is run on a daily basis to

give expected results in a certain range given by the manufacturer. Control is also run when a new bottle of reagent is used or after preventative maintenance is performed or a critical component is replaced. When the control results fall outside the upper or lower limits of the established ranges indicate the assay may be out of control.

The following corrective measures are taken in such situations

- Repeat the same controls
- If the repeated controls are out of side the limits, fresh control serum is prepared and the test is repeated
- If the results are still out of control, recalibration with a fresh calibrator is done and the test is repeated
- If results are still out of control, calibration is done with a freshly prepared reagent and the test repeated.
- If results are still out of control the Technical Services/Local distributor is called in.

Calibration Done using a suitable aqueous standard or serum based calibrator. The frequency of the automated machines is according to manufacturers specifications. Calibration stability is contingent upon optimum instrument performance and the use of reagents which have been stored as recommended. Recalibration is recommended at anytime if the following events occur:

- The lot number of reagent changes.
- Preventative maintenance is performed or a critical component is replaced.
- Control values have shifted or are out of range and a new trial of control does not rectify the problem.

Levy Jenny curve

Every end of the week the machine prints out a graphical curve, to show the Standard Distribution Index (SDI) of measured values during the week. If there happens to be skewed results the machine is re-calibrated.

3.6.2.3Precautions taken during measurements

An elevation in the serum creatinine concentration (SCr) usually reflects a reduction in the glomerular filtration rate .There are, however, a variety of settings in which the SCr can increase acutely independent of the GFR and therefore in which there is no true change in overall kidney function. This may be due to one of three factors: decreased creatinine secretion; interference with the serum assay; or enhanced creatinine production.

3.6.2.3.1 *Decreased creatinine secretion*; Creatinine is an organic cation in the physiologic pH range and is secreted by the organic cation secretory pump that can be inhibited by other organic cations. The antimicrobial trimethoprim (which is most often given in combination with sulfamethoxazole) and the H2-blocker cimetidine are drugs that can inhibit this process, resulting in a self-limited and reversible rise in the SCr of as much as 0 4 to 0.5 mg/dL (35 to 44 µmol/l) .Drug history of patients will be analysed.

3.6.2.3.2 *Interference with serum assay*; Serum creatinine is most often measured by the alkaline picrate method. This colorimetric assay can recognize other compounds as creatinine chromagens, particularly acetoacetate in diabetic ketoacidosis. In this setting, the SCr can rise by 0.5 to 2 mg/dL or more (44 to 176 µmol/L), a change that is rapidly reversed with insulin therapy. Cefoxitin and flucytosine are other drugs that can produce a similar effect. This will be taken into consideration during analysis

3.6.2.3.3 *Enhanced creatinine production*; The SCr varies during the day, rising by as much as 0.5 to 1.0 mg/dL (44 to 88 µmol/L) from Proteins in the serum, as well as glucose give rise to creatinine levels. Exercise causes muscle breakdown and this may falsely elevate creatinine levels. The children will have the blood samples drawn in morning before any meal and play begins

3.6.3Methodology of creatinine measurement

3.6.3.1 Specimen collection and handling; the method used will be that of non-hemolysed serum.0.5ml of blood will be collected and put in red tubes (without anticoagulant).Samples will be sent to the renal laboratory for analysis immediately after collection. Serum samples are stable for at least 2 days at room temperature (18-25°C) or for 1 week at 4°C.

3.6.3.2. Centrifugation/Spinning of the samples will be done to extract serum from the clot and the serum sample is then fed onto the machine for assaying.

3.6.3.3. Assaying In the machine creatinine reacts with alkaline pictrate (main component of the reagent) to produce a reddish color (the Jaffe reaction).The red color formed is directly proportional to the creatinine concentration and is measured photometricaily at 500nm

3.6.3.4 Creatinine reagent is made of 2 active ingredients; Picric acid (32mmol/L and Sodium Hydroxide 300mmol/L) mixed in equal volumes. Prior to use the reagent is stored at 2-25°C and protected from direct sunlight is stable until expiry date on bottle is reached. The working reagent is stable for 14 days when stored capped at 2-8°C or 5 days at room temperature. Signs of reagent deterioration are turbidity, working absorbance of >o.6 AU at 500nm and failure to recover control values within the assigned range.
Unit conversion mmol/L x11.3=mg/dL

3.6.3.5. Expected values: renal laboratory reference intervals

Males 60- 120 umol/L (0.7 -1.4mg/dL)

Females 50-105umol/L (0.6-1.2mg/dL)

Children 40- 60 umol/L (0.3-0.7mg/dL)

CHAPTER 4

4.1 RESULTS

From May to October 2010, a total of 115 patients on childhood cancer chemotherapeutic treatment had their GFR evaluated. Their median age was 7 years and the range was between 4-9years.Out of 115 children 60% of them were males (male: female ratio of 1.5:1).The median courses of chemotherapy treatment was 11 courses(Range 8-13 courses).Majority of the patients in the study were from the surrounding environs of Nairobi i.e. Central and Eastern Province. Proximity to the hospital could be the main reason.

Table 4: Socio-Demographic Factor (n=115)

Factor	Frequency	Median /Percentage
Age (in years)		
Median		7.0
Range	2 to 12	
• < 5	30	26.1
• 5 to 8	50	43.5
• > 8	35	30.4
Sex		
• Male	69	40.0
• Female	46	60.0
Number of Courses Received (no.)	11.0	(8-13)

Figure 1: Type of Malignancy

The spectrum of malignancies seen included Leukemia in 43(37%) children, followed by Burkitts lymphoma 18(16%), Wilms tumor and Rhabdomyosarcoma 14(12%) each. Other malignancies were Retinoblastoma, Kaposi sarcoma, Hodgkin's Lymphoma and other solid tumors (Neuroblastoma, Osteogenic sarcoma and Yolk sac tumors

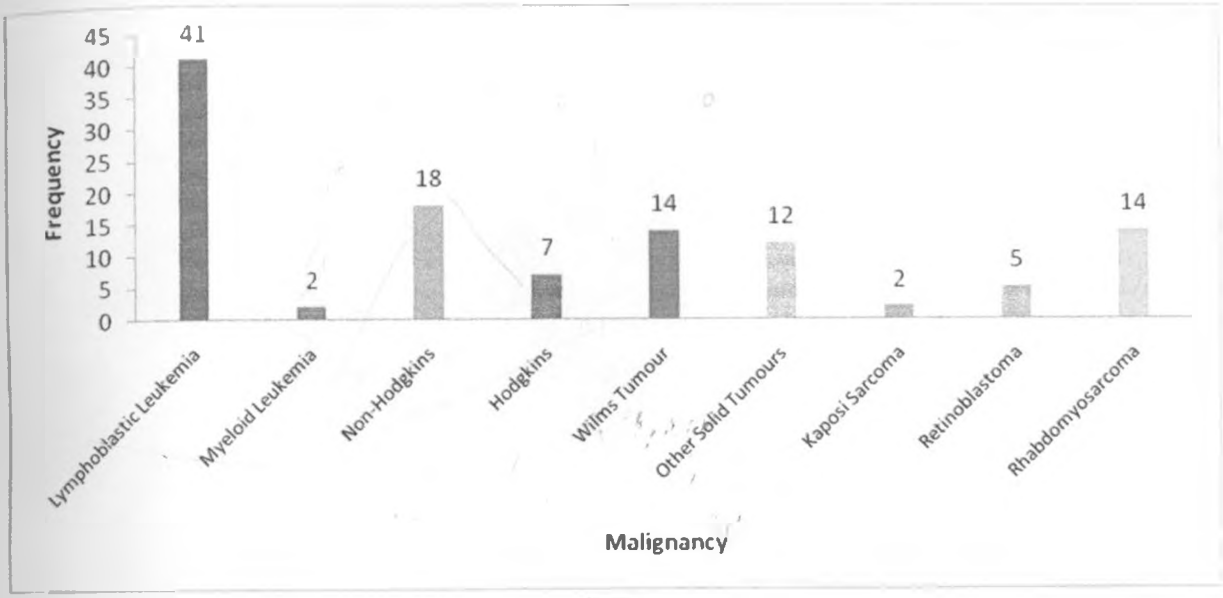
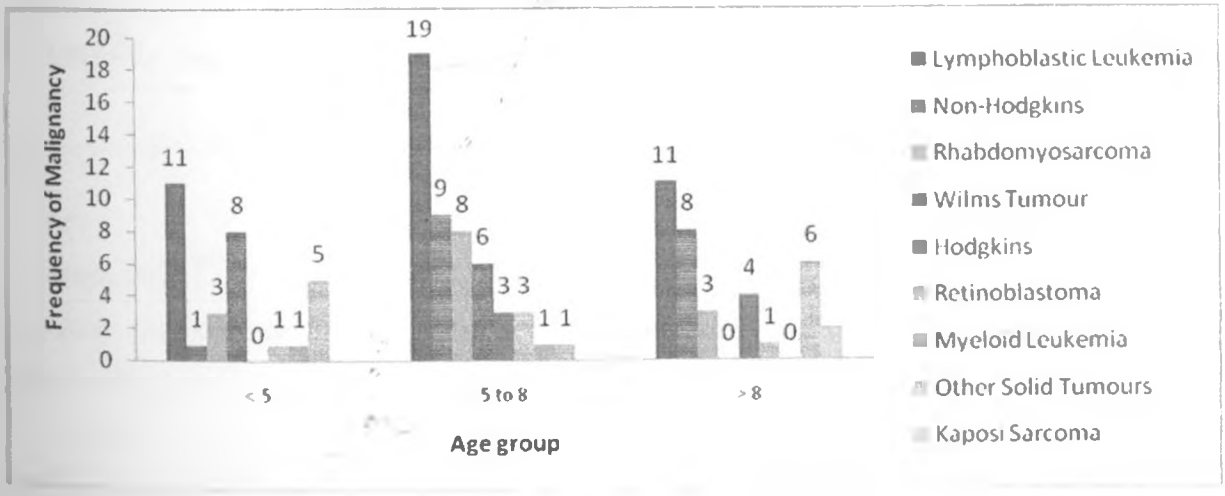


Figure 2: Frequency of malignancies in the different age groups



Children in the age group of 5-8yrs had the highest incidence of malignancies; the most common being lymphoblastic leukemia, Burkitt's lymphoma, rhabdomyosarcoma and wilms tumor. Lymphoblastic Leukemia was the most common malignancy in all the age groups.

PREVALENCE OF LOW GLOMERULAR FILTRATION RATE IN CHILDREN ON CANCER CHEMOTHERAPY AT KNH

Out of the 115 children enrolled in the study 43 had abnormal kidney function. This gave a prevalence of 37% (95%CI 28-46).The other 72 children had normal kidney function

Figure 3: Prevalence of low GFR after Chemotherapy

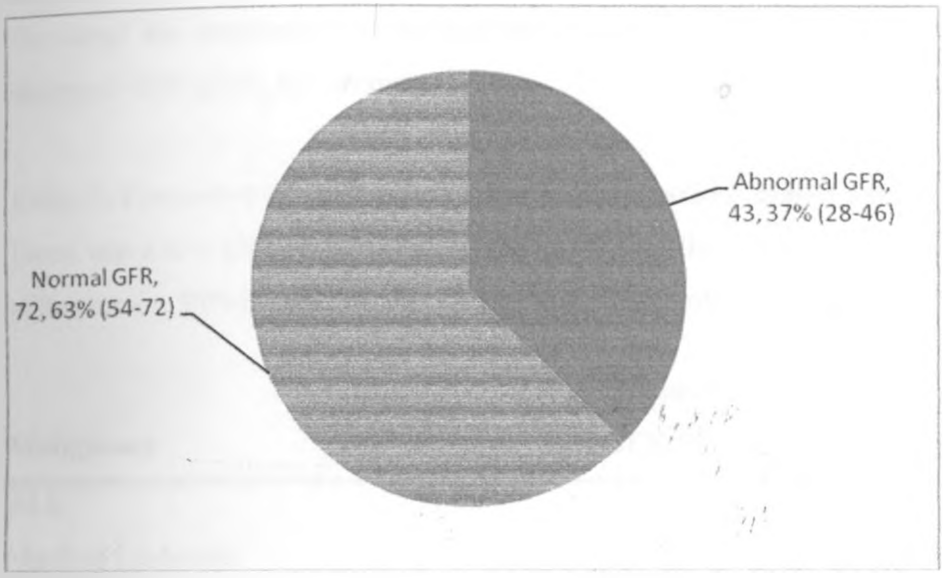


Table 5: Gender in relation to GFR;

33.3 % of the males had an abnormal GFR compared to 43.5% of the females.

SEX	Abnormal GFR
Male	33.3 (22.0 – 44.7)
Female	43.5 (28.8 – 58.2)

P-value is 0.271

The table above shows that the difference isn't statistically significant.Both sexes were equally affected

Table 6: Age in relation to the GFR;

Children less than 5 yrs of age had more kidney compromise in comparison to those older than 5years. More than half of the patients in this age group (53%) had a GFR of less than 60ml/min/1.73m2

Age	Abnormal GFR%	Odd ratio
< 5	53.3 (34.9-71.7)	1.00
5-8	34.0 (20.5-47.4)	0.49
> 8	22.9 (8.6-37.1)	0.30

• value is 0.023

The trend for association shows that there is an increase in number of patients with abnormal GFR as the age decreases.

Table 7: Frequency of patients with low GFR in various malignancies

There was a low glomerular filtration rate in 29% of the children with leukemia, 57% in wilms tumor, 58% in solid tumors and 40% in rhabdomyosarcoma and at least 14% in all

Malignancy	Proportion with abnormal GFR(95% Confidence interval
ALL	29.3 (15.0-43.5)
Myeloid Leukemia	50.0 (49.0-149.0)
Non-Hodgkins	27.8 (6.3-49.3)
Hodgkins	14.3 (-14.0-42.3)
Wilms Tumour	57.1 (29.9-84.3)
Other Solid Tumours	58.3 (28.9-87.8)
Retinoblastoma	40.0 (-8.5-88.5)
Rhabdomyosarcoma	35.7 (9.4-62.0)
Total	**43**

he other tumors. However the estimates had very wide confidence intervals because of he small numbers as shown in the table.Solid tumor patients(including wilms retinoblastoma and rhabdomyosarcoma) had a large proportion of patients with abnormal GFR.

Table 8: GFR in comparison to number of courses received

TREATMENT	GLOMERULAR FILTRATION RATE	
No ofCourses	**Percentage (conf. interval)**	**odds ratio**
≤10	41.1(27.9- 54.2)	1.00
10+	33.9(21.5-46.2)	0.4

P –value is 0.427

A lower GFR of 33.9mls/min was seen in patients who had received more than 10 courses of chemotherapy as compared to 41.1mls/min in patients who had received less than 10 courses

Fig 4: Frequency of patients with abnormal GFR on various chemotherapeutic drugs HT

The main nephrotoxic drugs used in KNH cancer treatment protocols are the platinum based compounds (cisplatin and carboplatin) and the alkylating agents (cyclophosphamide and ifosfamide. The figure shows the GFR median values for the cytotoxics. We see that for all drugs, there was a minimum of 30% prevalence in decline in the GFR,i.e is either below or bordering on 60ml/min/1.73m2. Ifosfomide had the highest number of patirnts with abnormal GFR.

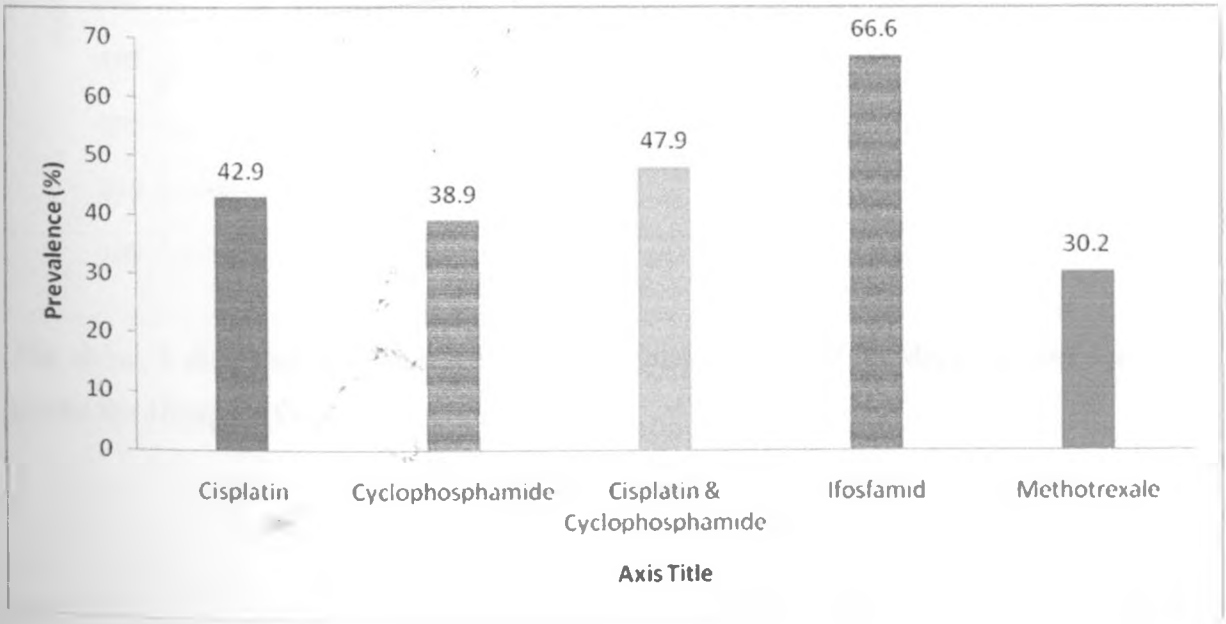


Figure 5: Change in renal function and cumulative dose of Cyclophosphamide (mg)

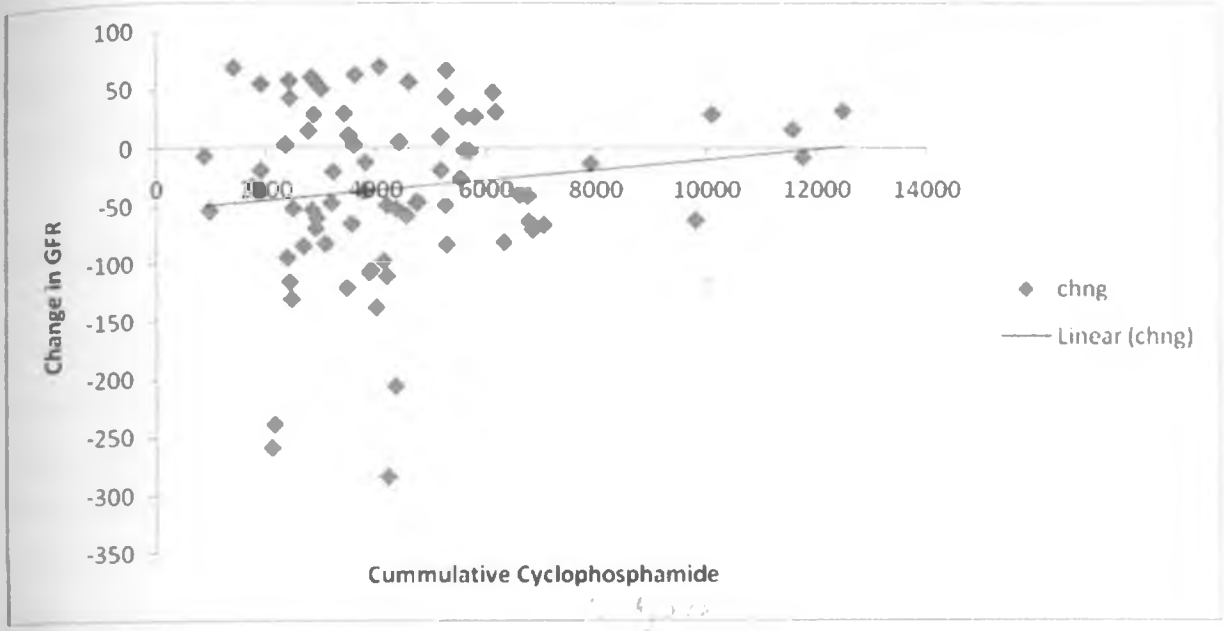
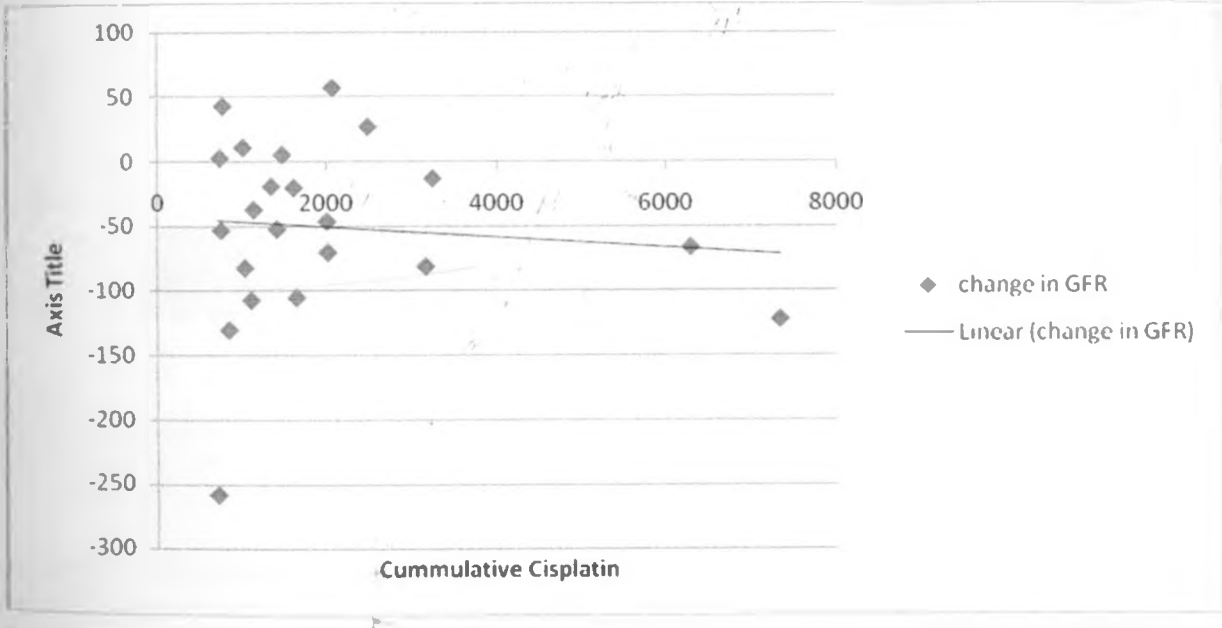


Figure 6: Change in renal function and cumulative dose of cisplatin (mg)



The above 2 diagrams illustrate that as the cumulative dose of the drug increase the greater the change in GFR

Table 9: Creatinine and GFR changes following at least 6 months of chemotherapy

Kidney	Period	median	IQR	p-value
Creatinine(mmol	Before	49.0	37 to 63	<0.001
	After	66.0	50 to 79	
GFR(ml/min	Before	123.0	86 to 167	<0.001
	After	102.0	84 to 127	

At the long-term assessment of GFR, patients had significantly lower renal function values after more than 6 months of treatment than the beginning of treatment p<0.001. Initial GFR had a median value of 123 ml/min/1 .73 m2 (range 86-167). Final median GFR was 102 ml/min/1.73 m2 (range 84-127).This is represented by the figure below

Figure 7: Box plot GFR for the Two Periods

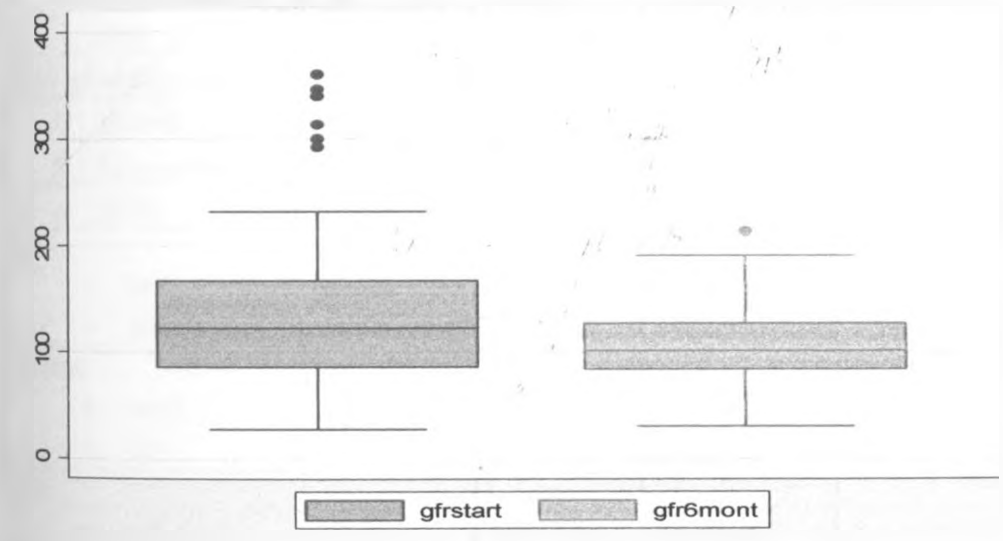


Table 10: GFR changes before and after chemotherapy

		AFTER 6 MONTHS		
		NORMAL	ABNORMAL	TOTAL
GFR BEFORE	NORMAL	58 (81)	27 (63)	85 (74)
	ABNORMAL	14 (19)	16 (37)	30 (26)
	TOTAL	72 (100)	43 (100)	115 (100)

The number of patients with impaired renal function increased from 30 at diagnosis to 43 at the long-term follow-up. Serum creatinine concentrations show an increase after at least 6 months of treatment with chemotherapeutic agents. A statistically significant fall in GFR is observed in 43 patients (36%) (Mean [95% confidence limits] fall 35.1 [22.1–47.9] ml/min/ 1.73 m2; paired *t*-test, $t = 8.96$ P-VALUE = *0.036*

Table 11: Association between GFR and Selected Risk Factors

Risk Factor	GFR Status		OR 95% CI	p-Value
	Abnormal, (43), n (%)	Normal, (72) n (%)		
Treatment Regimen				
• None of the Nephrotoxic drugs	8 (19)	11 (15)		
• Drugs Cisplatin/Cyclophosphamide/ both	35 (81)	61 (85)	1.3 (0.5 to 3.4)	0.642
Type of Malignancy				
• Leukemia	13 (30)	30 (42)	0.7 (0.3-1.5)	0.348
• Lymphoma	8 (19)	17 (24)	0.5 (0.2-1.4)	0.169
• Solid	22 (51)	25 (35)	2.2(1.7 to 4.9)	**0.038**
Sex				
• Male	23 (53.5)	46 (63.9)		
• female	26 (46.5)	26 (36.1)	1.5 (0.7-3.3)	0.271
Course				
• <=10	23 (53.5)	33 (45.8)		
• 10+	29 (46.5)	39 (54.2)	0.7 (0.3-1.5)	0.427
Age				
• < 5	16 (37.2)	14 (19.4)	1	
• 5-8	18 (41.9)	32 (44.4)	2.0 (0.7-5.7)	0.129
• 8+	9 (20.9)	26 (36.1)	3.3 (1.0-10.8)	***0.023***

The type of chemotherapeutic agent used, the sex and the courses of treatment did not confer a great risk to development of a decline in GFR. Nevertheless the type of malignancy conferred a double likelihood of developing an abnormal GFR. There was a positive trend in association in that the older one was the less likelihood of developing an abnormal GFR.

4.2 DISCUSSION

Childhood cancers continue to be an area of importance in paediatrics.The harmful side effects of the various chemotherapeutic agents versus their useful anticancer effects present a challenge in management. With regard to long term survivors, the possible effects of late treatment and their consequences on the quality of life are a major concern. Kidney disease frequently complicates malignancy and its treatment.

In this study glomerular filtration rates were evaluated in a total of 115 paediatric cancer patients. The patients studied were recruited from the pediatric cancer wards and had been on treatment for a period of at least 6 months.

The pattern of malignancies among our study patients was Leukemia in 43(37%) children, followed by children with Burkitts lymphoma 18(16%), children with Wilms tumor and Rhabdomyosarcoma 14(12%) each. Other malignancies were Retinoblastoma, Kaposi sarcoma, Hodgkin's Lymphoma and other solid tumors (Neuroblastoma, Osteogenic sarcoma and Yolk sac tumors. Highest number of malignancies was seen in the age group between 5-8yrs .This compares to a study done in indigenous Zambian children where the pattern of malignancies seen during a 10yr period(1980-1989), revealed a total of 525 neoplasms with peak prevalence in the 5-9 year age group. Non-Hodgkin's lymphoma (17.5%) was the most common disorder followed by Burkitt's lymphoma (13.9%), retinoblastoma (11.4%), Kaposi's sarcoma (8.8%), Hodgkin's disease (5.9%), Wilms' tumour (5.9%), acute lymphocytic leukaemia (4%), rhabdomyosarcoma (3.4%), nasopharyngeal carcinoma (2.7%) and osteogenic sarcoma (2.1%). (10)

A standard guideline set by the National Kidney Foundation (NKF) and Kidney Disease Outcomes Quality Initiative (K/DOQI) was used to calculate GFR and categorize patients as either having normal or abnormal kidney function (79). Patients with GFR of less than 60ml/min were grouped as having an abnormal GFR. Various risk factors were evaluated including age, type of tumor, duration of treatment and chemotherapeutic agents such as use of platinum based compounds and alkylating agents. Change in GFR over a period of at least 6 months was also evaluated and documented.

The point prevalence of abnormal glomerular filtration rates in children on treatment for cancer was 37% (95%CI 26.8-44.5). Nephrotoxicity was observed in a substantial proportion of patients. This represents about a third of the patients on treatment and has a higher frequency than previously documented in other studies.The postulated reasons of this are higher rates of malnutrition and sepsis which are conditions that also interfere with kidney function and decrease GFR. The relative risk of developing a decline in GFR while on nephrotoxic chemotherapy has been documented as 21% by Pinkerton et al (81) and 8 % by Womer et al.(39)

There was a greater predisposition of younger patients to the development of nephrotoxicity as seen both in our study and Ashraf et al(51). Reduction of serum creatinine level secondary to loss of muscle mass or limited protein intake can cause artifactual overestimation of creatinine clearance and glomerular filtration rate. A decreased muscle mass secondary to disease or treatment-related effects reduces creatinine production with a subsequent reduction in serum creatinine level. Reasons for loss of muscle mass in the younger patient with cancer include decreased nutritional intake, cachexia, decreased physical activity, corticosteroid-induced myopathy and limb amputation(20) In the paediatric patient, developmental changes occurring from term to 3 to 5 years of age effecting proximal tubular function and, to a lesser degree, glomerular function may increase the vulnerability of young kidneys to toxic insults.(51)

Children with solid tumors including wilms had a high prevalence of abnormal GFR; these can be attributed to the fact that they receive both nephrotoxic drugs i.e. platinum and alkylating agents in their treatment regimes. Hartmann et al performed a randomized trial comparing the nephrotoxicity of cisplatin/ifosfamide-based combination chemotherapy with or without amifostine in patients with solid tumors. In the amifostine-group GFR was fully maintained after application of two cycles of chemotherapy, whereas in the control group a > 30%-reduction of median GFR (108 to 80 ml/min) was observed ($p < 0.001$). In our study the main solid malignancies in the group were the osteogenic sarcoma, rhabdomyosarcoma, retinoblastoma and neuroblastoma .The GFR of 40% of these patients was decreased.P-value of 0.038 .Use of cisplatin concurrently with other nephrotoxic agents, particularly ifosfamide, increases the risk of renal injury (47)

Duration of chemotherapy has been shown to be directly proptional to a decline in GFR.A lower GFR of 33.9mls/min was seen in patients who had received more than 10 courses of chemotherapy as compared to 41.1mls/min in patients who had received less than 10 courses.

The decrease in median GFR in comparison with the pretreatment value was 15.5% at the start of the maintenance therapy, 23% at the end of the maintenance therapy and 15.5% 1 year after termination of therapy shown by Meijer et al who determined GFR Glomerular filtration rate (GFR) in 8 patients with disseminated testicular carcinoma before, during and 1 year after termination of a combination of chemotherapy with cis-diamminedichloroplatinum (CDDP). At all intervals the changes in GFR were significantly reduced in comparison with pretreatment values.

Our study confirms previous observations that cisplatin-based chemotherapy leads to decrease in renal function ,40% of patients on platinum based therapy had a GFR of <60 ml/min. Kintzel et al showed a 67% in patients with GFR <60 ml/min(15). Our mean decrease in renal function of 14% confirms the observation of Osanto et al(10) who reported a 15% reduction of creatinine clearance after five cycles of cisplatin-based chemotherapy. Our percentage of patients with impaired renal function after chemotherapy (36%) is in agreement with the range of 20–30% reported by Kollmannsberger et al. (18)

Cisplatin and carboplatin cause dose-related renal dysfunction. In addition to increased serum creatinine levels and uraemia as shown by Kintzel et al. The concentration of cisplatin during the days of chemotherapy has also been discussed as a predictor of the development of reduced renal function. The cumulative dose rather than the serum concentration of cisplatin seems to be responsible for the reduction of renal function in the oncology patients. If the standard dose of cisplatin (100 mg/m^2) is given over 2 days, as suggested by the results of a recently published large trial (20). Retrospective analysis of 22 patients with testicular cancer treated with 1 to 5 cycles of cisplatin-based chemotherapy reported a reduction in mean GFR from 137 ml/min to 106 ml/min. GFR was evaluated in patients who had received a cumulative cisplatin dose of 180 to

900mg.[81], renal function become more impaired, even though only three chemotherapy cycles had been applied. Long-term effects of continuously elevated serum concentrations of cisplatin (21) may also, over years, reduce renal function. 43% of patients in our study on platinum based regimens had a GFR of less than 60ml/min/1.73m2.Fossa et al showed a reduction of mean GFR from 109 ml/min to 68 ml/min following three 21 day cycles of cisplatin 200 mg/m2 (40 mg/m2/day for 5 days) is reported.[10]. Total cumulative dose of cisplatin in patients in the study was ranging from 612-7333mg/m2. Use of cisplatin concurrently with other nephrotoxic agents, particularly ifosfamide, increases the risk of renal injury.Long-term effects of continuously elevated serum concentrations of cisplatin [21] may also, over years, reduce renal function. In this regard, clinicians should be aware that serum levels of creatinine do not sufficiently mirror the changes in renal function, as demonstrated by previous reports [7, 10, and 11.

Cyclophosphamide and ifosfamide are alkylating agent which have been incorporated into firstline therapy for a number of malignant paediatric tumours. Recent data appears to suggest that tubular dysfunction may result from incorporation of this drug into chemotherapy schedules and that toxicity may be dose related.In the present study,out of the 95 patients who were on alkylating agents 40% had abnormal renal function and cumulative doses of cyclophosphamide ranged from 875-15 500mg/m2. Ifosfamide has been shown to be more nephrotoxic than cyclophosphamide.

A number of risk factors for chronic ifosfamide nephrotoxicity have been proposed. These include cumulative dose (> 60-100 g/m2) , age < 3-5 years, concurrent or previous platinum therapy . The most important predictive risk factor for toxicity appears to be the cumulative dose of ifosfamide .(53, 54, 57, 61, 62)

Cumulative cyclophosphamide dose exceeding 1000mg/m2 and patient age are the 2 greatest predictors of risk for development of nephrotoxicity.[91,93-96] The likelihood of renal dysfunction increases as the cumulative dose of cyclophosphamide increases.[91,93-96].

In addition, the incidence and severity of nephrotoxicity is greater in patients younger than 5 years. Paulino et al who evaluated 174 paediatric patients (median age 8.7 years, range 0.4 to 21 years) receiving treatment with monthly ifosfamide (median cumulative

dose 45.5 g/m2, range 12.4 to 76.6 g/m2) revealed that the median age of patients developing severe drug-induced nephrotoxicity was 2.2 years compared with 7.0, 8.2 and 10.5 years for patients experiencing moderate, mild and no nephrotoxicity, respectively.(57) Previous or concurrent administration of cisplatin increases the risk of nephrotoxicity. In fact, increased cumulative cisplatin dose has been associated with increased severity of ifosfamide-induced renal dysfunction. Administration of ifosfamide as a continuous infusion versus intravenous bolus does not have an apparent effect on the likelihood of nephrotoxicity.(59)

Whether the risk of long-term nephrotoxicty of alkylating agents can be weighed against the apparent therapeutic efficacy of such a drug can only be answered when sufficient data in these important areas becomes available. In the meantime, judicious monitoring of patients on treatment and discontinuation of this agent when generalised, albeit subclinical, dysfunction is documented, may well be warranted.

Nephrotoxicity occurs primarily with high dose methotrexate therapy; however, it can also occur with long term administration of conventional dose methotrexate.(67-69). Acute tubular necrosis subsequent to crystallisation of parent drug and the metabolite 7-hydroxymethotrexate within renal tubules is the purported underlying mechanism of methotrexate-induced renal dysfunction.[70,71].All the patients on methotrexate were found to have an abnormal GFR

In Our study there was a statistically significant change in both the creatinine and GFR before and after in children on cancer chemotherapy at KNH.The number of patients with abnormal kidney function at the beginning and the end of the study was 30 and 43.Shows that there is a decline in renal function following cancer chemotherapy. Initial GFR had a median value of 123 ml/min/I .73 m2 (range 86-167). Final median GFR was 102 mlimini1.73 m2 (range 84-127). A statistically significant fall in GFR is observed in 43 patients (36%) (Mean [95% confidence limits] fall 35.1 [22.1–47.9] ml/min/ 1.73 m2; paired *t*-test, $t = 8.96$ P-VALUE = *0.036*

The above results have been duplicated in other studies. Pinkerton et al showed a median reduction in GFR of 32 ml/min/1.73 m2 (-46 to 134). Measurement of creatinine

clearance at 6 month intervals in 15 patients with testicular cancer receiving 3 or more cycles of cisplatin 100 mg/m2 (20 mg/m2/day for 5 days) repeated every 21 days revealed a reduction in mean creatinine clearance from 112 ml/min to 68 ml/min during the initial 6 month period following initiation of treatment [43]. Retrospective analysis of 22 patients with testicular cancer treated with 1 to 5 cycles of cisplatin-based chemotherapy reported a reduction in mean GFR from 137 ml/min to 106 ml/min. GFR was evaluated by serial measurement of 51Cr-EDTA clearance. [80]

4.3 CONCLUSIONS AND RECOMMENDATIONS

Many individuals treated for childhood cancer are at risk for renal late effects, and these late effects may require ongoing medical management. Function and quality of life may be impaired. Exposure-based risk assessment is key for identification of long-term renal complications. Timely and appropriate treatment, often coordinated with a nephrologist, may diminish symptoms and/or prevent further damage, and may improve function and quality of life.

CHAPTER 5

5.1 STATISTICAL ANALYSIS

Statistical Package for Social Scientists (SPSS version 17.0) was used.Demographic factors of paediatric cancer patients were tabulated using simple frequencies. Descriptive statistics for the study patients were summarized as n (%) and also using measures of central tendency and dispersion for continuous variables. Univariate analysis was performed to determine factors associated with any changes in the GFR. Chi-squared tests for categorical variables and t-tests for continuous variables.

Non parametric test (Mann Whitney Test) were used to evaluate skewed continous variables.

5.2 STUDY LIMITATIONS

1. This was a cross sectional study and was not be able to adequately describe the GFR changes as they occur.
2. Information bias was an issue due chart reviews.

ETHICAL CONSIDERATIONS:

1. Permission was sought from the Kenyatta Hospital Ethics Research Committee to collect and analyze data collected in the study as part of the Thesis Dissertation. Copies of the Protocol, the Informed Consent Form as well as the subsequent modifications to either document was presented to the above named committee for written approval prior to commencing the study.

2.Any Modifications to the Study Protocol that affected the Patient's volition to take part in the study, the intent of the study or patient safety was submitted to the KHERSC for written approval prior to incorporating these changes in the study procedure.

3. The purpose of the Study was carefully explained to the Children's Parents or Guardians with a view to obtain Written Consent prior to enrolling any child in the study.

4. Blood samples were drawn from the patient to assess the creatinine levels.Chart reviews were also done to abstract biodemographics and previous creatinine values.

5. Benefits that participants accrued from the study included receiving education regarding various components that contribute to deterioration in kidney function. Better understanding of signs of renal failure and reasons for routinely checking renal function were explained to the patient

6. Strict Confidentiality was observed throughout the entire study period, held in trust by participating investigators, research staff and the study institutions. The Study Participants were given study identification numbers and no personal identification data was recorded. No Information concerning the individual study findings was released to any unauthorized third party without prior written approval of the study institution or the Ethics Research Committee

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APPENDIX 1

CONSENT FORM

Patient's Study Number: **Date:**

Study Title: **ASSESSMENT OF GLOMERULAR FILTRATION RATE PROFILES OF PATIENTS ON CANCER CHEMOTHERAPY AT THE KENYATTA NATIONAL HOSPITAL**

Investigator: **Dr. Muthoni Mburu (MB ChB) Paediatric Resident, University of Nairobi. Tel Number:- 0734-758611**

Supervisors: 1.Dr Dalton Wamalwa (MB ChB, M. Med, MPH) Senior Lecturer
Department of Paediatrics and Child Health, University of Nairobi

2. Dr Lucy N. Wainaina (MB Ch B, M.Med, F. Endocrinology. Lecturer,
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Department of Paediatrics and Child Health, University of Nairobi

3. Dr Admani Bashir(MB Ch B, M.Med, F. Nephrology.) Lecturer,
Paediatric Nephrologist
Department of Paediatrics and Child Health, University of Nairobi

4. Prof Julius Meme (MB ChB, M.Med,FAAP,MBS,EBS,CBS),Professor
Department of Paediatrics and Child Health, University of Nairobi

Investigator's Statement:

We are requesting you and your child to kindly participate this research study. The purpose of this consent form is to provide you with the information you will need to help you decide whether to participate in the study. This process is called 'Informed Consent'. Please read this consent information carefully and ask any questions or seek clarification on any matter concerning the study with which you are uncertain.

Introduction:

Renal failure remains an important complication of cancer and its treatment and this is often multifactorial in origin, Measurement of renal function may be important in monitoring the nephrotoxic effects of drugs such as cisplatin and ifosfamide.

Several factors can potentiate renal dysfunction and contribute to the nephrotoxic potential of antineoplastic drugs. It is necessary to exclude all other causes of renal dysfunction (pre-renal, obstructive, iatrogenic or cancer-related).

Assessment of the toxicity caused by chemotherapy in children with cancer has become more important as the number of long-term survivors has continued to increase. It is vital to monitor both acute life-threatening adverse effects and long-term toxicity that may impair the child's development and cause permanent morbidity.

This study aims at assessing the kidney fuction of your child and taking necessary measures to prevent or stop deterioration in function occuring

Benefits:

The results of the study will be shared with you and your doctor. You will also receive information on the status of your childs kidney fuction .The results of the research will also be used by the caregivers in this clinic and other clinics to take better care of other children with asthma.

Risks:

There will be drawing of a blood sample to be sent to the laboratory for analysis. There will be no invasive procedures carried out in the study that may harm your child.Refusal to participate will in no way jeopardize the treatment of your child in any way.

Voluntariness:

The study will be fully voluntary. There will be no financial rewards to you for participating in the study. One is free to participate or withdraw from the study at any point. Refusal to participate will not compromise your child's care in any way.

Confidentiality: The information obtained about you, your child and your family will be kept in strict confidence. No specific information regarding you, your child or your

family will be released to any person without your written permission. We will, however, discuss general overall findings regarding all children assessed but nothing specific will be discussed regarding your child's asthma. We will also, not reveal the identity of you or your child in these discussions.

Problems or Questions:

If you ever have any questions about the study or about the use of the results you can contact the principal investigator, **Dr Muthoni Mburu** by calling **0734-758611.**

If you have any questions on your rights as a research participant you can contact the **Kenyatta National Hospital Ethics and Research Committee (KNH- ESRC)** by calling **2726300 Ext. 44355.**

Consent Form: Participant's Statement:

I _____having received adequate information regarding the study research, risks, benefits hereby AGREE to participate in the study with my child. I understand that our participation is fully voluntary and that I am free to withdraw at any time. I have been given adequate opportunity to ask questions and seek clarification on the study and these have been addressed satisfactorily.

Parents Signature: _____ Date _____

I _____ declare that I have adequately explained to the above participant, the study procedure, risks, benefits and given him /her time to ask questions and seek clarification regarding the study. I have answered all the questions raised to the best of my ability.

Interviewers Signature _____ Date _____

APPENDIX 2

DATA SHEET: Study to determine the GFR of paediatric patients on cancer chemotherapy for at least 6 months at the Kenyyatta National Hospital .

PATIENT DATA

Date of assessment.....

Patient ID number..... Study number .....

Age ..... Sex 1) Female.....

2) Male.....

Weight at baseline..... .....Weight after 6 months of treatment.....

Height at baseline .....Height after 6 months of treatment.....

Residence.....Admission ward at KNH.....

Malignancy.....

Date of diagnosis.....Method of diagnosis 1) Fine needle aspirate

2) Bone marrow

3) Excision biopsy

Date treatment initiated.....Treatment Regimen.....

SURFACE AREA

AT SART OF TREATMENT	6 MONTHS OR LATER	VARIATION

TREATMENT REGIMEN:

DRUGS	DOSE/M2	DATE BEGUN	CUMULATIVE DOSE/M2

INVESTIGATION

LABORATORY FINDINGS

TEST	After at least 6 months of treatment	At start of treatment	VARIATION
CREATININE			
GFR			

APPENDIX 3

KENYATTA NATIONAL HOSPITAL

Hospital Rd. along, Ngong Rd.
P.O. Box 20723, Nairobi.
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP", Nairobi.
Email: KNHplan@Ken.Healthnet.org

Ref: KNH-ERC/ A/499

11th June 2010

Dr. Muthoni Mburu
Dept.of Paediatrics & Child Health
School of Medicine
University of Nairobi

Dear Dr. Mburu

RESEARCH PROPOSAL: "ASSESSMENT OF GLOMERULAR FILTRATION RATE PROFILES OF PAEDIATRIC PATIENTS AGED 12 YEARS AND BELOW ON CANCER CHEMOTHERAPY AT THE KENYATTA NATIONAL HOSPITAL" (P102/03/ 2010)

This is to inform you that the KNH/UON-Ethics & Research Committee has reviewed and **approved** your above revised research proposal for the period 11th June 2010 to 10th June 2011.

You will be required to request for a renewal of the approval if you intend to continue with the study beyond the deadline given. Clearance for export of biological specimens must also be obtained from KNH/UON-Ethics & Research Committee for each batch.

On behalf of the Committee, I wish you a fruitful research and look forward to receiving a summary of the research findings upon completion of the study.

This information will form part of the data base that will be consulted in future when processing related research study so as to minimize chances of study duplication.

Yours sincerely

PROF A N GUANTAI
SECRETARY, KNH/UON-ERC

c.c. Prof. K. M. Bhatt, Chairperson, KNH/UON-ERC
The Deputy Director CS, KNH
The Dean, School of Medicine, UON
The Chairman, Dept. of Paediatrics & Child Health, UON
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