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Evaluation of the Kidney Disease Developed in Malignancy Patients

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Background: Renal involvement in malignant patients may lead to kidney disease indirectly for a number of reasons, including direct metastasis or dehydration, hyperuricemia and tumor lysis syndrome. We aimed to evaluate malignant patients who developed kidney disease in our study.
Method: This study was performedin malignant patients who applied to the Kahramanmaraş Necip Fazıl City hospital between 2015-2017. Blood urea nitrogen, serum creatinine, uric acid, sodium, potassium, calcium, phosphorus, glucose, complete urine output and hemogram were noted in patients with kidney disease.
Results: A total of 688 cancer patients were included in the study. 53.6% of the patients were female and 46.2% were male. The average age of the patients was found as 60.23±13.25 (21-94). Acute kidney injury was detected in %17,1. When the patients diagnosed with kidney disease were evaluated; serum uric acid levels were higher in 46.2% of patients, calcium-level was low in 7.7% of patients and high in 3.6% of patients, serum potassium level was high in 21.1% of patients, phosphorus level was high in 42.9% and serum sodium level was low in 17.2% of patients. According to Kidney Disease Improve Global Outcomes, acute renal injury was detected in 42.4% of stage-I, 25.4% of stage II, and 32.2% of stage-III. 33 of 118 patients with acute renal injury died.
Conclusion: In our study, the incidence of acute renal injury was 17.1% in the cancer patients. The mortality rate was higher in the patients with acute renal injury.

Key Words: Malignancy, acute renal injury, glomerular filtration rate

Introduction

The development of kidney disease in cancer patients may lead directly to kidney metastasis and infiltration, ischemia, obstruction. Indirectly dehydration, hypercalcemia, infection, sepsis, acute renal failure, disseminated intravascular coagulation, renal vein thrombosis, amyloidosis, glomerulopathy, nephrocalcinosis can also affect the kidney. In addition, anti-cancer drugs (cisplatin, platinum, ifosfamide, pemetrexed, gemcitabine, mitomycin C, cyclosfamide) used in the treatment of cancer nephrotoxic, use of nephrotoxic drugs other than anti-cancer agents (contrast agent, bisphosphonates, analgesic drugs) radiation nephritis, tumour lysis syndrome, urate nephropathy can cause acute renal injury. Risk factors for acute renal damage in cancer patients include age (>65), congestive heart failure, chronic renal disease, volume deficiency for any cause, cancers (such

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as multiple myeloma, other haematological malignancies and liver cancer), tumourlysis syndrome, linked glomerular disease and cancer infiltration of the kidneys (1-3).

Tumor lysis syndrome is a clinical picture that occurs when tumoral cells are rapidly destroyed and which is accompanied by life-threatening metabolic disorders. The diagnosis of TLS is made by the involvement of two or more of the laboratory criteria (hypercalcemia, hyperphosphatemia, hyperuricemia, hypocalcemia) and one or more of clinical manifestations (acute renal failure, convulsions, arrhythmia/ sudden death)(4).

Materials and Methods

The study was performed in malignant patients who applied to the Kahramanmaraş Necip Fazıl City hospital between 2015-2017. Patients younger than 18 years of age, head and neck tumors, renal tumors, malignant melanomas were excluded from the study. Blood urea nitrogen, serum creatinine, uric acid, sodium, potassium, calcium, phosphorus, glucose, complete urine output and hemogram were noted in patients with kidney disease.

Patients' diagnoses, chemotherapy, and renal failure treatments were noted. According to kidney disease improve global outcomes, acute kidney injury is stage-I serum creatinine 1.5-1.9 times increase or ≥0,3mg/dl increase or urine output 6-12 hours<0.5 ml/kg/h, stage-II serum creatinine 2-2.9 times increase or urine output ≥12 hours, <0.5 ml/kg/h, stage-III serum creatinine 3 times increase or serum creatinine ≥4mg/dl or renal replacement therapy or under 18 years of age eGFR <35ml/min or ≥24 hours 0,3ml/kg/h or ≥12 hours anuric. The chronic renal disease was evaluated as stage-I ≥90 ml/min, stage-II 60-89 ml/min, stage-III 30-59 ml/min, stage-IV 15-29 ml/min, and stage-V <15 ml/min.

Statistical Analyze

The data of our study are uploaded to the SPSS (Version 22) program and the difference between the two means is tested for significance in the independent groups if the data is normalized, Man-Whitney U test if not normal distribution, Chi-square test or Fisher exact Chi-square test for categorical data. If our data show normal distribution on the tables, the arithmetic mean±standard deviation will be displayed median and quarterly intervals if not normal distribution. Also, if necessary, the data will be given in frequency and %. A p value of less than 0.05 would be considered significant.

Results

A total of 688 cancer patients were included in the study. 53.6% of the patients were female and 46.2% were male. The average age of the patients was found as 60.23±13.25 (21-94). A total of 172 patients had renal disease. The average age of these patients was 65.74±11.58 (28-89). There was acute kidney injury in 118 patients and chronic kidney disease in 54 patients.

When the patients diagnosed with kidney disease are evaluated; serum uric acid was high in 46,2% of patients (>8 mg/dl), normal in 50,4% of patients (3-8mg/dl) and low in 3,4% of patients (<3mg/dl). Calcium level was low in 7.7% of the patients, was normal 88,8%of the patients and was high 3,6%of the patients. Serum potassium level was high in 21,1% of the patients, was normal 18,2% of the patients and was low 5,8% of the patients. Phosphorus level was high in 42,9% of the patients, was normal 51,8%of the patients and was low 5,4% of the patients. Serum sodium level was low in 17,2% of the patients, was normal 81,7% of the

patients and was high 1,2% of the patients. Anemia was detected in 72.7% of the patients. The laboratory data of the patients are given in table 1.

Breast cancer was most frequently detected, but acute kidney injury was detected in the presence of hepatocellular carcinoma. Cancer types of patients and prevalence of acute kidney injury development in cancer patients are given in table 2.

Acute renal failure was detected as 17.1%. According to Kidney Disease Improve Global Outcomes, the acute renal injury was detected in 42.4% of Stage-I, 25.4% of Stage-II, and 32.2% of Stage-III. The rate of glomerular filtration was found to be 39.33±18.21 ml/min with Modification of Diet in Renal Disease.

Chronic kidney disease was found to be as 0,6% in Stage I, 13,5% in Stage-II, 56,7% in Stage-III, 16,4% in Stage-IV, 12,9% in Stage-V. When all cancer patients were treated, the glomerular filtration rate was found to be <90 ml/min at 24.7%. Chronic kidney disease was found to be as 3,3 % in Stage-I, 14,1% in Stage-II, 14,1% in Stage-III, 4,1% in Stage-IV, 3,2% in Stage V.

Tumour lysis syndrome was found to be 2.7% among all patients, in 16.1% of malignant patients with acute kidney injury, Tumour lysis syndrome was detected. This was found in the cases of hepatocellular cancer in a patient, over cancer in a patient, stomach cancer in 7 patients, lung cancer in 3 patients, pancreatic cancer in 2 patients, breast cancer in a patient,

Table 1. Laboratory data of patients diagnosed with kidney disease

Parameters	Number	Average ± Standard Deviation
BUN (mg/dl)	172	103,31±88,08 (20-566)
Creatinine (mg/dl)	172	2,45±2,38 (1,2-22,4)
Glucose (mg/dl)	172	134,11±70,86 (60-603)
Uric acid (mg/dl)	119	8,31±3,74 (0,2-20)
Calcium (mg/dl)	169	9,00±1,13 (5,1-17)
Potassium (mmol/L)	171	4,86±1,17 (2,5-11,6)
Phosphor (mg/dl)	56	4,79±1,79 (2,4-14)
Sodium (mlEq/L)	169	136,10±6,22 (118-154)
Haemoglobin(gr/dl)	161	10,94±2,03 (7-17)
Haematocrit (%)	161	33,64±6 (21-51,6)

Table 2. Patients' diagnose, and prevalence of acute renal failure

Diagnosis	% (Number/Total)	AKD % (Number/Total)
Lung Cancer	11,5% (79/688)	22,7% (18/79)
Gastric Cancer	16,7% (115/688)	17,3% (20/115)
Pancreatic Cancer	4,7% (32/688)	37,5% (12/32)
Hepatocellular Cancer	2,8% (19/688)	52,6% (10/19)
Colon Cancer	20,3% (140/688)	16,4% (23/140)
Prostate + Bladder Cancer	11,8% (81/688)	19,7% (16/81)
Breast Cancer	26,6% (183/688)	7,1% (13/183)
Over-Cervix-Endometrium Cancer	5,7% (39/688)	15,3% (6/39)

AKD: Acute Kidney Damage

colon cancer in 3 patients and prostate cancer in one patient. Seven of these patients died. There was also clinical and laboratory Tumor lysis syndrome in 6 patients with postrenal acute renal damage and 4 patients with hyperbilirubinemia. Postrenal acute renal damage was detected in 12 patients. Rarely, in one case, breast cancer developed as a result of ureteral metastasis. There were also hyperbilirubinemia in 8 patients. When all patients were evaluated, the rate of patients using at least one chemotherapeutic drug was 84.7%. Of the patients who had acute kidney injury, 63.5% were using at least one chemotherapeutic drug. Chemotherapeutic drugs used in malignants are given in table 3.

Twelve of the patients who had acute kidney injury had hypertension. 30 patients had diabetes mellitus, 8 patients had coronary artery disease, 7 patients had hypertension+ diabetes mellitus, 7 patients had nephrolithiasis, one patient had diabetes mellitus + autosomal dominant polycystic kidney disease and one patient had diabetes mellitus + nephrolithiasis.

Haemodialysis was performed in 11% of patients with an acute kidney injury. The mortality rate in malignant patients with acute kidney injury was found to be as 27.9%. Patients who died, subarachnoid hemorrhage in one patient, multi-organ failure in 7 patients, and sepsis mortality in 16 patients.

Table 3. Drugs in the patients with acute renal failure and all patients

Drug Types	All Patients	Patients with ARF
Cisplatin	6% (41/688)	13,5% (16/118)
Oxaliplatin	12,2% (84/688)	14,4% (17/118)
5 fluorouracil	13,2% (91/688)	16,1% (19/118)
Paclitaxel	8,7% (60/688)	3,3% (4/118)
Docetaxel	6,4% (44/688)	3,3% (4/118)
Carboplatin	3,8% (26/688)	1,6% (2/118)
Gemcitabine	3,5% (24/688)	8,4% (10/118)
Capecitabine	10,3% (71/688)	8,4% (10/118)
Leucovorin	5,1% (35/688)	6,7% (8/118)
İrinotecan	3,6% (25/688)	4,2% (5/118)
Etoposide	1% (7/688)	2,5% (3/118)
cyclophosphamide	6% (41/688)	1,6% (2/118)
Doxorubicin	3,3% (23/688)	0,8 (1/118)
Adriamycin	2,3% (16/688)	1,6% (2/118)
Bicalutamide	1,3% (9/6889	-
Leuprolide acetate	1,5% (10/688)	1,6% (2/118)
Transtuzumab	6,4% (44/688)	2,5% (3/118)
Premetrexed	1,3% (9/688)	1,6% (2/118)
Bevacizumab	1% (7/688)	-
Others	6,5% (44)	9,3% (11/118)

Others (among all patients): Methotrexate 0,3%, steroid 0,4%, letrozole 0,7%, vinorelbine 0,1%, abirateron 0,4%, panitumumab 0,4%, tamoxifen 0,9%, erlotinib 0,4%, epirubicin 0,7%, goserelin 0,9%, sorafenib 0,3%, fulvestrant 0,4%, Kabazitaksel 0,6%. **Others (in patients with Acute kidney damage):** Kapazitaksel 0,8%, steroid 0,8%, vinorelbine 0,8%, letrozole 0,8%, panitumumab 0,8%, tamoxifen 0,8%, epirubicin 0,8%, fulvestrant 0,8%, sorafenib 0,8% andabirateron 1,6%. **ARF**: Acute Renal Failure

Discussion

In our study, acute kidney injury was detected as 17.1%. According to Kidney Disease Improve Global Outcomes, acute kidney injury was detected in 42.4% of Stage-I, 25.4% of Stage-II, and 32.2% of Stage-III. The rate of glomerular filtration was found to be 39.33±18.21 ml/min with Modification of Diet in Renal Disease of Patients with an acute kidney injury. In addition, the glomerular filtration rate was found to be 86% in patients with acute kidney injury <60/min. When all cancer patients were treated, the glomerular filtration rate was found to be <90 ml/min at 24.7%. Chronic kidney disease was found to be as 3,3% in Stage-II, 14,1% in Stage-III, 4,1% in Stage-IV, 3,2% in Stage-IV. In a study by Launay-Vacher et al., an acute renal failure was found in 9.2% of patients with anemia. In this study, the glomerular filtration rate calculated by Cockcroft and Gault formula was found to be 33% <80ml/min (28% for 50-80ml/min, 5% for <50ml/min)(5). In IRMA study, The rate of glomerular filtration with Cockcroft and Gault was found to be 57,4% (glomerular filtration rate of 60-89 ml/min at 37.6%, 30-59 ml /min at 18.5%, 1,3% at the <30 ml/min) and the rate of glomerular filtration with modification of diet in renal disease was found to be 52,9% (glomerular filtration rate 40.9% 60-89 ml/min, 11.1% at 30-59 ml/min and 0.92% at <30 ml/min) <90 ml/min. The increase in serum creatinine level was found in 1,7% of breast cancer patients and 14,9% of prostate cancer patients (6). In BIRMA study, 64% of patients were found to have a glomerular filtration rate <90 ml/min with modification of diet in renal disease.

The prevalence of serum creatinine levels ≥1.2 ml/dl was found to be as 14.9% (7). In the study done by Doğan et al., the serum creatinine level of 5,9% of the patients was found to be 1,2 mg/dl. In 27.1% of the patients, the rate of glomerular filtration with Cockcroft and Gault was found to be below <90ml/min. Glomerular filtration rate was found to be as 60-89ml/min in 19,8% of patients, 30-59ml/min in 6,2% of patients, 15-29ml/min in 0,6% of patients and <15ml/min in 0,6% of patients (8).

Renal compression or obstruction in urinary system in cancer can lead to kidney failure. Tumors leading to postrenal acute renal injury are usually those developing near the kidney. For example, postrenal acute kidney damage is common in over and bladder tumors. Metastatic tumors also occur, but postrenal acute kidney damage is rare in lung, breast or colon cancer metastases. Metastatic solid tumors usually lead to ureteric obstruction and acute kidney damage by the involvement of lymph nodes that cause vascular occlusion. Clinical findings vary according to location, grade, and rate of obstruction. Urinary findings are not classically diagnostic. Renal ultrasonography continues to be preferred method to investigate outflow obstruction.

Obstructive uropathy can occur without hydronephrosis during the first few days. The postrenal acute renal injury is the keystone of percutaneous nephrostomy or ureteral stenting (9-10). In our study, the postrenal acute renal damage was found to be 1.7% among all patients and 10.1% among acute renal damage. The main cause of acute renal damage in hypercalcemia is volume depletion due to urinary sodium loss, nausea, vomiting, and polyuria associated with nephrogenic diabetes insipidus. In addition, calcium-induced renal vasoconstriction reduces renal blood flow, acute nephrocalcinosis a rare cause of cancer patients. Hypercalcemia in malignancy seen in

10-30%. It leads to acute renal damage, with very poor prognosis (11-12). The uric acid level of patients with malignancy who developed renal disease was found to be 8.31±3.74mg/dl. Serum uric acid level was found to be high in 46,2% of patients.

Hyperuricemia is a well-known mechanism that causes acute renal damage in acute tumor lysis syndrome via a crystal-dependent mechanism. Here, the pathogenesis of acute renal damage is caused by the collapse of uric acid-containing crystals in the kidney, distal and collecting tubules leading to obstruction. There is growing evidence that uric acid may lead to acute renal damage through a crystal-independent mechanism.

Uric acid accumulation leads to increased tubular pressure, increased intrarenal pressure, and com-pression of venules. With increased renal vascular resistance with increased tubular pressure, reduced renal blood flow reduces glomerular filtration rate and acute kidney damage (13-15).

In our study, breast cancer was the most common cancer, followed by colon and stomach cancers. Acute kidney damage was most frequently detected in hepatocellular carcinoma, pancreatic cancer, and lung cancer. In IRMA study, the most common tumors were breast cancer, colorectal cancer, lung cancer, over cancer and prostate cancer respectively. When the Cockcroft-Gault formula is used to calculate glomerular filtration rate, prevalence of renal failure among different cancer types is highest, over cancer, prostate cancer, lung cancer, colorectal cancer and breast cancer respectively and the overall prevalence is more than 50% (6). Glomerular filtration rate with Modification of Diet in Renal Disease was found to be <90ml/min in breast cancer 67.8%, colorectal cancer 59.5%, lung cancer 52.6% prostate cancer 62.6% and gynecologic cancer 69.6%. In the study by Yao et al., renal failure rates in cancer patients were found to be 38.2% in uterine cancer, 10.2% in breast cancer, 9.2% in prostate cancer, and 7.2% in liver cancer (16).

In the IRMA study, 53.3% of drugs were emphasized to be nephrotoxic. Potential nephrotoxic drugs include epirubicin, gemcitabine, carboplatin, doxorubicin, paclitaxel, cisplatin, oxaplatin, irinotecan, trastuzumab, zolendronic acid and methotrexate (6). In BIRMA study, at least one of 78.1% of the patients had nephrotoxic drug use history. The potential nephrotoxic drug was identified as 53.7%. Gemcitabine, cisplatin paclitaxel, oxaplatin, irinotecan, cetuximab; in rare cases, epirubicin, transtuzumab, paclitaxel, doxorubicin, and tamoxifen (7).

In a study conducted by Yao et al., Urinary obstruction rate in renal failure etiology was 41.2%, drug-induced acute renal failure was 19.8%, and acute renal failure due to the fluid loss was 12.2%, 19.8% of hypertensive patients and 0.8% of diabetes mellitus have been reported. Percutaneous nephrostomy was performed in 6.8% of patients with haemodialysis and 6.1% of patients with acute renal failure. The mortality rate in patients with renal insufficiency was 13% (16).

In conclusion, acute renal failure is a common complication in cancer patients. The development of acute renal failure in malignant patients is a life-threatening complication. It is important to perform a multidisciplinary approach in these patients to reduce morbidity and mortality. It is also important to evaluate the renal function before chemotherapy and to closely follow it during the treatment.

Conflict of Interests

The authors declare that they have no conflict of interest in the current study.

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