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Original Article

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Evaluation of Kidney Function in Patients on Chemotherapy

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ABSTRACT

Objective: We aimed to study whether long-term kidney function would be affected by different chemotherapy regimens in patients with malignancy.
Methods: In this study, 500 cancer patients between the ages of 18 and 85 years were included. Estimated glomerular filtration rate (eGFR) calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula was used to evaluate renal function. Patients with eGFR less than 60 mL/min/1.73 m^2 before chemotherapy were excluded. Demographic and clinical data were recorded. Patients were divided into 4 groups according to the chemotherapy protocols: cisplatin-containing regimens, carboplatin-containing regimens, oxaliplatin-containing regimens, and platinum-free regimens. eGFR, urea, and creatinine values of 0th, 7th, 30th,and 180th days were recorded.
Results: In 180 days of treatment, eGFR decreased in 69 (13.8%) patients, whereas it increased in 46 (9.2%) patients ($P = .001$) and remained unchanged in 385 patients (77%). The cisplatin group had lower eGFR at the 180th day compared to the carboplatin ($P = .033$), oxaliplatin ($P = .007$), and platinum-free groups ($P < .001$). The median eGFR at the 180th day was lower in the cisplatin group compared to baseline ($P < .001$), while eGFR levels were not changed in the carboplatin and oxaliplatin groups and were significantly increased in the platinum-free group ($P = .004$).
Conclusion: Cisplatin-based treatment protocols were shown to worsen renal function during long-term follow-up. It is important to monitor kidney function closely for early intervention.
Keywords: Chronic kidney disease, glomerular filtration rate, chemotherapy, cisplatin, outcome

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INTRODUCTION

Renal dysfunction can be a major health problem in cancer patients and may be due to urinary obstruction, tumor lysis syndrome, drugs used for treatment of pain (mainly non-steroidal anti-inflammatory drugs; NSAIDs), systemic symptoms causing decreased fluid intake, malignancy-associated glomerulonephritis, and thrombotic microangiopathy.[1–4] Besides these tumor-related factors, cancer patients face an increased risk for renal disease due to the effect of the drug used for the treatment of the disease. Gastrointestinal side effects leading to hypovolemia, direct nephrotoxic effects, and thrombotic microangiopathy due to drugs are among them.[5]

With the introduction of new chemotherapeutic drugs, the diversity of renal manifestations has increased. The majority of the literature data is about the short-term effects of chemotherapeutics on renal functions.[6]

In our study, we aimed to evaluate the long-term renal functions of patients who received different chemotherapy regimens for cancer treatment.

MATERIALS AND METHODS

This retrospective study included 500 cancer patients aged between 18 and 85 years who received chemotherapy treatment between 2015 and 2018. Demographic

data (age, gender), body mass index (BMI), risk factors for decreased renal function, such as diabetes mellitus (DM) and hypertension (HT), smoking and alcohol use history were recorded. Patients were divided into 2 groups according to age (age 65 and below). The tumor types were grouped as breast cancer, colorectal cancer, gastric cancer, other gastrointestinal tumors (tumors of esophagus, liver, pancreas, bile ducts, and small intestine), lung cancer (either small cell or non-small cell), genitourinary cancers (tumors of kidney, ovary, uterus, cervix, vagina, bladder, and testicles), prostate cancer, head and neck cancers, and soft tissue neoplasms. Chemotherapy regimens were grouped as cisplatin-containing regimens, carboplatin-containing regimens, oxaliplatin-containing regimens, and platinum-free regimens, and the groups were named accordingly as cisplatin group, carboplatin group, oxaliplatin group, and platinum-free group. The presence of metastatic disease was also recorded. Creatinine, urea, and estimated glomerular filtration rate (eGFR) levels of the groups were recorded at 0th, 7th, 30th, and 180th days. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. Patients with eGFR less than 60 mL/min/1.73 m^2 before chemotherapy were not included in the study.

Cisplatin, carboplatin, oxaliplatin, and platinum-free groups were compared with each other for renal function at the 0th, 7th, 30th, and 180th days of chemotherapy. Besides, each subgroup was examined for change in the eGFR during follow-up, and the groups were compared with each other regarding the change in eGFR.

The study was approved by the Universities ethics committee (no. 15/165).

Main Points:

- Renal dysfunction in cancer patients may be due to urinary obstruction, tumor lysis syndrome, drugs, hypovolemia, malignancy-associated glomerulonephritis, and thrombotic microangiopathy.
- The introduction of new chemotherapeutic drugs has diversified renal manifestations. The available data mostly give information on the short-term effects of chemotherapy drugs.
- In the study, the median eGFR level at the 180th day was significantly lower in the cisplatin group compared to the carboplatin group ($P = .033$), oxaliplatin ($P = .007$), and platinum-free groups ($P < .001$). No statistically significant difference was detected in other inter-group comparisons.
- An increase in eGFR was observed in some patients treated with platinum-free regimens. Hydration, the removal of postrenal factors, and the decrease in creatinine value due to a decrease in muscle mass may be the possible causes.
- Cisplatin-containing regimens used in the treatment of malignancy patients worsened renal function in long-term follow-up.

Statistical Analysis

Statistical analyses were performed using SPSS, version 22 (IBM SPSS Statistics for Windows, Armonk, NY; IBM Corp.). First, a Kolmogorov–Smirnov test was used to determine which variables should be included in the data analysis and whether the data for the variables were normally distributed, but the data were not normally distributed. Therefore, non-parametric tests were used. As univariate analyses, the Spearman correlation coefficient was used to examine the relationship between 2 numerical variables. The Kruskall–Wallis test was applied as a comparison of 3 and more independent groups. Post hoc comparisons of the variables were found to be significant according to the DUNN test. The Wilcoxon Signed Ranks test was used for intra-group comparisons of Before-After tests. The Friedman test was used for intra-group comparisons of more than 2 "time periods." The Wilcoxon matched-pair signed-rank test from post hoc tests was used for pairwise comparisons. The chi-square test and Fisher's exact test were used to compare categorical variables between 2 groups. The median (Q1 (1st quartile)-Q3 (3rd quartile)), frequency and percentage, correlation coefficient (r_s) were reported as descriptive statistics. The statistical significance level was set to $P < .05$.

RESULTS

Among the patients 55.8% (279) were female and 54.2% (221) were male. The mean age was 55.77 ± 11.15 years. Seventy-two (14.4%) patients had DM, 109 (21.8%) patients had HT, 168 (33.6%) had a history of smoking, and 25 (5%) had a history of alcohol use. One hundred thirty-three (26.6%) patients had metastatic disease and 100 (20%) patients were older than 65 years. The BMI, the ratio of patients with eGFR below or above 90 mL/min/1.73 m^2, tumor types, chemotherapy regimens, and the treatment intervals of the patients are presented in Table 1.

Before treatment, a significant negative correlation was observed between eGFR and age ($r = -0.562$, $P < .001$) and BMI ($r = -0.187$, $P < .001$). We found the same results after treatment, and a significant negative correlation was observed between eGFR and age ($r = -0.607$, $P < .001$) and BMI ($r = -0.169$, $P < .001$).

Creatinine, urea, and eGFR levels at the 0th, 7th, 30th, and 180th days are presented in Tables 2, 3, and 4. In the platinum-free group, statistically significant differences were detected between the 0th, 7th, 30th, and 180th days in terms of median creatinine value while it was not changed in the other groups ($P < .001$). Median creatinine values at 0th versus 30th($P = .016$), 0th versus 180th ($P = .001$), 7th versus 30th ($P = .017$), and 7th versus 180th ($P = .001$) days were significantly different. No significant differences were found at the 0th versus 7th and 30th versus 180th days. In the cisplatin, carboplatin, and oxaliplatin groups, statistically significant differences were not detected at 0th, 7th, 30th, and 180th days in terms of median creatinine value.

Table 1. Baseline Characteristics of the Studied Patients

Variable	Descriptive Statistics
Body mass index, kg/m^2	(*n*, %)
<18	9 (1.8%)
18-25	156 (31.2%)
25-30	188 (37.6%)
30-35	100 (20%)
>35	47 (9.4%)
Basal eGFR > 90 mL/dk/1.73 m^2	341 (68.2%)
Basal eGFR = 60-89 mL/dk/1.73 m^2	159 (31.8%)
Type of cancer	
Breast cancer	167 (33.4%)
Colorectal cancers	87 (17.4%)
Lung cancer	79 (15.8%)
Gastric cancer	41 (8.2%)
Other gastrointestinal cancers	39 (7.8%)
Genitourinary cancers	38 (7.6%)
Head and neck cancers	27 (5.4%)
Prostate cancer	14 (2.8%)
Soft tissue cancers	8 (1.6%)
Chemotherapy regimens	
Platinum-free regimes	232 (46.1%)
Oxaliplatin-containing regimens	121(24.2%)
Carboplatin-containing regimens	80 (16%)
Cisplatin-containing regimens	67 (13.4%)
Treatment interval of chemotherapy regimens	
Per week	106 (21.2%)
Every 2 weeks	141 (28.2%)
Every 3 weeks	223 (44.6%)
4 weeks	30 (6%)

eGFR, estimated glomerular filtration rate.

Table 2. Creatinine Levels at the 0th, 7th, 30th, and 180th Days of Therapy

Drugs	0 day (Median, IQR 25-75)	7 day (Median, IQR 25-75)	30 day (Median, IQR 25-75)	180 day (Median, IQR 25-75)	*P*
Cisplatin (*n* = 67)	0.77 (0.77-0.86)	0.78 (0.72-0.89)	0.79 (0.71-0.90)	0.81 (0.74-0.98)	.70
Carboplatin (*n* = 80)	0.76 (0.67-0.88)	0.78 (0.66-0.83)	0.75 (0.66-0.83)	0.76 (0.68-0.87)	.05
Oxaliplatin (*n* = 121)	0.80 (0.71-0.87)	0.78 (0.71-0.87)	0.77 (0.72-0.90)	0.78 (0.69-0.86)	.07
Platinum free (*n* = 232)	0.74 (0.68-0.80)	0.73 (0.68-0.81)	0.72 (0.67-0.78)	0.72 (0.66-0.80)	**<.001**

Friedman test and post hoc analysis were performed in the platinum-free group. 0thday versus 180thday, *P* = .001; 0th day versus 30th day, *P* = .016; 7th day versus 30th day, *P* = .017; 7th day versus 180th day, *P* = .001.
IQR, interquartile range; Bold values indicate statistical significance

Table 3. Urea Levels at the 0th, 7th, 30th, and 180th Days of Therapy

Drugs	0 day (Median, IQR 25-75)	7 day (Median, IQR 25-75)	30 day (Median, IQR 25-75)	180 day (Median, IQR 25-75)	*P*
Cisplatin (*n* = 67)	33.0 (27.0-39.0)	33.0 (26.0-42.0)	32.0 (25.0-40.0)	35.0 (27.0-44.0)	.182
Carboplatin (*n* = 80)	32.0 (27.25-40.75)	32.0 (27.0-38.75)	32.0 (25-41)	33.0 (28.0-41.0)	.864
Oxaliplatin (*n* = 121)	30.0 (24.0-37.0)	29.0 (23.0-37.0)	28.0 (23.0-35.50)	28.0 (21.0-34.0)	.135
Platinum free (*n* = 232)	28.0 (23.0-34.75)	28.0 (22.0-34.0)	26.50 (21.0-33.75)	28.0 (22.0-35.0)	.720

Friedman test.
IQR, interquartile range.

Table 4. eGFR Levels at the 0th, 7th, 30th, and 180th Days of Therapy

Drugs	0 day (Median, IQR 25-75)	7 day (Median, IQR 25-75)	30 day (Median, IQR 25-75)	180 day (Median, IQR 25-75)	*P*
Mean					
Cisplatin (*n* = 67)	96.59 (85.34-102)	93.92 (87.29-101.62)	94.51 (83.58-101.89)	89.27 (77.92-99.21)	**.001**
Carboplatin (*n* = 80)	91.92 (83.41-100.12)	93.20 (88.90-100.13)	94.66 (87.68-100.80)	92.89 (83.16-98.56)	.111
Oxaliplatin (*n* = 121)	94.90 (86.91-102.36)	95.51 (86.40-101.29)	94.11 (86.92-102.21)	96.23 (85.50-102.85)	.056
Platinum free (*n* = 232)	95.27 (87.23-102.45)	95.98 (86.92-104.04)	97.09 (89.32-104.39)	96.48 (87.58-104.91)	**.004**

Friedman test and post hoc analysis were performed in the cisplatin and platinum-free group. Cisplatin 0th day versus 180th day, *P* = .001; platinum free 7th day versus 30th day, *P* = .049; platinum free 0th day versus 180th day, *P* = .004.
eGFR, estimated glomerular filtration rate; IQR, interquartile range; Bold values indicate statistical significance

The median urea value was not changed in all groups.

The median eGFR values were decreased significantly in the cisplatin group when compared at 0th and 180th day (*P* = .001). There were no statistically significant differences at 0th versus 7th, 0th versus 30th, 7th versus 30th, 7th versus 180th, and 30th versus 180th days. The median eGFR value increased in the platinum-free group when compared between the 0th and 180th (*P* = .004) days and 7th versus 30th days (*P* = .049). No significant differences were found at the 0th versus 7th, 0th versus 30th, 7th versus 180th, and 30th versus 180th days. In the carboplatin and oxaliplatin groups, statistically significant differences were not detected at the 0th, 7th, 30th, and 180th days in terms of median eGFR value.

The median eGFR level at the 180th day was significantly lower in the cisplatin group compared to the carboplatin group (*P* = .033), oxaliplatin (*P* = .007), and platinum-free group (*P* < .001). No statistically significant difference was detected in other inter-group comparisons.

Of the 341 patients who initially had eGFR ≥ 90 mL/min/1.73 m^2, eGFR decreased to 60-89 mL/min/1.73 m^2 in 52 patients and 30-59 mL/min/1.73 m^2 in 6 patients on the 180th day of treatment (Figure 1).

Of the 159 patients who initially had eGFR 60-89 mL/min/1.73 m^2, 46 had improvement in renal function (eGFR ≥ 90 mL/min/1.73 m^2), eGFR was stable in 102 patients, while eGFR decreased to 30-59 mL/min/1.73 m^2 in 9 patients and to 15-29 mL/min/1.73 m^2 in 2 patients at 180th day of treatment (Figure 2). Acute kidney injury (AKI) was detected in 3 patients.

Patients were grouped according to the change in eGFR at the 180th day of treatment as those with decreasing eGFR (*n* = 69; 13.8%), those with increasing eGFR (*n* = 46; 9.2%), and those with unchanged eGFR (*n* = 385; 77%). The decrease in eGFR was more frequent in the cisplatin group as can be seen in Table 5.

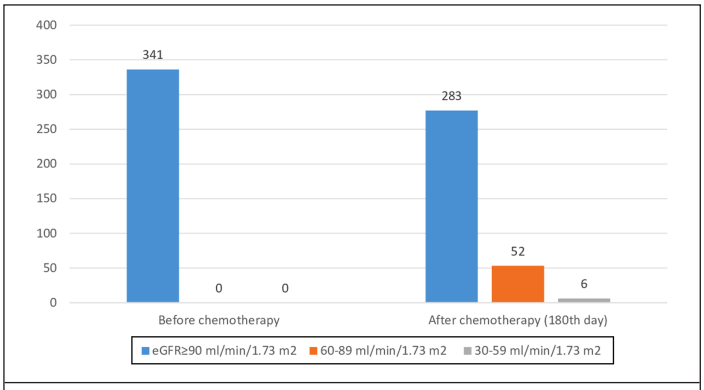

Figure 1. eGFR values on the 180th day of patients with eGFR ≥ 90 mL/min/1.73 m^2.

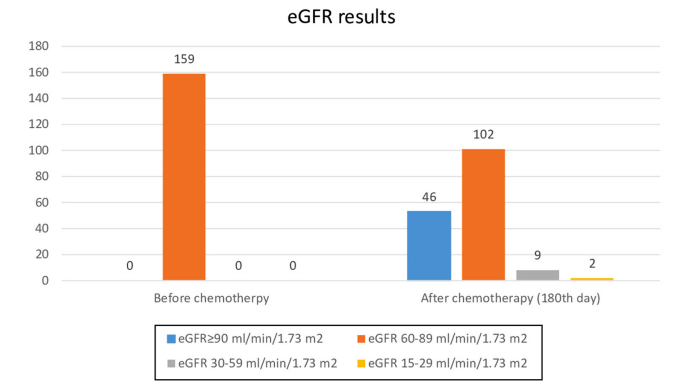

Figure 2. eGFR values on the 180th day of patients with eGFR 60-89 mL/min/1.73 m^2.

BMI, presence of HT, smoking, and alcohol use history were not found to have a significant effect on eGFR change ($P = .124$, $P = .108$, $P = .475$, respectively). DM history and the presence of metastasis, on the other hand, were found to have a significant effect on eGFR decrease ($P \leq .001$, $P = .014$, respectively).

Patients were divided into 2 groups according to age. In this study, 110 patients were aged 65 years and more and 390 patients were younger than 65 years. The median eGFR at the start and at the 180th day of treatment was 94.47 (90.01-103.76) mL/min/1.73 m^2 and 98.45 (88.71-105.12) mL/min/1.73 m^2, respectively, in patients aged less than 65 years ($P = .406$). The corresponding values were lower in patients aged 65 years and more, namely 86.28 (76.30-92.33) mL/min/1.73 m^2 and 84.99 (77.08-92.85) mL/min/1.73 m^2 ($P = .712$). Although in 110 patients aged 65 years and more, renal function was found to be worse on the 180th day, this finding did not reach statistical significance.

Table 5. Comparison of the Groups Regarding the Change in eGFR

	Decreasing eGFR*, *n* (%)	Increasing eGFR*, *n* (%)	Unchanged eGFR*, *n* (%)	*P*
Cisplatin group (*n* = 67)	**21 (31%)**	4 (6%)	42 (63%)	**.001**
Carboplatin group (*n* = 80)	6 (7.6%)	9 (11.2%)	65 (81.2%)	
Oxaliplatin group (*n* = 121)	19 (15.7%)	12 (9.9%)	90 (74.4%)	
Platinum-free group (*n* = 232)	23 (9.9%)	21 (9.1%)	188 (81%)	
Total	69	46	385	

The statistic was performed with a chi-square test.
eGFR, estimated glomerular filtration rate.

DISCUSSION

Various chemotherapeutic drugs have potential nephrotoxic effects. Some cause nephrotoxicity by causing acute tubular necrosis as in cisplatin-induced AKI, drugs such as protein kinase inhibitors cause thrombotic microangiopathy, drugs such as immunomodulators cause interstitial nephritis.[2] Whatever the mechanism is, the detection of risk factors for renal injury, proper preventive measures, early diagnosis, and appropriate management of renal dysfunction have prime importance to decrease morbidity and mortality, and to maintain the continuity of the treatment of cancer patients.

Platinum-containing drugs are among the potential nephrotoxic drugs.[7] Cisplatin is the most frequently accused one.[8] There are many studies about the nephrotoxic effect of platinum-containing chemotherapy drugs in the literature.[9–11] Nephrotoxicity of cisplatin was described in the literature 40 years ago.[12] The aim of developing carboplatin and oxaliplatin was to minimize the toxic effects of cisplatin.[13–16] AKI, tubular dysfunction, and electrolyte disturbances are the nephrotoxic side effects of platinum-containing chemotherapy drugs.[11] It causes DNA damage in the tubular cells which results in mitochondrial dysfunction, oxidative stress, inflammation, and release of cytokines-like tumor necrosis factor, overexpression of p21 (and hence, the distorted cell cycle), activation of p53, caspase activation, and so on.[8] The final effect is increased necrosis and apoptosis in the kidney. However, there is a limited number of publications about how kidney functions are affected in the long term after platinum-containing combined chemotherapy treatment. In our study, we aimed to evaluate the long-term renal function of patients who receive different chemotherapy regimens for cancer treatment. According to the literature, cisplatin regimens were found to have a negative effect on renal function in the long term.[9]

Advanced age is one of the factors related to AKI and CKD.[17,18] A significant negative correlation was observed between eGFR and age before and 6 months after the chemotherapy, which is consistent with the literature. Duan et al. published a meta-analysis in which elderly patients were found to have increased risk for platinum-induced nephrotoxicity.[19]

Chemotherapy protocols have been diversified with the introduction of new chemotherapeutic drugs in clinical use. All have a different spectrum of side effects. Modern medicine searches for treatment modalities with less toxicity in both the short and also long terms. Most of the reports in the literature are about the acute side effects of chemotherapeutic drugs regarding renal function. We aimed to compare renal function at the 6th month of treatment. During this period, the median eGFR values were decreased in the cisplatin group and increased in the platinum-free group, whereas it was not changed in the other groups. eGFR level at the 180th day was significantly lower in the cisplatin group compared to other groups. The main factor

associated with the decrease in eGFR in the groups involved in our study was the use of cisplatin-containing regimens. Cisplatin has been proven to be more nephrotoxic than other platinum drugs in the literature.[7] A recent report evaluated the long-term effects of cisplatin on renal function. Latcha et al. analyzed the renal function of patients who underwent cisplatin treatment during a follow-up period of at least 5 years.[9] They observed AKI cases at the acute phase, and then eGFR declined slowly within years. In our study, AKI was found in 3 cases, but during the long-term follow-up renal function worsened in 69 (13.8%) patients.

Carboplatin is also a platinum-based agent with a lower potential for nephrotoxicity even if it cannot be considered as a non-nephrotoxic agent. Naganuma et al. reported more than 430 000 events related to platinum compounds between April 2004 and November 2016 in Japan.[20] 201 events (1.5%) of AKI and 238 events (1.8%) of renal impairment were reported in the cisplatin group, while the corresponding values were 38 (0.5%) and 35 (0.4%) in the carboplatin group, and 83 events (0.7%) of AKI were reported in the oxaliplatin group. So, carboplatin and oxaliplatin can be preferred in patients at risk of AKI. On the other hand, there are reports of renal toxicity after oxaliplatin treatment, especially when used in high doses.[21,22] Even though there was no statistically significant result, renal function was decreased in carboplatin and oxaliplatin groups in our study. Six patients (7.6%) in the carboplatin group and 19 (15.7%) patients in the oxaliplatin group were found to have decreased renal function.

Fifty-eight patients among 341 patients (17%) with basal eGFR $\geq$ 90 mL/min/1.73 m^2 had a decrease in eGFR during 6 months of follow-up, whereas 11 patients among 159 patients (6.9%) with eGFR < 90 mL/min/1.73 m^2 had a decrease in eGFR. This may be perceived as a contradictory finding but there may be many factors operating on the process such as other risk factors, comorbidities, medications other than chemotherapeutics, etc., and the attitude of the oncologist about the preventive measures for preserving kidney function in patients with already known renal dysfunction. It is difficult to comment on this finding as data about medications other than chemotherapy is lacking and the premedication protocol was different for each regimen. An increase in eGFR was observed in some patients treated with platinum-free regimens. Although it is not possible to clearly understand the reasons for this, the possible causes can be careful adjustment of hydration, the removal of postrenal factors that worsen kidney function, and the decrease in creatinine value due to a decrease in muscle mass. Latcha et al. [9] reported on patients who recovered from CKD stage 2 to stage 1 and from stage 3 to stage 2. The authors did not comment on causality.

Máthé et al.[23] studied 38 patients with lung cancer after treatment with cisplatin. They reported that patients with DM and ischemic heart disease have more renal events than those without.[23] In our study, there were no significant differences between HT, smoking, and alcohol use before and after treatment in our study. DM history and the presence of metastasis were found to have a significant effect on eGFR decrease. The small number of patients included in the study or the relatively short follow-up period may have prevented us from drawing more accurate conclusions on renal function.

A previous study conducted by Lichtman et al.[24] reported the rate of renal toxicity due to cisplatin as 9% in 34 patients aged 75 years or more. There have been many studies on this subject. A recent review analyzed 34 studies about the nephrotoxicity of platinum-containing chemotherapy regimens in elderly patients.[19] The authors found that renal toxicity was more frequent in elderly patients, but the rate of discontinuation of treatment was the same as the younger counterparts. Moreover, the reported toxicities were defined to be clinically less severe.[19] In our study, although in 110 patients (aged 65 years and more) renal function was found to be worse on the 180th day, this finding does not reach statistical significance.

The retrospective nature of the study, the low number of patients, the variety of chemotherapy protocols, additional treatments that are not recorded in the patient files having adverse effects on renal function (NSAIDs, herbal remedies, etc.) and pre-existing diseases (gastroenteritis, etc.) were the limitations of the study.

CONCLUSION

In this study, it was shown that cisplatin-containing regimens used in the treatment of malignancy worsened renal function in long-term follow-up. Therefore, it is important to closely monitor the renal function of the patient group receiving cisplatin-containing chemotherapy regimens for early intervention. They should be protected from factors that may negatively affect renal function not only at the time of chemotherapy but also during the following months and years.

Ethics Committee Approval: Ethics committee approval was received from the Ethics Committee of Bezmialem Medical Faculty (Number: 15/165).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – E.H., M.G., M.S.; Design – E.H., M.G., M.S.; Supervision – R.T.K., M.S., H.M.T.; Data Collection and/or Processing – E.H., O.C.E., A.A., T.D.; Analysis and/or Interpretation – A.S.A., A.T., M.G.; Writing - E.H., M.G., H.M.T., R.T.K., A.S.A.; Critical Review - H. M.T., M.G., R.T.K., O.C.E., M.S.

Conflict of Interest: The authors have no conflicts of interest to declare.

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