Original Article

Renal function in late survivors of Iranian children with cancer: Single centre experience

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Abstract

CONTEXT: One of the side-effects of chemotherapy is nephrotoxicity, whose incidence rate has reportedly been higher in pediatrics. Early diagnosis of renal dysfunction may decrease the morbidity in those with partial or complete remission by avoiding nephrotoxic agents and promoting regular follow-up. **AIMS:** We studied the frequency of renal dysfunction in pediatric patients whose therapy was completed regardless of the type of chemotherapy. **SETTINGS AND DESIGN:** Prospective cross sectional study in Hematoncology department of children's hospital. **MATERIALS AND METHODS:** One hundred and eight pediatric cancer patients (44 females, 64 males), who were at least one year off therapy, enrolled in the study from 2003 to 2005. Demographic data, mean dosages of anticancer drugs, history of other nephrotoxic agents, nephrectomy, radiotherapy and acute renal failure were recorded. Fasting blood and urine samples were collected to calculate fractional excretion of magnesium, calcium, phosphate, urine protein to urine creatinine ratio, creatinine clearance (using Schwartz formula), urine analysis, urine osmolality and blood gas analysis. **STATISTICAL ANALYSIS USED:** T-test, Chi square and binary logistic regression were used to compare means, frequency and correlation respectively. *P* values < 0.05 were considered significant. **RESULTS:** Renal dysfunction was seen in 25.2% of cases. These abnormalities included hypercalciuria (7.2%), phosphaturia (13.5%), magnesuria (3.6%), glomerular filtration rate less than 90 ml/min (7.5%), metabolic acidosis (3%), metabolic alkalosis (10%), urinary concentration defect (19%), proteinuria (7.2%), glycosuria (2%), microscopic hematuria (4%), sterile pyuria (6%), and hypertension (8%). We found only Procarbazin as an independent variable of nephrotoxicity (*P*<0.05). **CONCLUSIONS:** Mild to moderate tubular dysfunction has been observed in the survivors of cancer disease.

Key words: Cancer, chemotherapy, late survivors, nephrotoxicity, tubular dysfunction

Introduction

Although it improves the survival of children with cancer, chemotherapy is accompanied by late side-effects including organ dysfunction, second malignant neoplasm and adverse psychological sequelae. Tubular dysfunction, hypertension, renal failure, and bladder fibrosis have been reported as the predominant sequelae of radiotherapy, and Platinum, Ifosfamide, or Methotrexate chemotherapy.[1-6] Young age during treatment, higher cumulative doses, concurrent nephrotoxins administration, previous unilateral nephrectomy, and pre-existing renal impairment are listed as potential risk factors of nephrotoxicity.[7-16] We studied the frequency of nephrotoxicity in pediatric patients whose therapy was completed with no regard to the type of chemotherapy.

Materials and Methods

One hundred and eight (64 male, 44 female) children aged two months to 15 years old at the time of diagnosis of neoplastic disease, in whom therapy was discontinued for at least one year, enrolled in a prospective cross sectional study in the oncology department of our hospital from 2003 to 2005. Informed consent was taken from patients or parents.

All information about demographic data, recurrence of disease, cumulative doses of anticancer drugs, tumor

lysis syndrome, history of nephrectomy (predominantly in Wilms' tumor), radiotherapy, and other nephrotoxic antibiotics (including Aminoglycoside, Amphotericin B, Vancomycin, Acyclovir) were recorded. A complete physical examination was done and blood pressure was checked by standard sphygmomanometer. Blood pressure levels above 95% were defined as hypertension, using the Task Force normogram for age and height. Fasting blood and urine samples were sent to a laboratory to calculate the fractional excretion of calcium (FE_{Ca}), magnesium (FE_{Mg}), phosphate (FE_{Ph}), urine protein to creatinine ratio (UP/UCr), and glomerular filtration rate (GFR) (using Schwartz formula). Urine analysis was performed to detect glycosuria, albuminuria, hematuria or pyuria; fasting urine specific gravity and urine osmolality was used to detect urinary concentration ability. Heparinized blood samples were taken for blood gases. Renal sonography was performed in all cases.

Nephrotoxicity was defined by the presence of hypertension, hypercalciuria (FE_{Ca} >5%), hypermagnesuria (FE_{Mg} >4%), phosphaturia (FE_{Ph} >25%), diluted urine (urine osmolality < 350 mosol/kg/H_2O and specific gravity <1.015), acidosis (PH <7.35 and HCO3 <20) or alkalosis (PH >7.45 and HCO3 >26), proteinuria (UP/UCr >0.2 and positive dipstick for albumin), GFR <90 ml/min/m^2, or glycosuria. We used T-test, *Chi square* and binary logistic regression to evaluate means, frequency and correlation. *P* values less than 0.05 were considered significant.

Results

The average age of patients was 12.9 years (± 5.12 SD). Seventy-nine out of 108 patients had lymphoproliferative malignancies including leukemia (n=59) and lymphoma (n=20). Twenty-nine had solid tumors which consisted of Wilms' (n=14), neuroblastoma (n=5), rhabdomyosarcoma (n=5), retinoblastoma (n=4) and yolk sac tumor (n=1). The mean length of therapy was 35.44 months (± 28.53 SD). Treatment was discontinued for 52.48 months (± 40 SD) on average. Table 1 shows the type, mean dosage and the number of recipient of chemotherapy drugs. A few patients were treated by Ifosfamide or Platinum agents.

7.5% of patients had GFR less than 90 ml/min. Hypercalciuria and phosphaturia was observed in 7.2% and 13.5%, respectively. Magnesuria was detected in 3.6% of patients. Three percent of patients had metabolic acidosis and metabolic alkalosis was seen in 10% of them.

Urine concentration defects were found in 19%. Proteinuria was detected in 7.2% of cases. Glycosuria was observed in 2%. Microscopic hematuria was found in 4%, and 6% of patients had sterile pyuria with negative urine culture. Hypertension was detected in 8% of children. These renal dysfunctions were not correlated with the type of chemotherapy, sex, age of starting therapy, history of radiotherapy, nephrectomy, or administration of other nephrotoxic agents (Binary logistic regression, $P>0.05$).

25.2% of patients had more than one parameter of nephrotoxicity (13 of leukemia, seven of lymphoma, three of Wilms' tumor, one of neuroblastoma, and two each of retinoblastoma and rhabdomyosarcoma). Using binary logistic regression analysis, we found a correlation only between nephrotoxicity and Procarbazin (odd ratio 6.5, 95% Confidence Interval 1.12-37.7, $P= 0.038$). The type of chemotherapy, age at start of therapy, sex, nephrectomy, radiotherapy, and use of other nephrotoxic agents showed no correlation with nephrotoxicity ($P >0.05$).

Discussion

We have shown that there is some degree of renal dysfunction in long-term follow-up of children with a history of chemotherapy. This abnormality was not correlated with the type of chemotherapeutic drugs or the neoplastic disease. A minority of patients were treated by Ifosfamide or Platinum agents but one-third of cases generally had mild to moderate renal dysfunction.

A number of studies have been done on the long-term outcome of renal function in survivors of childhood cancer. The majority of studies are concerned with nephrotoxicity in the acute phase of therapy especially induced by Ifosfamide, Cisplatin and Methotrexate.[3,5,7-11,13-15,17]

Reduction of glomerular filtration rate has been reported after completion of therapy in 13% of patients.[2,3,5,18-19] However, this reduction of GFR is subclinical or mild and is detected by elevation of serum levels of Cystatin C, serum creatinine, or by iGFR (chromium EDTA).[1,3-4,17,19] High dose of Methotrexate, older age at the time of diagnosis, Wilms' tumor, and triple therapy (surgery, chemotherapy and radiation) have been reported as risk factors.[17,18] None of these publications reported severe chronic renal failure and Koch Nogueira *et al*, observed that all long term survivors of osteosarcoma had GFR more than 80 ml/min despite receiving Ifosfamide, Cisplatin and Methotrexate.[3] A few of our patients showed mild reduction of GFR using the Schwartz formula; this effect was more

Table 1: Mean dosage of the chemotherapy drugs and the number of patients who were treated

Chemotherapy	Number of patients	Mean dosage (mg/m²)
Vincristine	110	61
Actinomycin	21	14802
Adriamycin	44	152
Cyclophosphamide	85	4423
Methotrexate	66	3723
Etoposide	15	1224
Ifosfamide	5	11284
Prednisolone	79	4545
Cisplatin	8	380
VM26	7	1251
Camustine	1	113
Cytarabine	64	816
L-Asparaginase	56	52503
Lanvis	15	17771
DNR	58	55
Lomustine	1	62
Vinblastine	9	32
Dacarbazine	9	1541
MUSTIN	9	25.4
Procarbazin50	6	1262
Bleomycin	11	69
Mercaptopurine	58	31139
Carboplatin	3	2770

prominent in those who received nitrogen mustard. Serum Cystatin C is more sensitive in detecting GFR changes compared to serum creatinine.[1,17] Petal *et al*, showed that during chemotherapy iGFR had a value of 20% below GFR calculated by the Schwartz formula.[19]

Tubular dysfunction is more persistent after chemotherapy has ended, and dysfunction of the organic anion transporter has been suggested as the probable mechanism.[2] In our study the urinary concentration defect was generally followed by phosphaturia and hypercalciuria. Detection of metabolic acid–base disorders, tubular proteinuria, glycosuria and diluted urine might suggest involvement of different parts of the nephron. No risk factor was detected for this tubular dysfunction but impaired urinary concentration was pronounced in those with solid tumors. Similar disorders have been reported in the literature.[1,3,5] Kveder *et al*, found normal fractional excretion of sodium, potassium, calcium and phosphate after 22 years follow-up on average. The urinary N-acetyl-B-glucosaminidase (NAG) /creatinine ratio was highest in those patients who received triple therapy.[18] Proteinuria was more frequent in Kopecna's study on survivors of acute lymphoblastic leukemia.[4] These reports may suggest proximal tubular dysfunction. Phosphaturia, calciuria, and metabolic acidosis made the children prone not only to osteoporosis but also to urolithiasis.[20-22] None of our patients had nephrolithiasis in renal sonography and another project is being conducted to evaluate bone densitometry in late survivors.

Hypertension has been reported as a late sequel of radiotherapy due to renal artery stenosis.[23] However, only 1.6% of all hypertensive patients in our group had a history of receiving radiotherapy. Acrolein, a metabolite by-product of Cyclophosphamide and Ifosfamide, may cause hemorrhagic cystitis and bladder fibrosis and increase the risk of developing bladder cancer.[24-26] Only 4% of those who received Nitrosourea had microscopic hematuria. Because of an insufficient number of cases, we could not find any correlation between hematuria and those therapies.

Few studies have been done about the overall incidence of nephrotoxicity in the survivors of chemotherapy. Putting all of the parameters together, one third of our patients showed mild to moderate nephrotoxicity independent of any risk factors. This finding shows the subclinical renal dysfunction in our survivors in whom its consequences must be determined.

In conclusion, mild to moderate tubular dysfunction has been observed in survivors of chemotherapy. Routine follow-up care of renal function is recommended.

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