# Natriuretic Peptides' Role in Determining the Chemotherapy-Induced Nephrotoxicity and Their Value in Follow-Up

Mehmet Ali Erkurt[a, d], Ismet Aydogdu[b], Irfan Kuku[a], Emin Kaya[a], Melda Comert[a], Yalcin Basaran[c]

## Abstract

**Background:** Chemotherapy-induced nephrotoxicity is an important handicap for optimal treatment. For this reason, we need useful markers for early detection of chemotherapy-induced renal disfunction. This study was performed to investigate the relationship between the plasma natriuretic peptides' (ANP and BNP) levels and chemotherapy-induced nephrotoxicity.

**Methods:** Thirty patients treated with cisplatin, cyclophosphamide, doxorubicin and cytosine arabinoside which having known nephrotoxic side effects, were enrolled in this study. Seventeen of the patients were male and 13 were female with a median age of 44. Also 30 healthy person were included to this study. Four chemotherapy courses were administered to each patient. Renal function tests (BUN, creatinin, urine micrototal protein/creatinin [Pr/Cr], glomeruler filtration rate (GFR) and urine Na) and plasma levels of ANP and BNP were measured before and after the treatments in both the patient and the control group.

**Results:** Before the treatment, there was no significant difference between the patients and the control group in comparison of renal function tests and plasma ANP-BNP levels. However, a decline in GFR, increase in urine Pr/Cr and plasma ANP-BNP levels were observed with subsequent courses of chemotherapy protocol, which were considered statistically significant (P < 0.001). The plasma levels of ANP and BNP appeared to be higher in patients treated with nephrotoxic anticancer agents.

**Conclusions:** The elevated levels of natriuretic peptides may be useful in determining the chemotherapy-induced nephrotoxicity earlier, which highlights their importance and role in follow-up.

**Keywords:** Anticancer agents; Chemotherapy; Natriuretic peptide; Nephrotoxicity

## Introduction

Chemotherapy-induced nephrotoxicity is an important obstacle for optimal treatment application in cancer patients. Several antineoplastic drugs may cause nephrotoxic effects which range from disorders of fluid and electrolyte balance, decreasing in GFR and permanent renal failure [1]. Earlier detection of renal dysfunction can prevent from chemotherapy-induced nephrotoxicity. For this reason, there are need useful biomarkers.

Natriuretic peptides consist a family of nine peptide hormones. Two of these peptides, ANP and BNP, are released from myocardial cells in the atrium and ventricles as a response to intravascular volume expansion and they have natriuretic and hypotensive effects [2]. They lower the resistance at the afferent arteriole and enhance the resistance at the efferent arteriole in the glomerulus. This results in augmented capillary hydraulic pressure which contributes to the increase in GFR and filtration fraction [3, 4]. It has previously been shown that the circulating concentrations of natriuretic peptides are higher in patients with chronic renal failure and in hemodialysis patients, which appear to reflect the volume status [5, 6]. Hemodialysis decreases the circulating concentrations of natriuretic peptides to be related with the volume status of the patients [7].

The nephrotoxic potential of cisplatin, cyclophosphamide, doxorubicin and high dose of cytosine arabinoside is known [1]. This current study was designed to investigate

the association of natriuretic peptides with the nephrotoxicity of these antineoplastic drugs, and to introduce the role of ANP and BNP in predicting the nephrotoxicity.

## Materials and Methods

Thirty patients who have treated with nephrotoxic antineoplastic drugs the Department of Hematology, Inonu University Faculty of Medicine, were enrolled in this study. Approval from the ethical review committee and ensuring informed consent from the patients and the control group, were obtained at the beginning of the study. Thirtytwo patients were enrolled in the study, but two of them were excluded due to chemotherapy related cardiac dysfunction during subsequent courses. Seventeen of the patients were male (57%) and 13 of them were female (43%). Their median age was 44 years (min: 20; max: 79). Twentysix of the patients were newly diagnosed and four of them were previously treated. The patients who were treated with drugs having proven nephrotoxic potency such as cisplatin, cyclophosphamide, doxorubicin and high dose cytosine arabinoside included in the study. Patients with a history of vascular disease, systemic hypertension, pulmonary hypertension, congestive heart failure, renal failure, hepatic cirrhosis, atrial fibrillation and tachycardia were excluded from the study. Patients with clinical findings such as edema, polyuria, and oliguria prior to the chemotherapy were also excluded. Serial echocardiographic evaluations before each course of chemotherapy were performed. Patients with left ventricular hypertrophy or cardiac dysfunction were excluded from the study. Fifteen healthy males and 15 healthy females who previously have not been treated with chemotherapeutic agents and who did not have renal dysfunction served as the control group. The control group also underwent an echocardiographic evaluation before the study and only healthy subjects served as control group. Their median age was 32 (min: 19; max: 66). Renal function tests and circulating ANP and BNP levels in both the patient and the control group were investigated before the treatment. Four courses of chemotherapy were given to each patient and after the treatment these tests were repeated (Table 1).

The GFR was estimated from the creatinine clearance. The creatinine clearance from a 24-hour urine collection was calculated using the following formula. Creatinine Clearance (mL/min) = Urine Creatinine (mg/dL) × Urine Volume (mL/day) / Plasma Creatinine (mg/dL) ×1440 [8]. The normal value for GFR was accepted as $128 \pm 26$ mL/min/1.73 m$^2$ for males, and $118 \pm 24$ mL/min/1.73 m$^2$ for females [9].

The proteinuria on the spot urine specimen was measured by nephelometric method using Dade Boehring BN-2 analyzer. The reference range of Pr/Cr ratio on a spot urine specimen was determined to be below 200 mg/dL [10].

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 early morning spot urine samples were collected at 8:00 a.m. and the measurements were performed at the Biochemistry Laboratory of Inonu University Faculty of Medicine.

An expert who was not informed of the clinical and laboratory characteristics of the patients performed the laboratory assessment of the natriuretic peptides. Each patient was hydrated the night before the chemotherapy with approximately 3 liters of intravenous fluid. Blood samples were taken prior to each course before the initiation of volume administration and further blood samples were drawn 48 hours later following the chemotherapy. Blood samples were collected at 08:00 am in the defined days and the measurements were performed. They were collected through brachial vein to chilled plastic tubes containing aprotinin and ethylenediaminetetraacetic acid by a 19 sized needle. Then immediately placed on ice and promptly centrifuged during 15 minutes at 3000 rpm (+ 4 °C). All samples were frozen and stored at – 80 °C for following analysis. Plasma samples were defrosted on the day after the fourth course and analyzed for the concentrations of natriuretic peptides. ANP and BNP was detected using fluorescence immunoassay (Biotek Diagnostics, CA; Reader: ELx800; Kit: Phoenix Pharmaceuticals Inc Harbor Boulevard, Belmond, California 94002). This test was at the quality of determining the circulating levels of ANP and BNP at 0.1 pg/mL - 100 pg/mL sensitivity. Prior to measurement, the plasma samples were raised to room temperature to become homogeneous and hemolytic samples were not used. A reaction was achieved principally by using murine ANP and BNP antibodies after transferring 50 µl of sample and polyclonal antibodies were labeled with fluorescent dye. Test apparatus was containing two internal controls and two external liquid controls, and QC simulator was used by the purpose of control.

### 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. Comparisons between quantitative data of different courses in patient group were made by using a one-way ANOVA with Tukey's pairwise comparison procedure to control for multiple testing. The determinants of natriuretic peptide levels were investigated by multivariate regression analysis. Differences were considered statistically significant if $P < 0.05$.

## Results

The patients were compared with each other according to

**Table 1.** Demographic Characteristics of Patients, GFR, Natriuretic Peptides and Chemotherapeutic Drugs

| Patient No | Age/Sex | Diagnosis | Course (Month) | Before the 1. Course | | | After the 4. Course | | | Total dose of |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | GFR ml/min/1.73m² | BNP pg/ml | ANP pg/ml | GFR ml/min/1.73m² | BNP pg/ml | ANP pg/ml | Chemotherapeutic drug/m² |
| 1 | 50/E | AML | 4 | 118 | 15.56 | 26.47 | 84 | 24.70 | 51.70 | Ara-C (72 gr) |
| 2 | 53/E | AML | 4 | 141 | 14.42 | 27.60 | 98 | 23.60 | 49.40 | Ara-C (72 gr) |
| 3 | 44/E | AML | 4 | 128 | 12.89 | 25.82 | 96 | 26.90 | 45.20 | Ara-C (72 gr) |
| 4 | 44/K | AML | 4 | 158 | 10.78 | 27.21 | 88 | 23.70 | 45.80 | Ara-C (72 gr) |
| 5 | 58/E | AML | 4 | 95 | 14.50 | 29.80 | 26 | 27.90 | 49.80 | Ara-C (72 gr) |
| 6 | 20/K | AML | 4 | 141 | 13.13 | 26.86 | 106 | 25.96 | 39.15 | Ara-C (72 gr) |
| 7 | 41/E | AML | 4 | 121 | 14.41 | 28.47 | 77 | 24.99 | 42.50 | Ara-C (72 gr) |
| 8 | 21/E | AML | 4 | 123 | 10.58 | 25.25 | 90 | 22.48 | 40.30 | Ara-C (72 gr) |
| 9 | 46/E | AML | 4 | 158 | 13.36 | 26.15 | 100 | 24.87 | 49.60 | Ara-C (72 gr) |
| 10 | 29/E | Anaplastic Lymphoma | 4 | 140 | 12.48 | 22.50 | 98 | 21.70 | 42.10 | CMP (3 gr), ADR (200 mg), VCR (6.4 mg), PSN (800 mg) |
| 11 | 41/K | DLBCL | 4 | 137 | 14.20 | 24.50 | 76 | 24.40 | 47.90 | CMP (3 gr), ADR (200 mg), VCR (6.4 mg), PSN (800mg) |
| 12 | 39/E | Mantle Cell Lymphoma | 4 | 120 | 15.80 | 25.10 | 76 | 25.10 | 49.20 | CMP (3 gr), ADR (200 mg), VCR (6.4 mg), PSN (800 mg) |
| 13 | 79/E | DLBCL | 4 | 64 | 15.89 | 31.23 | 48 | 28.98 | 51.85 | RTX (1.4 gr), CMP (3 gr), ADR (200 mg), VCR(6.4mg), PSN(800mg) |
| 14 | 34/K | DLBCL | 4 | 122 | 13.39 | 26.60 | 72 | 26.40 | 47.60 | RTX (1.4 gr), CMP (3 gr), ADR (200 mg), VCR (6.4 mg), PSN (800 mg) |
| 15 | 38/K | DLBCL | 4 | 145 | 12.90 | 25.80 | 94 | 24.70 | 46.30 | RTX (1.4 gr), CMP (3 gr), ADR (200 mg), VCR (6.4 mg), PSN (800 mg) |
| 16 | 72/K | DLBCL | 4 | 122 | 15.74 | 30.80 | 65 | 28.10 | 50.70 | RTX (1.4 gr), CMP (3 gr), ADR (200 mg), VCR (6.4 mg), PSN (800 mg)) |
| 17 | 66/K | DLBCL | 4 | 88 | 14.60 | 29.20 | 56 | 27.90 | 47.80 | RTX (1.4 gr), CMP (3 gr), ADR (200 mg), VCR (6.4 mg), PSN (800 mg)) |
| 18 | 77/K | DLBCL | 4 | 87 | 15.60 | 31.80 | 55 | 26.40 | 49.60 | RTX (1.4 gr), CMP (3 gr), ADR (200 mg), VCR (6.4 mg), PSN (800 mg)) |
| 19 | 28/E | Hodgkins Lymphoma, Mix Cell | 4 | 211 | 11.10 | 25.40 | 133 | 23.40 | 45.80 | ADR (200 mg), BLM (40 mg), VCR (6.4 mg), DTIC (1.4 gr) |
| 20 | 24/E | Hodgkins Lymphoma, Nodular Scl. | 4 | 179 | 11.12 | 24.60 | 96 | 24.80 | 50.50 | ADR (200 mg), BLM (40 mg), VCR (6.4 mg), DTIC (1.4 gr) |
| 21 | 52/E | Hodgkins Lymphoma, Nodular Scl | 4 | 142 | 12.34 | 29.80 | 85 | 27.20 | 49.50 | Ara-C (16 gr), CDDP (400 mg), DEX (100 mg) |
| 22 | 38/K | Breast CA | 4 | 151 | 13.32 | 27.40 | 96 | 25.80 | 45.20 | CMP (2.4 gr), ADR (240 mg) |
| 23 | 41/K | Thymoma | 4 | 149 | 12.10 | 29.80 | 94 | 23.50 | 47.10 | CMP (2 gr), ADR (240 mg), CDDP (360 mg), PSN (800 mg) |
| 24 | 37/E | Gastric Adeno CA | 4 | 171 | 14.30 | 28.40 | 95 | 25.60 | 43.40 | DTX (300 mg), CDDP (300 mg), 5-FU (4 gr) |
| 25 | 45/E | Gastric Adeno CA | 4 | 113 | 13.35 | 29.50 | 74 | 24.10 | 48.50 | DTX (300 mg), CDDP (300 mg), 5-FU (4 gr) |
| 26 | 58/E | Lung CA | 4 | 117 | 14.19 | 30.45 | 68 | 27.58 | 50.30 | CDDP (240 mg), VNR (120 mg) |
| 27 | 44/K | Cervix CA | 4 | 111 | 11.20 | 29.70 | 82 | 26.70 | 44.60 | CDDP (400 mg), 5-FU (3.85 gr) |
| 28 | 66/E | Gastric Adeno CA | 4 | 71 | 14.70 | 33.20 | 56 | 27.90 | 54.10 | DTX (300 mg), CDDP (300 mg), 5-FU (4 gr) |
| 29 | 58/K | Angiosarcoma | 4 | 105 | 13.10 | 32.80 | 71 | 26.20 | 52.70 | IFO (8 gr), ADR (240 mg) |
| 30 | 60/E | Sarcoma | 4 | 126 | 15.54 | 32.40 | 80 | 27.20 | 62.40 | IFO (8 gr), ADR (240 mg) |

AML: acute myeloid leukemia; DLBCL: diffuse large b cell lymphoma; Ara-C: cytosine arabinoside; CMP: cyclophosphamide; ADR: doxorubicin; VCR: vincristine; PSN: prednisolone; RTX: rituximab; BLM: bleomycin; DTIC: dacarbazine; CDDP: cisplatin; DEX: dexamethasone; DTX: docetaxel; 5-FU: 5 fluorouracil; IFO: ifosfamide.

**Table 2.** The Relationship Between Plasma Natriuretic Peptides and Renal Function Tests According to Chemotherapy Courses

| | Patients (n = 30) | | | | Control group (n = 30) | |
|---|---|---|---|---|---|---|
| | BNP (pg/ml) | ANP (pg/ml) | GFR (ml/min) | Pr/Cr (mg/dL) | BNP (pg/ml) | ANP (pg/ml) |
| 1. course before treatment (I) | 13.5 ± 2.3 | 28.1 ± 4.2 | 128.5 ± 31.2 | 28.4 ± 2.5 | 13.7 ± 1.8 | 25.4 ± 3.3 |
| 1. course after treatment (II) | 16.4 ± 2.7 | 30.9 ± 4.8 | 108.3 ± 31.7 | 121.1 ± 10.8 | 13.9 ± 2.1 | 24.8 ± 3.7 |
| 2. course before treatment (III) | 15.5 ± 2.8 | 28.9 ± 3.5 | 114.3 ± 29.2 | 98.3 ± 12.3 | 14.0 ± 1.7 | 24.3 ± 2.6 |
| 2. course after treatment (IV) | 19.0 ± 3.2 | 35.8 ± 4.5 | 97.6 ± 25.4 | 257.4 ± 34.6 | 13.8 ± 1.6 | 25.9 ± 2.8 |
| 3. course before treatment (V) | 18.4 ± 2.9 | 32.3 ± 6.5 | 103.2 ± 26.7 | 148.2 ± 17.3 | 13.6 ± 1.8 | 25.3 ± 3.1 |
| 3. course after treatment (VI) | 23.3 ± 3.2 | 40.5 ± 9.5 | 90.1 ± 24.1 | 382.6 ± 20.3 | 14.3 ± 2.2 | 24.9 ± 3.5 |
| 4. course before treatment (VII) | 20.1 ± 2.1 | 34.3 ± 11.1 | 94.6 ± 26.4 | 325.4 ± 40.1 | 14.1 ± 1.5 | 24.6 ± 3.2 |
| 4. course after treatment (VIII) | 25.6 ± 3.4 | 48 ± 16.9 | 81.2 ± 20.6 | 492.3 ± 62.4 | 14.5 ± 1.7 | 24.7 ± 3.8 |
| ANOVA | | | | | NS | NS |
| F value | 44.16 | 69.88 | 64.91 | 21.48 | NS | NS |
| P value | < 0.001 | < 0.001 | < 0.001 | < 0.001 | NS | NS |
| TUKEY HSD | II,III,IV,V | II,III,IV,V | II,III,IV,V | II,III,IV,V | NS | NS |
| (comperison according to I) | VI,VII,VIII | VI,VII,VIII | VI,VII,VIII | VI,VII,VIII | NS | NS |
| P value | < 0.001 | < 0.001 | < 0.001 | < 0.001 | NS | NS |

NS:Non significant.

chemotherapy courses. Before the first course, mean GFR in the patient group was 128 mL/min and 130 mL/min in the control group. There was no significant difference between the groups (P = 0.17). Mean GFR significantly decreased with subsequent courses. The values of GFR before the first course, during the treatment and after the fourth course (F: 64.91 P < 0.001) indicated in Table 2.

In a patient (patient no 5, 3.3%) although the GFR before the first course was within normal levels (95 mL/min), renal disfunction progressed (26 mL/min) after the fourth course. Dialysis was not required. After the fourth course, reduction in GFR was detected in other patients but no uremic complications were observed. Mean GFR values returned to normal spontaneously and gradually within two months.

Before the first course, mean Pr/Cr ratio in the patient group was 28.4 mg/dL, while it was 26.2 mg/dL in the control group. There was no significant difference between the groups (P = 0.12). Mean Pr/Cr ratio significantly increased with subsequent courses. Mean Pr/Cr ratio significantly increased in parallel with a significant decline in mean GFR with subsequent courses (F: 21.48 P < 0.001) (Table 2). After the fourth course, the mean Pr/Cr ratio returned to normal spontaneously within two months. After the third course, Pr/Cr ratio was exceed 1500 mg/day in a patient (patient no 21, 3.3%). After supportive treatment it fall dawn to normal range.

Mean serum creatinine level before the first course was 0.69 ± 0.11 mg/dL and 1.1 ± 0.29 mg/dL after the fourth course, respectively. Mean serum creatinine levels after the treatment were determined significantly higher (P < 0.001), when compared with the levels before the treatment.

Before the first course, mean ANP levels in the patient group was 28.1 pg/mL, while it was 25.4 pg/mL in the control group. There was no significant difference between the groups (P = 0.19). After the fourth course, mean ANP levels in the patient group was 48 pg/mL, while it was 24.7 pg/mL in the control group. Mean ANP levels significantly increased with subsequent courses (F: 69.88, P ≤ 0.001) (Table 2).

Before the first course, mean BNP levels in the patient group was 13.5 pg/mL, while it was 13.8 pg/mL in the control group. There was no significant difference between the two groups (P = 0.21). After the fourth course, mean BNP levels in the patient group was 25.6 pg/mL, while it was 14.5 pg/mL in the control group. Mean BNP levels significantly increased with subsequent courses (F: 44.16, P < 0.001) (Table 2).

A marked decline in GFR was observed with subsequent courses. ANP, BNP levels and urine Pr/Cr ratio progressively increased. Differences in variables with subsequent courses were considered statistically significant compared with the first course (P < 0.001) (Table 2).

Levels of natriuretic peptides increased in parallel with aggravation of kidney function tests. Kidney function tests decreased to baseline levels gradually within two months after the completion of fourth chemotherapy. A permanent kidney dysfunction did not develop.

## Discussion

Nephrotoxicity is one of the most important side effects of the chemotherapeutic agents. Antimetabolites, alkylating agents and anthracyclines are most commonly used antineoplastic drugs that can cause nephrotoxicity [11]. Nephrotoxicity is an adverse effect that can disrupt regularly administration of anticancer treatments. Chemotherapeutic agents affect different segments of the nephron, which is the basic unit of the kidney: especially the glomerulus, proximal and distal tubules [1]. In this study, chemotherapy-induced nephrotoxicity which including progressive reduction in GFR and concurrent elevation in serum creatinine and urine Pr/Cr ratio was observed. In our study, gradual improvement of renal function tests of the patients were established within two months after completion of chemotherapy. Permanent renal dysfunction was not occured in any patient. This situation can be explained by relatively small size of our study group.

ANP and BNP are produced predominantly by atrial and ventricular cells generally in response to volume or pressure overload and they both exerts natriuretic and vasodilatory effects [2]. They decrease the resistance at the afferent arteriole; and increase the resistance at the efferent arteriole in the glomerulus. Thus, resulting in augmented capillary hydraulic pressure which contributes to the increase in GFR and filtration fraction [3, 4]. A number of studies have shown that the circulating concentrations of natriuretic peptides are higher in patients with congestive heart failure, essential hypertension, hepatic cirrhosis, atrial fibrillation and tachycardia which appear to reflect volume status [12, 13]. The disease state associated with the highest intravascular overload is renal failure because of the reduction of GFR. Plasma levels of ANP and BNP are almost always raised in end stage renal disease patients undergoing hemodialysis and in the late predialysis stage [5, 7, 14]. Fluid removal by hemofiltration lowers the plasma ANP levels [7].  In addition to a reduction in the blood urea nitrogen and plasma creatinine concentration, a reduction in circulating ANP levels by 34 - 42 percent may occur by hemodialysis. The number of natriuretic peptide clearance receptors decreases by the loss of the renal parenchymal mass in chronic kidney disease. The circulating concentrations of the natriuretic peptides normalizes within a week after the treatment of the end stage renal disease with renal transplantation.

Decreased renal parenchyma functions results with decreased degradation of ANP and BNP and higher circulating concentrations of these peptides than the other diseases associated with intravascular overload [14]. A significant increase in ANP and BNP levels after the treatment was observed in

this study between both the same and the different courses of the chemotherapy, compared with the control group. This increase was negatively correlated with the reduction in GFR that was used clinically to assess the degree of kidney impairment and positively correlated with the rise in urine Pr/Cr ratio. The most likely causes of the increase in natriuretic peptide levels in our patients receiving chemotherapy are decline in the GFR produced by chemotherapy-induced nephrotoxicity resulting in retention of water and sodium, and the volume expansion due to renal dysfunction, as mentioned above. Chemotherapy can potentiate renal dysfunction and contribute the nephrotoxic potential, thus further increase in circulating levels of natriuretic peptides is expected with subsequent courses. Monitoring plasma levels of ANP and BNP in patients receiving chemotherapy may reflect a chance of the nephrotoxicity to be detected earlier. Although impairment in renal functions was statistically significant, it was not severe enough to require discontinuation of the chemotherapy. We reported the results in patients treated with median 4 course regimens of chemotherapy. However, some types of cancer require administration more courses of chemotherapy. High dose chemotherapy or prolonged time may aggravate renal dysfunction resulting in discontinuation of the therapy. Throughout these results, it is not possible to determine a threshold plasma level of natriuretic peptides after each subsequent chemotherapy course for discontinuation of therapy or limitation of dose in follow-up of chemotherapy-induced nephrotoxicity. To draw such conclusion further prospective studies are needed in a large number of patients.

In many studies, the circulating levels of natriuretic peptides have been reported to be higher in patients with kidney disease. Among these studies, only Franz et al reported patients with impaired renal function to have a dramatic increase of circulating levels of ANP and BNP even before serum creatinine levels start to rise [15]. Currently, in the literature there is still not enough knowledgement about the relationship between the nephrotoxicity of patients treated with chemotherapeutic drugs and circulating levels of ANP and BNP. In this study, the circulating levels of ANP and BNP were found to be higher in antineoplastic nephrotoxic agents receiving patients. This study highlights the importance of natriuretic peptide levels in determining the chemotherapy-induced nephrotoxicity and their role in follow-up. They may be useful in considering some preventive strategies in the patients treated with antineoplastic drugs before the development of nephrotoxicity. In diary pratice, creatin level is used for detection of nephrotoxicity. However, creatin level is not a sufficient indicator in the patients with low muscle mass and elderly. Therefore, in these patients, elevated levels of natriuretic peptides may be useful in determining the chemotherapy-induced nephrotoxicity earlier, which highlights their importance and the role in follow-up.

In conclusions, the circulating concentrations of ANP and BNP appear to be suggestive indicators of the chemotherapy-induced nephrotoxicity and may be useful in long term follow-up. However, further studies are required in a larger number of patients to confirm our findings.

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