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GLOMERULAR FILTRATION RATE PROFILES OF PAEDIATRIC PATIENTS ON CANCER CHEMOTHERAPY AT THE KENYATTA NATIONAL HOSPITAL, KENYA
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M. MBURU, D. WAMALWA, A. BASHIR and L. WAINAINA

ABSTRACT

***Background*: An accurate estimation of renal function in children is important in optimising the dose of many drugs used in paediatric oncology for allowing clinical monitoring of the nephrotoxic effects of cytotoxic agents such as cisplatin. The glomerular filtration rate (GFR) is widely accepted as the best index of renal function in patients. Chemotherapy is the mainstay of treatment in the paediatric oncology unit at the Kenyatta National Hospital.**

***Objectives:* To determine the glomerular filtration rate profiles of paediatric oncology patients and to assess changes that had occured over a period of at least six months of continuing cancer chemotherapy.**

***Design:* Cross-sectional hospital based survey.**

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

***Subjects:* Paediatric patients who had an established diagnosis of cancer and had been on chemotherapy for at least six months.**

***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 five years and those with solid tumors had a higher likelihood of having an abnormal GFR compared to their older counterparts and those with lymphomas and leukemias.**

***Conclusions:* Monitoring of GFR should be done regularly as decline occurs as one continues on chemotherapy especially for the ones below five years and those with solid malignancies.**

INTRODUCTION

Globally cancer-related deaths account for 13% annually and 70% of these are in the low- and middle-income countries (1).Worldwide, the annual number of new cases of childhood cancer exceeds 200,000 and more than 80% of these are from the developing world (2). The incidence of childhood cancer in most populations in the world ranges from 75 to 150 per million children per year(3).

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 (3) found hospital based prevalence to be 1.27%.

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. 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. 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:

- vincristine, doxorubicin or dactinomycin and cyclophosphamide(VAC) and
- cyclophosphamide, doxorubicin , vincristine and prednisone(CHOP)

Renal failure remains an important complication of cancer and its treatment and this is often multifactorial in origin. These may include cancer

cachexia, cancer chemotherapy, concomitant use of other nephrotoxic drugs eg gentamycin and investigations involving use of radiocontrast media. Nephrotoxicity is an inherent adverse effect of certain anticancer drugs and has been shown to be a leading cause of renal compromise in oncology patients (4). Measurement of renal function is important in monitoring the nephrotoxic effects of oncology drugs such as cisplatin and ifosfamide (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. At Kenyatta National Hospital, the main referral facility in the country, a multimodal approach is used for the treatment of the various paediatric cancers. The most widely used modality in pediatric cancer therapy is chemotherapy.

MATERIALS AND METHODS

This was a cross-sectional hospital based study of paediatric oncology patients aged less than 12yrs who had a confirmed histologic diagnosis of cancer and had been on chemotherapy for at least 6 months. Patients were seen between May 1st 2010 and 31st October 2010 in the General Paediatrics wards, Paediatric Ophthalmology ward, the Paediatric Oncology ward and Hemato-oncology clinic at Kenyatta National Hospital,Nairobi.

Paediatric patients who met the inclusion criteria were recruited and were enrolled into the study following obtaining of consent/assent. Blood samples to measure serum creatinine were taken and sent to the renal laboratory in the renal unit at the Kenyatta National Hospital for analysis. 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, estimated glomerular filtration rates were tabulated.

Information on patient characteristics (age,sex,height and weight) and disease specifics(diagnosis, treatment regime and duration of treatment) for each patient were recorded. Files were studied and pre-treatment creatinine levels were retrieved. Different malignancies, chemotherapeutic agents and age groups, cumulative doses of drugs were variables from which statistically correct conclusions were drawn. Data were entered in a preformatted data sheet in MS Access database and analysed using Staview stastistical package and analysis using Intercooled Stata version 9.0. Student T-test and Pearson's Chi-square were used to test associations as appropriate.

RESULTS

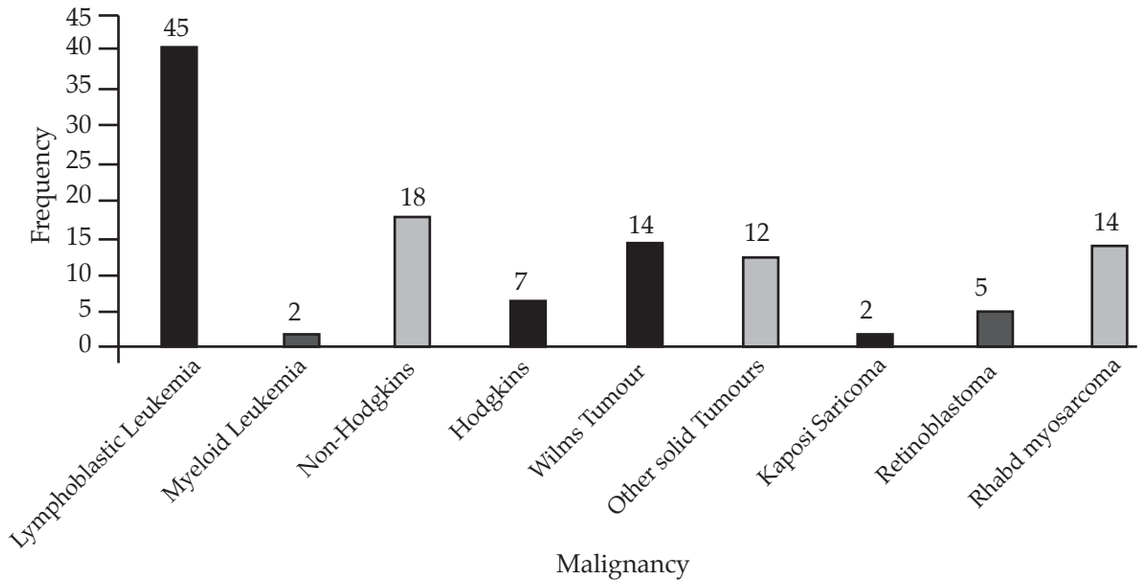
From May to October 2010, a total of 115 patients on childhood cancer chemotherapeutic treatment had their GFR evaluated. Their median age was seven years and the range was between four to nine years. Out of 115 children 60% of them were males (male: female ratio of 1.5:1) (Table 1).The median courses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

Table 1
Socio-Demographic Factor (n=115)

Factor	Frequency	Median /Percentage
Age (in years)		
Median		70
Range	2 to 12	
• <5	30	26.1
• 5 to 18	50	43.5
• >8	35	30.4
Sex		
• Male	69	40.0
• Female	46	60.0
Number of courses received	11.0	(8-13)

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). Children in the age group of 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.

Figure 1
Type of Malignancy



Glomerular filtration rates of children on cancer chemotherapy at Kenyatta National Hospital out of the 115 children enrolled in the study 43 had abnormal kidney function. This gave a prevalence of 37% (95%CI 28-46) as shown in Figure 2.The other 72 children had normal kidney function.

Figure 2
GFR after Chemotherapy

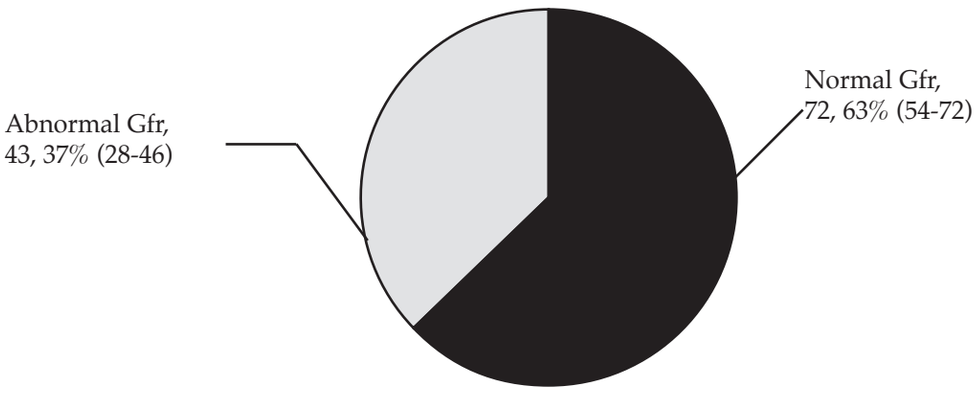


Table 2
Proportion of patients with low GFR in various malignancies

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

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 the other tumors. However, the estimates had very wide confidence intervals because of the small numbers (Table 3). Solid tumor patients (including wilms, retinoblastoma and rhabdomyosarcoma) had a large proportion of patients with abnormal GFR.

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. Figure 3 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 3
Frequency of patients with abnormal GFR on various chemotherapeutic drugs

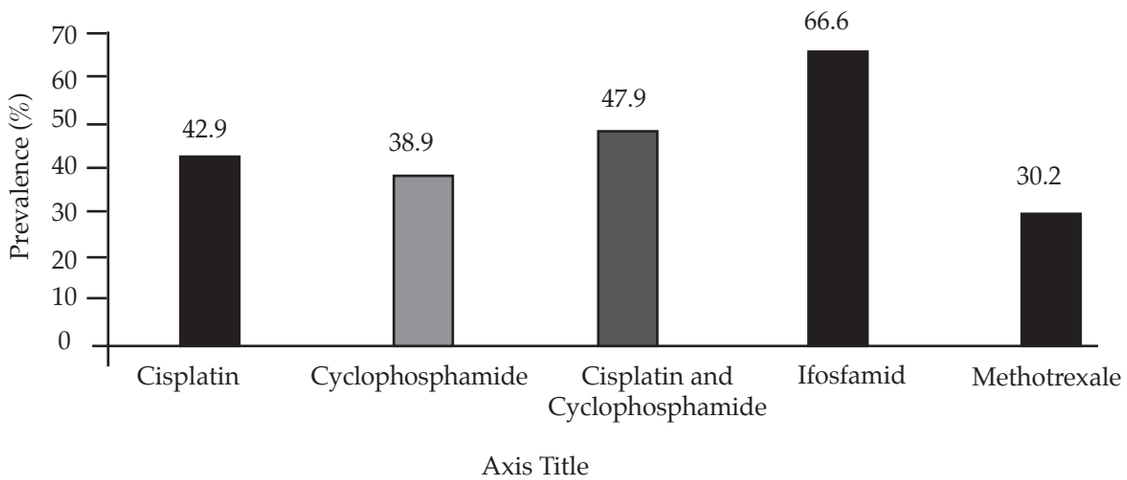


Table 3
Creatinine and GFR changes following at least 6 months of chemotherapy

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 at least six months of treatment than the beginning of treatment p<0.001. Initial GFR had a median value of 123 ml/min/I .73 m^2 (range 86-167). Final median GFR was 102 ml/min/1.73 m^2 (range 84-127). Two years was the longest duration of treatment in the study patients. (Figure 4)

Figure 4
GFR changes following at least 6 months of chemotherapy

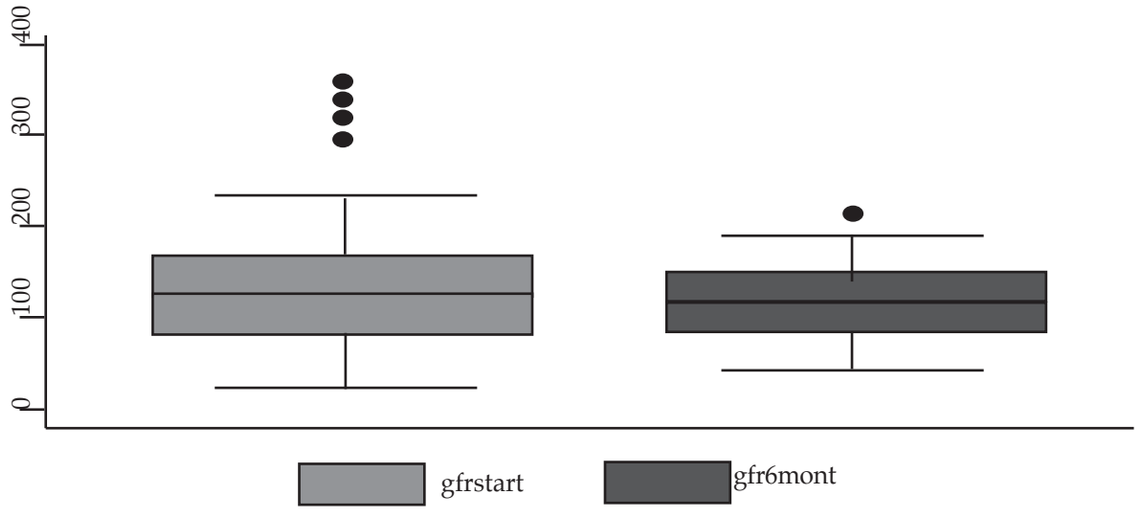


Table 4
Association between GFR and Selected Risk Factors

Risk Factor	GFR Status Abnormal, (43) n(%)	Normal, (72) n(%)	OR 95% CI	p-value
Treatment Regimen				
None of the Nephrotoxic drugs		8 (19)	11 (15)	
Drugs Cisplatin/Cyclopho-sphamide/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 as shown in Table 4.

DISCUSSION

The pattern of malignancies among our study patients was Leukemia 43(37%) in 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 five to eight years .This compares to a study done in indigenous Zambian children where the pattern of malignancies seen during a ten year period(1980-1989), revealed a total of 525 neoplasms with peak prevalence in the five to nine 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%). (5)

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 represented a third of the patients on treatment and has a higher frequency than previously documented in other studies. The relative risk of developing a decline in GFR while on nephrotoxic chemotherapy has been documented as 21% by Pinkerton *et al* (6). The postulated reasons of this are higher rates of malnutrition and sepsis which are conditions that also interfere with kidney function and decrease GFR, further studies would be required to ascertain this.

There was a greater predisposition of younger patients to the development of nephrotoxicity as seen both in our study and Ashraf *et al*. In the paediatric patient, developmental changes occurring from term to 3 to 5 years of age affecting proximal tubular function and, to a lesser degree, glomerular function may increase the vulnerability of young kidneys to toxic insults.(7)

Children with solid tumors including Wilms tumour had a high prevalence of abnormal GFR; these can be attributed to the fact that they receive both nephrotoxic drugs that is, platinum and alkylating agents in their treatment regimes. In the study the main solid malignancies in the group were 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 (8); Hartmann *et al* performed a randomised trial comparing the nephrotoxicity of cisplatin/ifosfamide-based combination chemotherapy with or without amifostine(medicine is used to decrease the side effects of certain cancer or radiation therapies) 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 ($p < 0.001$).

We confirm 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 67% in patients with GFR <60 ml/min(9). Our mean decrease in renal function of 14% confirms the observation of Jones *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 was chemotherapy (36%).

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. 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 (11). GFR was evaluated in patients who had received a cumulative cisplatin dose of 180 to 900mg, renal function become more impaired, even though only three chemotherapy cycles had been applied. Long-term effects of continuously elevated serum concentrations of cisplatin (12) may also, over years, reduce renal function. 43% of patients in our study on platinum based regimens had a GFR of less than 60 ml/min/1.73 m2. 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/m^2 (40 mg/m^2/day for 5 days) is reported. (13). Total cumulative dose of cisplatin in patients in the study was ranging from 612-7333mg/m^2. 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 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. Cyclophosphamide and ifosfamide are alkylating agents 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/m^2. 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/m^2), 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(8).Cumulative cyclophosphamide dose exceeding 1000mg/m2 and patient age are the 2 greatest predictors of risk for development of nephrotoxicity (14). The likelihood of renal dysfunction increases as the cumulative dose of cyclophosphamide increases.

In addition, the incidence and severity of nephrotoxicity is greater in patients younger than 5 years. Skinner 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/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 (15). 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. 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 (16). Acute tubular necrosis subsequent to crystallisation of the parent drug and the metabolite 7-hydroxymethotrexate within renal tubules is the purported underlying mechanism of methotrexate-induced renal dysfunction.All the patients on methotrexate were found to have an abnormal GFR.

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 which 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 ml, 1.73 m^2 (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 m^2; 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 m^2 (-46 to 134). Measurement of creatinine clearance at six month intervals in 15 patients with testicular cancer receiving three or more cycles of cisplatin 100 mg/m^2 (20 mg/m^2/day for five 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 (17).

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 eight patients with disseminated testicular carcinoma before, during and one 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 (18).

In conclusion, 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 treatment and their consequences on the quality of life are a major concern. Kidney disease frequently complicates malignancy and its treatment.

Our study showed that a third of our patients who had been on cancer chemotherapy had a GFR less than 60 ml/min and a decline in GFR occurs as ongoing cancer chemotherapy is given. Monitoring of kidney function should be done on a regular basis especially for the young (below five years) and those with solid tumors. The age of the patient is poses a risk for nephrotoxic damage due to immature structural development of the kidney in those less than five years. Patients with solid tumors receive 12 courses of combination chemotherapy in which cumulative doses of both platinum compounds and alkylating agents are known to cause kidney damage.

Function and quality of life may be impaired and 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.

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