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Assessment of acute kidney injury by urinary β2-MG and NAG in pediatric cancer patients prescribed with Cisplatin, Carboplatin, and Ifosfamide as the chemotherapeutic agents

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Abstract

Background: Acute kidney injury (AKI) is defined as a failure in renal function leading to insufficiency of fluid and electrolyte homeostasis. Thus, sensitive biomarkers of renal tubular injury are needed to detect AKI earlier. In this study, urinary beta 2-microglobulin (β2-MG) and urinary N-acetyl-β-D-glucosaminidase (NAG) were evaluated for AKI prognosis/diagnosis in pediatric patients suffering different cancers prescribed with Ifosfamide, Ifosfamide plus Carboplatin, and Ifosfamide plus Cisplatin.

Materials and Methods: In this prospective study done in Isfahan, Iran, urinary β2-MG, urinary NAG, blood urea nitrogen (BUN), and serum and urinary creatinine (Cr) were measured in 40 pediatric cancer patients less than 16 years old in three age groups during 61 courses of chemotherapy on day 0, three and six after the treatment.

Results: Using ANOVA and t-test, the mean levels of urinary β2-MG (p= 0.001), urinary β2-MG/Cr (p= 0.003) and urinary NAG/Cr (p= 0.001), before and on day six of the treatment were statistically significant (p< 0.05). Also, the mean levels of BUN (p= 0.01), urinary β2-MG (p= 0.001), β2-MG/Cr (p= 0.001) and NAG/Cr (p= 0.004) based on the gender groups, the mean levels of urinary NAG (p=0.001), NAG/Cr (p= 0.001) and β2-MG/Cr (p= 0.008) based on three age groups, and the mean levels of serum Cr (p= 0.047), urinary β2-MG (p= 0.005), β2-MG/Cr (p= 0.032) and NAG/Cr (p= 0.032) based on the Ifosfamide dosage were statistically significant during the time of the treatment.

Conclusion: Urinary β2-MG, urinary β2-MG/Cr, and urinary NAG/Cr are more significant biomarkers than serum Cr in earlier diagnosis and treatment of AKI in cancer patients. However, urinary NAG should be further studied to prove its reliability for AKI prognosis/diagnosis. It is suggested that urinary NAG can be used along with other renal biomarkers such as urinary β2-MG, kidney injury molecule-1(KIM-1), or interleukin-18 (IL-18) for AKI prognosis/diagnosis.

Keywords: Acute kidney injury, Beta 2-microglobulin, Chemotherapy, Creatinine; N-acetyl-β-D-glucosaminidase

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Introduction

Acute kidney injury (AKI), is known as a failure in renal function leading to insufficiency of fluid and electrolyte homeostasis (1). Comprehensively, AKI is caused by different reasons, including tumor lysis syndrome (TLS), nephrotoxic agents (such as chemotherapeutics, antimicrobials, and contrast media), infiltration of cancer cells into the genitourinary system, multiorgan failure following sepsis or other morbidities. AKI commonly occurs in pediatric cancer patients, who are treated with chemotherapeutic agents. Despite the increased survival of pediatric cancer patients prescribed with new medications, AKI is associated with long term side effects such as chronic kidney disease (CKD) (2). There are some criteria for the definition of AKI. Indeed, pRIFLE (pediatric RIFLE), including risk, injury,

failure, loss, and end-stage renal disease is developed to define AKI in pediatric patients (1). The determination of AKI is laid on the alteration of plasma creatinine (Cr) level (3). Despite Cr is a recognized biomarker for AKI (4), however, the earlier determination of AKI using further biomarkers may lead to ameliorate outcomes such as reduction of progression to CKD, reduction of hospital length of stay, and finally reduction of mortality (5). However, renal tubular damage does not possibly lead to increase serum Cr, immediately. Thus, sensitive biomarkers of renal tubular injury are needed to detect early kidney injury (6). In this field, two significant potential biomarkers arebeta 2-microglobulin (β2-MG) and N-acetyl-β-D-glucosaminidase (NAG). The β2-MG protein, weighted 11.8 kDa, is expressed on the cell surface of all nucleated cells and functioned as the light chain of MHC I antigen. Because of its small molecular weight, it can be easily filtered in the glomeruli and then reabsorbed by renal proximal tubular cells. During the renal tubular damage, the urinary β2-MG is elevated. Also, baseline urinary β2-MG is increased in cancer patients who have not been prescribed by chemotherapy agents (7-8).NAG is one of the proximal tubular lysosomal enzymes. As a high molecular weighted enzyme, 130-140 kDa, it may prevent glomerular filtration. Thus, elevated urinary NAG reflects tubular cell injury. After prescription of some drugs such as Gentamicin, Cisplatin, and Nedaplatin, in urinary tract infection and interstitial tubular damages, these elevated levels can be found in increased lysosomal activity without cellular damages (9-12).There are fewer studies about NAG and β2-MG as biomarkers (13-15). Hence, in this study, these two biomarkers for nephropharmacological assessment of pediatric malignant patients were evaluated. These patients suffered different cancers and prescribed with Ifosfamide, Ifosfamide plus Carboplatin, and Ifosfamide plus Cisplatin, as the chemotherapeutic agents. Indeed, early recognition of AKI in patients under chemotherapy may permit earlier prescriptions, beginning of accurate treatments, and obtaining successful outcomes.

Materials and Methods

Ethical statement

This research was performed under the Declaration of Helsinki. Informed consent was received from all parents of patients or patients before beginning the study. The research was approved by the ethics committee of Isfahan University of Medical Sciences with the approval code of IR.mui.rec.1396.3.552.

Collection of samples from pediatric cancer patients

As a prospective study, the pediatric patients (less than 16 years old) suffering from different cancers admitted from 2017 to 2018 in Seyed-al-Shohada Hospital, Isfahan, Iran were studied. The patients treated with Ifosfamide, Ifosfamide plus Carboplatin, and Ifosfamide plus Cisplatin were entered into the study. The patients with higher serum Cr level of 1.2 mg/dl before the treatment and those possessing fever and infection during five days of the treatment were prescribed with antibiotics (such as Aminoglycoside or Vancomycin). As an important factor, patients with discontinuation of the chemotherapy treatment were excluded from the study. The features of the selected patients including age, sex, and cancer type were recorded. In this study, 40 pediatric patients suffering from different types of cancers and treating with the chemotherapeutic agents were examined. Indeed, 61 courses of chemotherapy in these patients were considered. The AKI in pediatric patients were diagnosed following the RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage renal disease) criteria (1). Subsequently, 61 urine samples of patients were collected before the medication (as on day 0), day three (on day three), and six (on

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day six) after treatment according to the course of chemotherapy. Urine samples were obtained and centrifuged at 1970 rpm for 20 minutes to get the precipitants. Afterward, the precipitants were stored at -80°C until the assessment. Also, 61 blood samples from the pediatric patients were collected on day 0, day three, and day six of the treatment. Then, these samples were centrifuged at 2000 rpm for 5 minutes to obtain the serums.

ELISA

β2-MG and NAG levels in urine samples were determined by β2-Microglobulin ELISA Kit (AESKU, Germany) and N-Acetyl glucosaminidase ELISA Kit (HSL, UK) respectively. According to ELISA Kit's instructions, the normal range for urinary β2-MG and urinary NAG was 0-0.3 ng/dl and 0.3-12 IU/L, respectively. Also, the levels of urinary β2-MG/Cr and urinary NAG/Cr were considered on day 0, day three, and day six after treatment.

Blood and urine chemistry analysis

Blood urea nitrogen (BUN), serum, and urinary Cr were determined using Chemistry Analyzer BT3000 (Biotecnica, Italy) before and after the medication.

Statistical analysis

Data were analyzed using the SPSS version 25.0 Statistical Package (SPSS Inc., USA). Quantitative and qualitative data were shown as mean ± SD and frequency (percentage). The normality of continuous data was assessed using the Kolmogorov-Smirnov test. The repeated measures ANOVA as the main statistical method, was applied for evaluating within and between groups comparisons. Sphericity assumption was evaluated using the Mauchly test. When it was violated, a multivariate approach was adopted. The among-group comparisons were evaluated in each time point using independent samples t-test. One Way ANOVA test was used for comparing data among groups. Qualitative data were compared among groups using the chi-square test. The statistical significance level was set at $p< 0.05$.

Results

Out of 40 pediatric patients, 28 (70%) were male and 12 (30%) were female. The patients were classified into three age group (<5, 5-10 and >10 years old) as shown in Table I. Also, the different cancer types among these pediatric patients were shown in Table II. Amongst, 28 pediatric patients (70%) were prescribed with Ifosfamide, 5 of pediatric patients (12.5%) were prescribed with Ifosfamide plus Carboplatin and 7 (17.5%) of them were prescribed with Ifosfamide plus Cisplatin (Table III). There were three groups prescribed with Ifosfamide; 17.8% of patients were treated with low dose (1200-1800 mg/m2), 53.5% treated with intermediate-dose (1800-2000 mg/m2) and 28.5% treated with high dose (> 2000 mg/m2) (16). According to the treatment protocols of the hospital, the patients were prescribed with the same and constant dosages of Ifosfamide plus Carboplatin and Ifosfamide plus Cisplatin. Among 61 courses of chemotherapy, according to RIFLE criteria, 5 pediatric cases (8.2%) indicated AKI, 45 pediatric cases (73.8%) showed the elevated urinary NAG and 49 pediatric cases (80.3%) demonstrated the elevated urinary β2-MG. On day 0, 18 cases showed a normal range of urinary NAG (0.3-12 IU/L), and 50% represented enhanced urinary NAG on day six after medication (Figure 1). Also, on day 0, 24 cases showed a normal range of urinary β2-MG (0-0.3 ng/dl) and75% displayed enhanced urinary β2-MG on day six after medication (Figure 2).

As the results of blood chemical analyses in three chemotherapeutic agents, the mean levels of BUN and serum Cr at the beginning of the treatment, and on day six of the treatment were not significant and shown in detail by Table IV. The mean levels of urinary NAG on day 0 and day six of the treatment in three chemotherapeutic

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agents were not statistically significant (0. 072) (Table IV). The mean levels of urinary β2-MG, urinary NAG/Cr, and urinary β2-MG/Cr were significantly increased during the time (Table IV). Also, the mean levels of BUN and urinary β2-MG based on the gender groups were statistically significant during the time of the treatment ($p< 0.05$) (Table V). Also, the mean levels of urinary β2-MG/Cr and urinary NAG/Cr during the time of the treatment based on the gender groups were statistically significant ($p< 0.05$) (Table V). The mean levels of urinary NAG, β2-MG/Cr, and NAG/Cr based on three age groups were statistically significant during the time of the treatment ($p< 0.05$) (Table VI). However, the mean levels of serum Cr during the time of the treatment based on three age groups were not statistically significant ($p> 0.05$). The mean levels of serum Cr, urinary β2-MG, β2-MG/Cr, and NAG/Cr, in pediatric patients treated with Ifosfamide based on the Ifosfamide dosage during the time of the treatment, were statistically significant ($p< 0.05$) (Table VII). After chemotherapy, there was no significant correlation between urinary β2-MG and serum Cr ($r= -0.103$, $p= 0.5$). Also, after that, there was no significant correlation between urinary NAG and serum Cr ($r= 0.148$, $p= 0.3$).

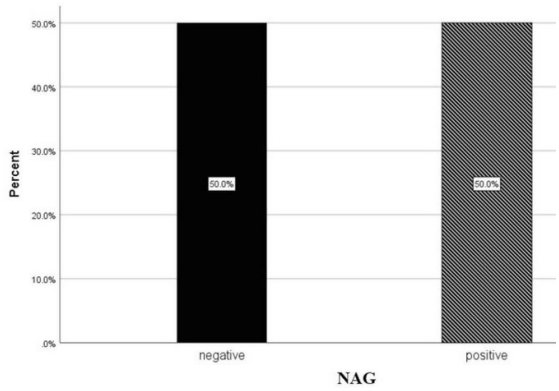

Figure 1. The 50% of cases represented enhanced NAG on day six after medication.

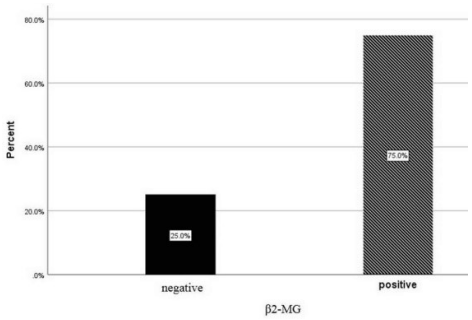

Figure 2. Seventy-five percent % of cases displayed enhanced β2-MG on day six after medication.

Table I. The demographic characteristics of the study.

Variable		Number (Percent)
Sex	Male	**28 (70%)**
	Female	**12 (30%)**
Age	<5	**7 (17.5%)**
	5-10	**22 (55%)**
	>10	**11 (27.5%)**

Table II. The types of different cancers in pediatric patients.

Type of cancer	Number (%)
Brain Tumor	9 (22.5%)
Rhabdomyosarcoma (RMS)	8 (20%)
Ewing Sarcoma	8 (20%)
Neuroblastoma (NB)	5 (12.5%)
Osteosarcoma	3 (7.5%)
Primitive neuroectodermal tumors (PNET)	2 (5%)
Wilms' Tumor	2 (5%)
Non-Hodgkin lymphoma (NHL),	1 (2.5%)
Undifferentiated pleomorphic sarcoma (UPS)	1 (2.5%)
Leukemia	1 (2.5%)

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Table III. The number of patients treated with different medications.

Medication	Number(Percent)
Ifosfamide	28 (70%)
Ifosfamide plus Carboplatin	5 (12.5%)
Ifosfamide plus Cisplatin	7 (17.5%)

Table IV. The mean levels of measured variables based on the chemotherapeutic agents during the time.

Measured variables	Ifosfamide	Ifosfamide+Carboplatin	Ifosfamide+Cisplatin	°p-value
BUN on day 0 (mg/dl)	9.14 ±3.49	9.0 ± 2.73	9.43 ±5.91	0.98
BUN on day three	7.61±2.13	6.20±2.05	8.57±4.69	0.337
BUN on day six	8.23±2.50	8.00±1.22	9.43±4.72	0.586
***p-value**	0. 338			
Cr on day 0 (mg/dl)	0.60 ±0.16	0.60 ± 0.07	0.56 ±0.53	0.754
Cr on day three	0.61±0.16	0.54±0.08	0.51±0.07	0.208
Cr on day six	0.55±0.13	0.48±0.15	0.61±0.09	0.219
***p-value**	0.317			
β2-MG on day 0 (ng/dl)	0.844 ±1.44	2.48 ± 2.21	0.19 ±0.16	0.028
β2-MG on day three	1.51±1.52	3.32±1.90	0.67±0.61	0.013
β2-MG on day six	1.80±1.70	3.84±1.48	1.25±1.69	0.029
***p-value**	0. 001			
NAG on day 0 (IU/L)	11.86 ±9.64	10.10 ± 6.71	5.59 ±4.91	0.248
NAG on day three	12.41±12.19	8.62±6.21	5.07±2.34	0.253
NAG on day six	15.18±14.36	18.50±15.06	8.20±5.49	0.367
***p-value**	0. 072			
NAG/Cr on day 0	0.24 ±0.23	0.17 ± 0.14	0.21 ±0.28	0.799
NAG/ Cr on day three	0.44±0.47	0.39±0.35	0.41±0.46	0.975
NAG/ Cr on day six	0.46±0.35	0.51±0.32	0.41±0.46	0.907
***p-value**	0. 001			
β2-MG/Cr on day 0	0.02 ±0.03	0.04 ± 0.04	0.00 ±0.00	0.258
β2-MG/Cr on day three	0.09±0.16	0.18±0.18	0.05±0.06	0.391
β2-MG/Cr on day six	0.07±0. 10	0.12±0.08	0.07±0.10	0.665
***p-value**	0. 003			

°Calculated p-value per day of course, *Calculated p-value during the course

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Table V. The mean levels of measured variables based on the gender groups of pediatric patients.

Measured variables	Female	Male	°p-value
BUN on day 0 (mg/dl)	9.33±4.39	9.11±3.63	0.866
BUN on day three	7.58±3.85	7.61±2.15	0.98
BUN on day six	8.42±3.80	8.41±2.40	0.992
***p-value**	0. 010		
β2-MG on day 0 (ng/dl)	1.19±1.64	0.82±1.50	0.5
β2-MG on day three	1.90±1.72	1.46±1.58	0.438
β2-MG on day six	1.86±1.52	1.99±1.93	0.827
***p-value**	0. 001		
β2-MG/Cr on day 0	0.23±0.04	0.02±0.03	0.53
β2-MG/Cr on day three	0.11±0.4813	0.09±0.17	0.624
β2-MG/Cr on day six	0.13±0.13	0.06±0.07	0.105
***p-value**	0. 001		
NAG/ Cr on day 0	0.32±0.34	0.19±0.15	0.105
NAG/ Cr on day three	0.48±0.48	0.41±0.44	0.643
NAG/ Cr on day six	0.58±0.46	0.41±0.30	0.173
***p-value**	0.004		

°Calculated p-value per day of course, *Calculated p-value during the course

Table VI. The mean levels of NAG, β2-MG/Cr, and NAG/Cr based on three age groups of pediatric patients.

easured Variables	<5 years old	5-10 years old	>10 years old	°p-value
NAG on day 0 (IU/L)	6.60±4.83	10.97±13.54	13.26±10.83	0.28
NAG on day three	5.73±3.96	9.73±9.42	16.78±16.43	0.026
NAG on day six	13.73±11.74	14.66±12.27	23.94±20.23	0.078
***p-value**	0.001			
β2-MG/Cr on day 0	0.03±0.04	0.00±0.00	0.01±0.02	0.195
β2-MG/Cr on day three	0.20±0.27	0.03±0.04	0.05±0.11	0.03
β2-MG/Cr on day six	0.05±0.09	0.06±0.07	0.11±0.11	0.406
***P-value**	0.008			
NAG/Cr on day 0	0.30±0.29	0.20±0.18	0.24±0.27	0.456
NAG/Cr on day three	0.60±0.51	0.38±0.43	0.34±0.30	0.212
NAG/Cr on day six	0.70±0.44	0.41±0.29	0.40±0.25	0.018
***p-value**	0.001			

°Calculated p-value per day of course, *Calculated p-value during the course

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Table VII. The mean levels of Cr, β2-MG, β2-MG/Cr, and NAG/Cr in pediatric patients treated with Ifosfamide based on the Ifosfamide dosage during the study time.

Measured Variables	Low dose	intermediate-dose	High dose	°p-value
Cr on day 0 (mg/dl)	0.62±0.16	0.59±0.13	0.65±0.21	0.511
Cr on day three	0.68±0.08	0.56±0.16	0.66±0.16	0.211
Cr on day six	0.54±0.11	0.50±0.07	0.64±0.19	0.06
***p-value**	0.047			
β2-MG on day 0 (ng/dl)	0.08±0.09	0.72±1.29	1.56±1.91	0.174
β2-MG on day three	0.57±0.83	1.69±1.68	1.51±1.52	0.329
β2-MG on day six	0.76±1.25	2.07±1.74	1.92±1.81	0.335
***p-value**	0.005			
β2-MG/Cr on day 0	0.00±0.00	0.02±0.04	0.03±0.03	0.472
β2-MG/Cr on day three	0.03±0.03	0.11±0.22	0.09±0.09	0.566
β2-MG/Cr on day six	0.03±0.03	0.07±0.09	0.10±0.14	0.399
***p-value**	0.032			
NAG/Cr on day 0	0.11±0.08	0.29±0.27	0.23±0.19	0.352
NAG/Cr on day three	0.38±0.48	0.39±0.51	0.57±0.42	0.665
NAG/Cr on day six	0.41±0.49	0.42±0.28	0.57±0.40	0.584
***p-value**	0.032			

°Calculated p-value per day of course, *Calculated p-value during the course

Discussion

Up to 80% of patients suffering cancers were prescribed with various types of chemotherapeutic agents. The follow-up of these patients has been revealed that the major part of them suffering proteinuria, electrolyte abnormalities, hypertension, tubulointerstitial damages, and glomerular disease (17). The most nephrotoxic chemotherapeutic agents include platinum compounds like Ifosfamide, Cyclophosphamide, Cisplatin, and Carboplatin (18). Thus, except the cancer treatment, monitoring the kidney function is needed during the prescription of these chemotherapeutic agents. This monitoring can be easily available by potent non-invasive biomarkers over the treatment of cancers by urinary and serum factors including kidney injury molecule-1 (KIM-1) (19-20), neutrophil gelatinase-associated lipocalin (NGAL) (21-23), tissue inhibitor of metalloproteinase-2 (TIMP-2) (24), interleukin-18 (IL-18) (25), NAG (26-28), α1-microglobulin (27), netrin-1 (29), β2-MG (30-32) and retinol-binding protein (33). Such biomarkers can be available from human biological sources by non-invasive procedures to decrease treatment costs, decrease potential side effects of pharmacologic responses to therapeutic intervention and increase the rate of prognosis/diagnosis in preclinical and clinical researches of the pathophysiology of AKI.Recently Tibúrcio et al. (2018) have revealed that urinary levels of β2-MGin studied cancer patients were higher than normal range after prescription with Cisplatin, Carboplatin, Ifosfamide, Cyclophosphamide, and Methotrexate (34). Remarkably, current results pertained to the elevated urinary levels of β2-MG, were in accordance with Tibúrcio et al. (2018) outcomes. Also, they showed that plasma creatinine in these patients was strongly and positively correlated with urinary levels of β2-MG (34). However, in this study, there was no significant correlation between urinary β2-MG and serum Cr. Indeed, they concluded that urinary levels of β2-MG and glomerular hyperfiltration may come into view as early biomarkers of nephrotoxicity

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in pediatric cancer patients prescribed with these chemotherapeutic agents. In accordance with Tibúrcio et al. (2018) results, it was concluded that the urinary β2-MG and urinary β2-MG/Cr can be more beneficial biomarker than serum Cr to diagnose AKI. In addition, George et al. (2017) have demonstrated a 3.3 fold enhancement in urinary β2-MG after Cisplatin treatment on day three and a decrease on day 10 after prescription (35). In addition, Zubowska et al. (2013) have concluded that among studied 85 children, urinary levels of β2-MGhave been considerably higher after chemotherapy (32). Here, urinary β2-MG levels were significantly elevated on day six after the treatment by three chemotherapeutic agents. The elevated levels of urinary β2-MG on day six after the treatment based on the gender groups were significant. Also, the portion of urinary β2-MG/Cr levels on day six after the treatment based on three chemotherapeutic agents, the gender groups, the age groups, and triple dosages of Ifosfamide was significantly increased. These results have not been achieved in other studies, thus, it can be suggested to further studies. There was a relationship between increased urinary β2-MG levels and patients 'age and gender. In addition, based on triple dosages of Ifosfamide, urinary β2-MG levels were significantly increased on day six after the treatment. The elevated levels of urinary β2-MG, serum Cr and BUN on day six after the treatment based on the age groups were not significant. So, in accordance with the studies mentioned above, it can be concluded that urinary β2-MG and urinary β2-MG/Cr can be more reliable biomarkers for AKI diagnosis than serum Cr.Maeda et al. (2017) have quantified urinary NAG, KIM-1, and NGAL in 40 cancer patients prescribed with Cisplatin on day one (before chemotherapy), day two, and day five after treatment. Also, they have measured serum Cr and compared on day seven and day 28 after Cisplatin administration vs. baseline. They have concluded that NAG, KIM-1, and NGAL have not been significantly increased on day five after prescription with the non-Cisplatin chemotherapy agent. Interestingly, these factors have been significantly higher on day five after prescription with Cisplatin compared to baseline. They have recommended that urinary NAG, KIM-1, and NGAL can identify AKI more accurately than serum Cr (36). However, the increased mean levels of urinary NAG during the time of treatment with Ifosfamide, Ifosfamide plus Cisplatin, and Ifosfamide plus Carboplatin were not statistically significant. On the contrary, the mean levels of urinary NAG/Cr showed a significant increase during the time. Possibly this can be proposed for early AKI diagnosis. Liangos and his colleagues (2007) have evaluated the relationship between urinary NAG and KIM-1 with AKI and adverse clinical outcomes of AKI in a cohort study in 201 hospitalized patients. They have concluded that urinary NAG and KIM-1 have been increased in patients with AKI earlier than serum Cr or oliguric conditions. Also, higher urinary NAG has been related to adverse outcomes such as dialysis requirement or hospital death (37). Sakallı et al. (2013) demonstrated that after prescription of Cisplatin in 30 patients, BUN and serum Cr have not been changed, but it has been shown an increase in 24 hour-urinary NAG. Also, there has been no significant correlation between NAG and Cr levels (38). Similarly, in the current study, there was no significant correlation between urinary NAG and urinary β2-MG with serum Cr. Although increased urinary NAG can be a diagnostic value for the early detection of acute kidney injury, it has been increased in some other diseases, because of renal damages, such as hypoxia, hypertension, hypercalciuria, nephrolithiasis, nephrocalcinosis, perinatal asphyxia, and diabetic nephropathy (8,39). Furthermore, this factor has been increased during normal pregnancy (40) and laryngeal cell carcinoma (41). It can be concluded that NAG biomarker needs to further study to prove its role in AKI diagnosis. The unsuitable features of urinary NAG (hindering by endogenous urea, plenty of nephrotoxic substances and magnesium and its increased levels which are observed in impaired glucose tolerance, rheumatoid arthritis, and hyperthyroidism) made this biomarker unreliable for AKI prognosis/diagnosis (42).

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Here, the portion of urinary NAG/Cr levels on day six after the treatment based on three chemotherapeutic agents, the gender groups, the age groups, and triple dosages of Ifosfamide was significantly increased. So, urinary NAG/Cr should be further studied to prove its role for earlier AKI diagnosis. As review literature, urinary NAG/Cr and urinary β2-MG/Cr have been not measured in cancer patients but urinary NAG/Cr portion has been measured for diagnosis of pyelonephritis in children (12). In addition, the elevated levels of urinary NAG on day six after the treatment based on the gender groups were not significant but based on the age groups were significant. The elevated levels of urinary NAG and BUN based on triple dosages of Ifosfamide were not significant. In case of BUN, the elevated levels of BUN among three chemotherapeutic agents on day six after the treatment were not significant. However, based on the gender groups, this value was significant. In case of serum Cr, the elevated levels based on the three chemotherapeutic agents and the gender groups were not significant, but these values based on the triple dosages of Ifosfamide on day six after the treatment were significant.Interestingly, the results showed that urinary β2-MG and β2-MG/Cr and NAG/Cr can be reliable as the potent biomarkers for AKI prognosis/diagnosis among three chemotherapeutic agents (Ifosfamide, Ifosfamide plus Carboplatin, and Ifosfamide plus Cisplatin). All in all, earlier recognition of AKI in patients under chemotherapy may permit earlier treatment and may progress patients' successful outcomes. It was noteworthy that there were some limitations in this study: (i) themonitoring of more patients for a long time follow-up to study the long term adverse effects such as CKD was not performed. (ii) The studying of more chemotherapeutic agents to evaluate AKI in pediatric cancer patients was not considered. (iii) In addition, the surveying of more biomarkers after treatment with the nephrotoxic chemotherapeutic agents was not focused.

Conclusion

Remarkably, urinary β2-MG, urinary β2-MG/Cr, and urinary NAG/Cr were more significant biomarkers compare to serum Cr in earlier diagnosis and treatment of AKI in cancer patients. However, urinary NAG should be further studied to prove its reliability for AKI prognosis/diagnosis. It is suggested that urinary NAG can be used along with other renal biomarkers such as urinary β2-MG, KIM-1, or IL-18 for AKI prognosis/diagnosis.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

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