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Anticancer Drug Induced Glomerular Dysfunction

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Abstract: For the purpose of studying renal side effects induced by anticancer drugs, we inspected glomerular damage as well as tubular damage of patients with anticancer chemotherapy. Thirty patients medicated with anticancer drugs, which are known to have nephrotoxic side effects were enrolled in this study. 17 of the patients were male and 13 female with a median age of 44. Four cycles of chemotherapy were administered to each patient. Renal function tests with classic parameters were measured before and after treatment in the patient. Before the treatment, there was no significant difference between the patients and the control group in comparison of renal function tests. A decline in GFR, an increase in urine pr/cr ratio, serum creatinine was observed with subsequent cycles of the chemotherapy, which was considered statistically significant ($p<0.001$). The values of urine sodium after chemotherapy were higher than those before chemotherapy. However, the difference was not significant ($p=0.1$). Urine pH was elevated in one patients (%3.3). These results show that anticancer drugs may not only induce tubular dysfunction but also glomerular dysfunction. The glomerular damage may be persistent and not correlated with tubular damage.

Key words: Antineoplastic agents · Glomerular basement membrane · Side effects · Glomerular filtration rate

INTRODUCTION

Nephrotoxicity is one of most common side effects of the anticancer drugs for solid and hematologic malignancy. Antimetabolites, alkylating agents and anthracyclines are commonly used anticancer drugs resulting in nephrotoxicity [1]. Renal tubular damage is a well-known renal complication induced by anticancer drugs [2-5]. However, There are several studies about glomerular dysfunction induced by anticancer drugs. The rate of glomerular damage may have been underestimated because tubular dysfunction can mask glomerular dysfunction [6-8].

Increased urinary excretion of alanine aminopeptidase, N-acetyl-β-D-glucosaminidase (NAG), á1-acid glycoprotein, or β2-microglobulin is used as a marker of proximal tubular lesions. Disruption of glomerular integrity is distinguished by proteinuria. Increased urinary excretion of albumin, or immunoglobulin is used as a marker of glomerular damage [1]. There are also many classic parameters to evaluate the renal damage such as serum creatinine, urea, uric acid, creatinine clearance, urine protein/creatinine ratio, urine sodium and urine pH.

In this report, we studied with classic parameters the glomerular and tubular function treated with anticancer drugs to evaluate of drug-induced glomeruler damage.

MATERIALS AND METHODS

Patients: Thirty patients medicated with nephrotoxic anticancer drugs were enrolled in this study between January-July 2006 at the Department of Hematology, Inonu University Medical Faculty. At the beginning of the study, an informed consent about the investigation was obtained from the patients. Patients with no renal impairment were enrolled to the study. Patients with clinical findings such as edema, polyuria, oliguria and hypertension prior to the chemotherapy were excluded. who previously had not been treated with anticancer drugs and who did not have renal dysfunction served as the control group. Nine patients with acute myeloblastic leukemia received high dose of cytosine arabinoside (72 gr/m^2/total); three with non Hodgkin's lymphoma received CHOP (cyclophosphamide 3g/m^2/total, doxorubicin 200 mg/m^2/total, vincristine 5.6 mg/m^2/total, prednisolone 240 mg/m^2/total) and nine of them were treated with RCHOP(rituximab 1.4g/m^2/total -CHOP);

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two patients with Hodgkin's lymphoma received ABVD(doxorubicin 100 mg/m^2/total, bleomycin 40 mg/m^2/total, vincristine 5.6 mg/m^2/total, dacarbazine 1.4g/m^2/total) and the other one DHAP (cytosine arabinoside 8gr/m^2/total, cisplatin 400mg/m^2/total, dexamethasone 400 mg/m^2/total); three patients with diagnosed gastric adenocarcinoma and three with diagnosed cervix carcinoma, thymoma and lung cancer were given a treatment with a combination of cisplatin (mean 300 mg); two patients with angiosarcoma and soft tissue sarcoma received IMA(ifosfamide 8 gr/m^2/total, doxorubicin 240 mgr/m^2/total) and a combination of cyclophosphamide (2.4 gr/m^2/total)and doxorubicin (240 gr/m^2/total) was used in a patient with breast cancer. Renal function tests in both the patient and the control group were investigated before the treatment. Four cycles of therapy were given to each patient and after the treatment these tests were repeated.

Assessment of kidney function

Evaluation of The glomerular filtration rate: The GFR was estimated from the creatinine clearance. The normal value for GFR was accepted as 128±26 ml/min/1.73 m^2 for males and 118±24 ml/min/1.73 m^2 for females [9].

The creatinine clearance was determined from a 24-hour urine collection. The creatinine clearance from a 24-hour urine collection was calculated using the following formula. Creatinine Clearance (mL/min) = Urine Creatinine (mg/dL) x Urine Volume (mL/day) / Plasma Creatinine (mg/dL) x 1440 [10].

Among patients with chronic kidney disease (CKD), the stage of disease was assigned based on the level of kidney function, according to the Dialysis Outcomes Quality Index (DOQI) guideline for CKD classification [11].

Assessment of proteinuria: The proteinuria on the spot urine specimen was measured by nephelometric method using Dade Boehring BN-2 analyzer. The reference range of the total pr/cr ratio on a spot urine specimen was determined to be below 200 mg/gr [12].

Evaluation of laboratory measurements for clinical assessment of renal disease: Blood urea nitrogen, creatinine, sodium, potassium, chloride, calcium, phosphate, magnesium, urine creatinine and urine sodium levels were examined by colorimetric method using Olympus 2700 analyzer. Blood and spot urine samples were collected at 08:00 am in the defined days and the measurements were performed at the Biochemistry Laboratory of Inonu University Medical Faculty.

Statistical methods: Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) Chicago USA for Windows 13.0 programme. Parametric data were expressed as mean±standard deviation and non-parametric data as percent. Categorical variables were compared using the Wilcoxon test and paired two-tailed t-test. And p values <0.05 were regarded as statistically significant.

RESULTS

Patients: 17 of the patients were male (57%) and 13 of them were female (43%). Their median age was 44 years (min: 20, max: 79). 26 of the patients were newly diagnosed and four of them were previously treated.

Glomerular damage

Glomerular filtration rate: The patients were compared with each other according to chemotherapy cycles. Before the first cycles, mean GFR in the patient group was 128 mL/min, while 130 ml/min in the control group, without significant difference between the two groups (p=0.17).

Mean GFR significantly decreased with subsequent cycles; before the first cycles, during the treatment and after the fourth cycles (p<0.001). (Table 1) (Fig. 1).

Although the GFR before the first cycles was within normal levels (95 ml/min) in a patient (patient no 5, %3.3), the severity of renal failure progressed to stage IV (26 ml/min) after the fourth cycles according to DOQI guideline. Dialysis was not required. A reduction in GFR after the fourth cycles was detected in other patients but no uremic complications was observed.

Urine protein/creatinine (Pr/Cr) ratio: The patients were compared with each other according to chemotherapy cycles. Before the first cycles, mean pr/cr in the patient group was 28.4 mg/gr, while 26.2 mg/gr in the control group, without significant difference between the two groups (p=0.12).

Table 1: Renal function tests before and after the treatment

	Before the treatment n:30		After the treatment n:30		
	GFR (mL/min)	Pr/Cr (mg/gr)	GFR (mL/min)	Pr/Cr (mg/gr)	p
1. cycles	128.5±31.2	28.4±2.5	108.3±31.7	121.1±10.8	<0.001
2. cycles	114.3±29.2	98 ±12.3	97.6±25.4	257.4±34.6	<0.001
3. cycles	103.2±26.7	148±17.3	90.1±24.1	382±20.3	<0.001
4. cycles	94.6±26.4	325±40.1	81.2±20.6	492±62.4	<0.001

Table 2: Urine sodium tests before and after the treatment

	Before the treatment n:30 meq/L	After the treatment n:30 meq/L	p
1. cycles	15.19±2.32	14.98±2.45	NS
2. cycles	14.67±3.01	15.12±2.96	NS
3. cycles	15.43±3.23	16.05±3.64	NS
4. cycles	15.37±2.72	16.17±2.93	NS

NS: Not significant

Mean pr/cr ratio significantly increased with subsequent cycles; before the first cycles, during the treatment and after the fourth cycles. Mean pr/cr ratio significantly increased in parallel with a significant decline in mean GFR with subsequent cycles ($p<0.001$) (Table 1) (Fig. 2). After the fourth cycles, the mean pr/cr ratio returned to normal spontaneously within two months.

After the third cycles, pr/cr ratio did exceed 1500 mg/day in a patient (patient no 21, %3.3). After supportive treatment it fall dawn to normal range.

Serum creatinine: Mean serum creatinine levels before the first cycles and after the fourth cycles were 0.69±0.11 mg/dL and 1.1±0.29 mg/dL, respectively. Mean serum creatinine levels after the treatment were significantly higher ($p<0.001$), when compared with the levels before the treatment. Mean serum creatinine levels significantly increased with subsequent cycles; before the first cycles, during the treatment and after the fourth cycles ($p<0.001$).

Tubular damage

Urine sodium: Mean urine sodium excretion before the first cycles and after the fourth cycles was 15.19±2.32 meq/L and 16.17±2.93 meq/L, respectively. Mean urine sodium excretion after the treatment was higher, when compared with excretion before the treatment; however, the difference was not significant ($p=0.1$). Although, mean urine sodium excretion tended to

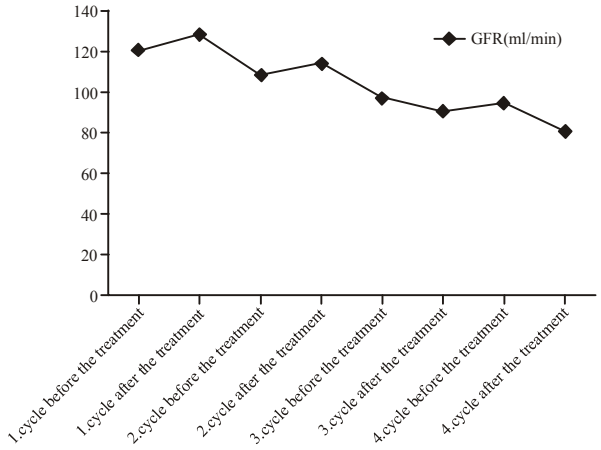

Fig. 1: Mean GFR before and after the treatment

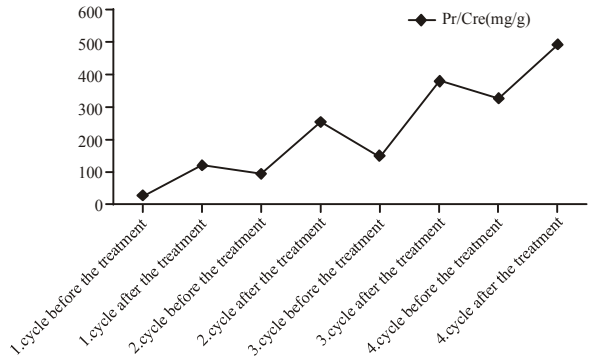

Fig. 2: Mean urine pro/cre before and after the treatment

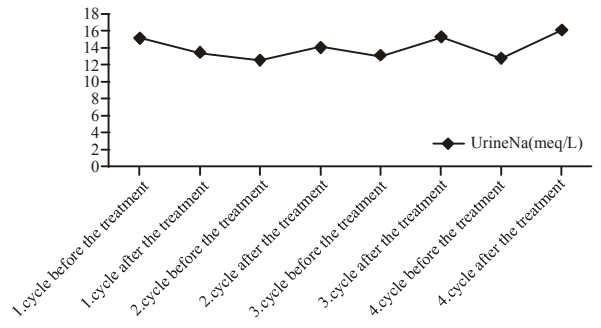

Fig. 3: Mean urine sodium before and after the treatment

increase with subsequent cycles; before the first cycles, during the treatment and after the fourth cycles, changes were not significant (Table 2) (Fig. 3).

Serum electrolytes: Serum concentrations of sodium, potassium, calcium, magnesium and phosphate after the treatment were not significantly different from values before the treatment. Moderate hypomagnesemia (1.4 mg/dl) in a patient (patient no 28, %3.3) receiving

cisplatin and in another (patient no 27, %3.3) mild hypokalemia (3.1 mmol/L) was observed.

Urine Ph: There were no significant differences in urine pH with subsequent cycles; before the first cycles, during the treatment and after the fourth cycles. Urine pH exceeded 7.0 in a patient (patient no 16, %3.3).

DISCUSSION

Renal toxicity is a common side-effect of chemotherapy with anticancer drugs [1]. Anticancer drugs affect different segments of the nephron, which is the basic unit of the kidney: especially the glomerulus, proximal and distal tubules [6]. Renal tubular damage is a well-known renal complication induced by anticancer drugs [2-5]. However, glomerular damage induced by anticancer drugs is not well understood. There have been only few reports concerning glomerular dysfunction [6-8]. Reduction in GFR due to glomerular dysfunction results in a rise in the plasma creatinine concentrations and in the urine protein/creatinine ratio. Proximal tubular dysfunction leads to a reduction in the serum levels of sodium, potassium, chloride, calcium, magnesium and phosphate and to an increase in urinary sodium excretion. Distal tubular dysfunction results in a rise in urinary pH and osmolality [13, 14]. In our study, no difference associated with proximal and distal tubular dysfunction, such as sdisorders of serum electrolyte levels and urinalysis was observed before and after the treatment. However, disorders associated with glomerular dysfunction, such as progressive reduction in GFR and concurrent elevation in serum creatinine and urine pr/cr ratio were detected. Tubular dysfunction was not observed, glomeruler dysfunction was observed. In several studies investigating these drugs [15-18] the association with glomerular dysfunction has been reported to be more evident than tubular dysfunction, similarly to our study. In our results indicate that anticancer drugs can not only induce tubular dysfunction but also glomerular dysfunction, which is persistent and independent of tubular dysfunction.

Antincancer drugs primarily damage the glomerulus, including fenestrated endothelial cells, visceral epithelial cells (podocytes), mesangial cells and Glomerular Basement Membrane (GBM). The endothelial cells and the podocytes are rich of sialoglycoproteins, which have a key role of the glomerular anionic surface coat. Damage to these cells leads to loss of charge selectivity function of GBM. In addition, the podocytes may be damaged by a variety of anticancer drugs. The integrity of the GBM alters by the detachment of podocytes. Morphological alterations of charge-selective barrier function of the GBM leads to increased glomerular permeability. That results in a fall of the GFR with a urinalysis showing proteinuria [15-17]. Experimental studies in rabbits have demonstrated doxorubicin to produce progressive glomerular changes [18]. Harmon et al, have reported glomerulosclerosis following treatment with cisplatin within 6-12 months after anticancer chemotherapy [8]. Nitrosoureas may produce dose related nephrotoxicity resulting in chronic interstitial nephritis or glomerular sclerosis. Proteinuria and nephrotoxicity (in the patients treated) associated with mitomycin C, which was related to cumulative dose, have been introduced [19]. In our study, two months later after the discontinuation of cisplatin therapy, kidney function tests of the patients regressed to the levels before the treatment. Progression to chronic kidney disease was not observed. Our population in the study was relatively small and various anticancer drugs were administered. High dose of cytosine arabinoside-containing consolidation regimen was carried as monotherapy only in 9 patients with Acute Myeloblastic Leukemia. For the treatment of patient with other malignancies, combination chemotherapy regimens were used. Therefore, we detected the glomerular dysfunction only in patients receiving high dose of cytosine arabinoside. However, by using a combination of agents it was unlikely to predict which one was responsible for glomerular dysfunction.

It has previously been shown that glomerular dysfunction may be related to the cancer itself. In the present study, it was suggested that the deposition of circulating immune complexes in the glomerulus and the antibodies reacting in situ within the glomerulus might cause glomerular damage in patients with cancer. Glomerular disorders occur primarily with malignancies, such as multiple miyeloma, carcinoma of the lung or colon, lymphoma or acute leukemia. It has been reported that membranous nephropathy is often associated with solid tumors such as carcinomas, while minimal change disease frequently occurs in association with lymphomas [1, 20]. The majority of the patients included in our study had the described carcinomas (9 patients with acute myeloid leukemia, 12 with lymphoma, 3 with gastric cancer and 1 with lung cancer). As mentioned previously, several factors including the cancer itself can potentiate glomerular dysfunction. There was no difference in kidney function tests between the patients and the control group before the treatment. Detailed immunohystochemical

investigation before the anticancer chemotherapy was not designed and we could not predict the immunologic damage in the kidney. More detailed studies are necessary in a larger number of patients to identify this relationship.

In conclusion, Our population in the study was relatively small. Further comprehensive studies are necessary to explain each drug's effect on glomerulus along with tubulus. In our study showed that glomerular damage should be also considered in the management of patients with anticancer chemotherapy.

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