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Onco-Nephrology: Unraveling acute Kidney injury in Cancer and its association with Nephrotoxic Medications and Biomarkers

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Abstract

Background: The patients with malignancies are at increased risk of infection, sepsis, tumor lysis syndrome, drug-related toxicity, and other comorbidities, leading to a significantly increased risk of acute kidney injury (AKI). This prospective study analyzed the clinical data of AKI in cancer patients and explored the predictive value of Cystatin C (CysC) and neutrophil gelatinase-associated lipocalin (NGAL) in the prognosis of cancer patients with AKI.
Methods: Patients with malignancies, attending the Service of Oncology, University Hospital Center "Mother Teresa "Tirana, Albania from September 2024 to February 2025 were enrolled according to inclusion and exclusion criteria.
Results: A total of 100 patients were included. Among them, 21 cases (21 %) had AKI, and 79 cases (79%) had no AKI. Among the AKI patients, in 17 of them (81 %) the renal function recovered. Serum CysC and NGAL levels persisted elevated in patients who didn't recover the renal function.

Conclusions: AKI is an important complication in cancer patients, treated with chemotherapy. Baseline NGAL and CysC levels are associated with the occurrence of AKI in cancer patients.

Keywords: Cystatin C (CysC); cancer; acute kidney injury (AKI), neutrophil gelatinase-associated lipocalin (NGAL).

1. Introduction

Acute kidney injury (AKI) is common complication in patients with malignancies treated with chemotherapy and serum creatinine (SCr), urine output are the main tools to diagnose AKI. Cisplatin ranks among so called alkylating cytostatics and is currently one of the most common chemotherapeutics (Maghsoudi, Mirjalili, Dolatabadi, Joshaghani, Zarea, Yahaghi and Mokarizadeh, 2015). Use of cisplatin is limited by side effects on the body. These are especially neurotoxicity and nephrotoxicity accompanied by higher risk of AKI. More than 50% of renal function must be lost before elevated SCr levels in blood are detectable and levels depend on age, gender body mass, and ethnicity (Herget-Rosenthal *et al., 2004).*

Cystatin C (CysC) is a 13 kD protease inhibitor located in nucleated cells, that is freely filtered through human glomeruli and is a useful test for early AKI diagnosis. Impairment of glomerular filtration rate (GFR) leads to its increased levels in plasma (Abrahamson, Olafsson, Palsdottir, *et al*., 1990). Further studies demonstrated the superiority of serum cystatin C compared to creatinine, especially to detect minor GFR reduction (Coll, Botey, Alvarez, et al., 2000; M. Mussap, M. Dalla vestra, P.Fioretto, et al., 2002).

Neutrophil gelatinase-associated lipocalin (NGAL) is a 25-kD protein involved in injury and repair of tubular cells and iron transport, and is expressed in proximal and distal tubules (Coll, Botey, Alvarez, et al., 2000; Scarr, Bjornstad, Lovblom, et al., 2019). The elevated plasma or urine concentrations of neutrophil gelatinase-associated lipocalin (NGAL), a 25 kDa protein bound to gelatinase from neutrophils, are detectable in patients with numerous pathological states (Romejko, Markowska, Niemczyk, 2023; Yong Wang, Jian-Ye Chen, Yue-Ming Jiang et al., 2007).

NGAL has been considered as an excellent biomarker predicting also early AKI occurrence in patients treated by chemotherapy. NGAL released during renal injury, can be identified as early as three hours post-cisplatin infusion, with higher levels after twelve hours, showing effectiveness in early cisplatin-induced AKI detection compared to traditional markers, cystatin C, and albuminuria (Bunel V, Tournay Y, Baudoux T, De Prez E, Marchand M, Mekinda Z, et al., 2017; Mishra, Mori, Ma, Kelly, Barasch, Devarajan, 2004; Peres, Cunha Júnior, Assumpção, Schäfer, Silva, Gaspar et al., 2014).

The comparison of serum NGAL and CysC levels in patients with malignancies treated with chemotherapy is limited, especially for those with a normal creatinine level. This prospective study aimed to evaluate the relationships between AKI, NGAL, Cystatin C, and the use of nephrotoxic medications, specifically focusing on drugs

like cisplatin, paclitaxel /carboplatin, gemcitabine/cisplatin, and bevacizumab.

2. Methods

Patients with malignancies, attending the Service of Oncology, University Hospital Center "Mother Teresa" Tirana, Albania from September 2024 to February 2025 were enrolled according to inclusion and exclusion criteria. The inclusion criteria for participants were the following: 1) age ≥18 years; 2) clear diagnosis of malignant tumor; 3) life expectancy ≥3 months; 4) history of chemotherapy; 5) CysC and NGAL tests results available in the baseline data; 6) regular renal function testing during the process of tumor treatment. The exclusion criteria for participants were the following: 1) severe heart failure, respiratory failure, liver failure; 2) active connective tissue disease; 3) incomplete follow-up data. This study was approved by the Ethics Committee of University of Medicine, Tirana. Written informed consent was obtained from the participants in the study. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013).

The clinical data of patients, including demographic data (gender, age, etc.), general data (height, weight, smoking history, etc.), basic medical history data (underlying diseases, baseline blood pressure, heart rate, routine blood test indicators, such as white blood cell count, hemoglobin concentration, liver function, renal function, electrolytes, blood lipids, blood glucose, CysC, NGAL, etc.), tumor-related data (tumor location, clinical stage, treatment methods, related drugs and their dosage), and follow-up data (outcome, changes in renal function, etc.), type of cancer treatment were collected. For evaluating the kidney function, we used the CKD-EPI formula, which is based on serum creatinine and urine output. The definition of AKI is judged and staged according to an elevated level of Scr and/or urine output: that is, 1) an increase in Scr within 48 hours exceeding 26.5 μmol/L, or an increase in Scr exceeding 1.5 times the baseline, either confirmed or speculated to occur within 7 days; or 2) urine output <0.5 mL/kg/h lasting for more than 6 hours (AKI can be diagnosed if one of the above conditions is met) (14). This clinical criterion solidifies the diagnosis of AKI in these patients.

Statistical analysis

Statistical processing was performed using SPSS 23.0 statistical software (IBM Corp., Armonk, NY, USA). Quantitative data were tested for normal homogeneity. If the data conform to a normal distribution are represented by mean ± standard deviation, comparisons between groups were processed by the *t*-test. If the data did not conform to a normal distribution are represented by medians, the comparison between groups was processed by the rank-sum test. The qualitative data are expressed by numbers and percentages, and comparison between groups was performed by χ^2 test or Fisher's exact test if theoretical number was less than 1. Logistic single factor and multivariate analyses of factors related to whether or not AKI could be resolved

were also performed. A P value <0.05 indicated that the difference was statistically significant.

3. Results

A total of 100 adult cancer patients were diagnosed and treated in our hospital from September 2024 to March 2025, aged between 36 and 85 (mean age 58.31 and SD was 58.31 ± 9.89 years) (Table 1, 2; Figure 1) underwent chemotherapy protocol. The patients were treated with the following chemotherapy agents:

- Chemotherapy Drugs: Cisplatin, Paclitaxel, Carboplatin, Oxaliplatin, Capecitabine, Gemcitabine, Doxorubicin, Irinotecan, 5-FU, Cyclophosphamide, Docetaxel, Epirubicin, Vincristine, Adriamycin, Etoposide, Ifosfamide, Leukovorin;
- Targeted Therapy Drugs: Bevacizumab, Pertuzumab, Trastuzumab, Cetuximab, Ribociclib, Palbociclib, Letrozole, Exemestane, Tamoxifen, Goserelin, Enzalutamide
- Immunotherapy Drugs: Pembrolizumab;
- Hormonal Therapy Drugs: Letrozole, Exemestane, Tamoxifen, Goserelin;

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Female	58	58.0	58.0	58.0
	M	42	42.0	42.0	100.0
	Total	100	100.0	100.0	

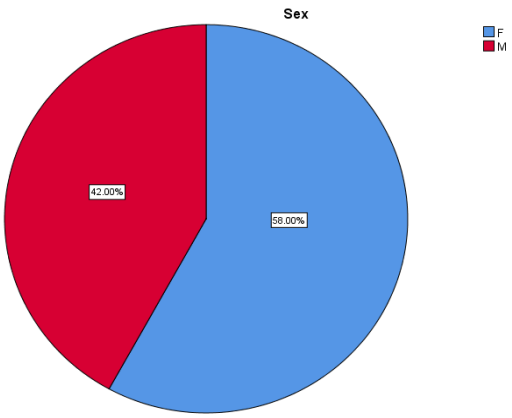

Figure 1. Distribution regarding the gender

Table 2. Distribution regarding the age

	N	Minimum	Maximum	Mean
Age	100	36.00	85.00	58.31
Valid N (listwise)	100			
Standard deviation	100			9.89

In Table 3 and Figure 2 is presented the distribution regarding the origin.

Table 3. Distribution regarding the origin

		Frequency	Percent	Valid Percent	Cumulative Percent
	Berat	3	3.0	3.0	3.0
	Burrel	3	3.0	3.0	6.0
	Durres	4	4.0	4.0	10.0
	Elbasan	4	4.0	4.0	14.0
	Erseke	1	1.0	1.0	15.0
	F.Kruje	1	1.0	1.0	16.0
	Fier	1	1.0	1.0	17.0
	Gjirokas	3	3.0	3.0	20.0
	Has	2	2.0	2.0	22.0
	Kavaje	1	1.0	1.0	23.0
	Korçe	4	4.0	4.0	27.0
	Kruje	1	1.0	1.0	28.0
	Kuçove	1	1.0	1.0	29.0
	Kukes	4	4.0	4.0	33.0
	Librazhd	1	1.0	1.0	34.0
	Lushnje	2	2.0	2.0	36.0
	Mat	1	1.0	1.0	37.0
	Permet	1	1.0	1.0	38.0
	Peshkopi	2	2.0	2.0	40.0
	Pogradec	2	2.0	2.0	42.0
	Puke	2	2.0	2.0	44.0
	Sarande	1	1.0	1.0	45.0
	Shijak	1	1.0	1.0	46.0
	Shkoder	2	2.0	2.0	48.0
	Tepelene	1	1.0	1.0	49.0

	Tirane	48	48.0	48.0	97.0
	TIrane	1	1.0	1.0	98.0
	Vlore	2	2.0	2.0	100.0
	Total	100	100.0	100.0	

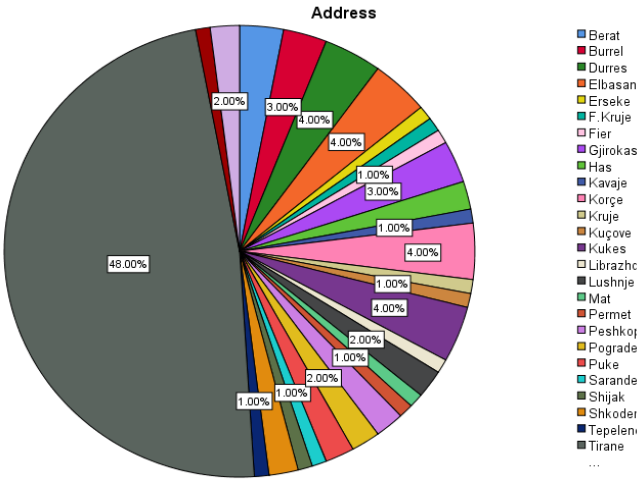

Figure 2. Distribution regarding the origin

Table 4. Smoker/Non-Smoker according to gender

		Smoker		
		No	Yes	Total
Gender	Female	48	10	58
	Male	15	27	42
Total		63	37	100

Table 5. Distribution of cancer type

		Frequency	Percent	Valid Percent	Cumulative Percent
	Esophageal-cardia cancer	2	2.0	2.0	2.0
	Cervical cancer	8	8.0	8.0	10.0
	Colon cancer	12	12.0	12.0	22.0
	Sigmoid colon cancer	3	3.0	3.0	25.0

Skin cancer	3	3.0	3.0	28.0
Breast cancer	21	21.0	21.0	49.0
Breast cancer + other	2	2.0	2.0	51.0
Nasopharyngeal cancer	3	3.0	3.0	54.0
Ovarian cancer	5	5.0	5.0	59.0
Pancreatic cancer	5	5.0	5.0	64.0
Vater's papilla cancer	1	1.0	1.0	65.0
Prostate cancer	1	1.0	1.0	66.0
Lung cancer	7	7.0	7.0	73.0
Rhabdomyosarcoma	1	1.0	1.0	74.0
Rectal cancer	5	5.0	5.0	79.0
Fallopian tube cancer	1	1.0	1.0	80.0
Tonsil cancer	1	1.0	1.0	81.0
Stomach cancer	8	8.0	8.0	89.0
Bladder cancer	3	3.0	3.0	92.0
Peritoneal carcinomatosis	1	1.0	1.0	93.0
Bile duct cancer	3	3.0	3.0	96.0
Fibrosarcoma	1	1.0	1.0	97.0
Melanoma	2	2.0	2.0	99.0
Kaposi's sarcoma	1	1.0	1.0	100.0
Total	100	100.0	100.0	

Table 6. Distribution of cancer type regarding the gender

	Sex		
Type of cancer	F	M	Total
Esophageal-cardia cancer	1	1	2
Cervical cancer	8	0	8
Colon cancer	5	7	12
Sigmoid colon cancer	2	1	3
Skin cancer	1	2	3
Breast cancer	23	0	23
Breast cancer + other	0	3	3
Nasopharyngeal cancer	5	0	5
Ovarian cancer	2	3	5
Pancreatic cancer	1	0	1
Vater's papilla cancer	0	1	1

	Prostate cancer	2	5	7
	Lung cancer	1	0	1
	Rhabdomyosarcoma	2	3	5
	Rectal cancer	1	0	1
	Fallopian tube cancer	0	1	1
	Tonsil cancer	1	7	8
	Stomach cancer	0	3	3
	Bladder cancer	1	0	1
	Cholangiocarcinoma	0	3	3
	Fibrosarcoma	1	0	1
	Melanoma	1	1	2
	Kaposi Sarcoma	0	1	1
Total		58	42	100

Twenty-one cases (21 %) had AKI, and 79 cases (79%) had no AKI. Among the AKI patients, in 17 of them (81 %) the renal function recovered, while in 4 patients (24 %) did not.
Among them, 21 cases (21 %) had elevated NGAL levels and 18 had elevated CysC. The patients' baseline information is shown in Table 7.

Table 7. AKI incidence and drug correlations

Medication	**Occurrences**	**AKI Incidence**	**Biomarker Correlation**
Cisplatin	18	High	NGAL, Cystatin C, CKD-EPI
Paclitaxel/Carboplatin	18	Moderate	NGAL, Cystatin C
Gemcitabine/Cisplatin	11	High	NGAL, Cystatin C
Bevacizumab	30	Moderate	Indirect (Blood Pressure)
Oxaliplatin/Capecitabine	16	Moderate	NGAL, Cystatin C

AKI – acute kidney injury; NGAL- neutrophil gelatinase-associated lipocalin

4. Discussion

This prospective study analyzed the clinical data of cancer patients with AKI in our hospital for six months and found that AKI is not rare in cancer patients (21 %). After AKI, none of patients required renal replacement therapy (RRT). Most of patients

who experienced AKI, recovered baseline levels as regards the renal function after the treatment. But, four patients experienced improved renal function after treatment but did not return to the baseline level.

Chemotherapy will inevitably damage normal tissues and organs, in which renal impairment is more common (15), and most chemotherapy drugs have varying degrees of renal toxicity. Chemotherapy-induced AKI presents a significant challenge at the intersection of oncology and nephrology, complicating cancer treatment, particularly with platinum compounds. Serum creatinine concentration and urine output are mostly used parameters AKI in clinical practice. But, creatinine, which could be influenced by many factors, is considered a delayed and insensitive biomarker of AKI.

Platinum is the main chemotherapy drug that causes renal impairment during the postoperative adjuvant chemotherapy in elderly patients with malignant tumors. The changes in renal function should be closely monitored when a platinum-based adjuvant chemotherapy regimen is used.

Although SCr and BUN do not significantly change during the postoperative adjuvant chemotherapy in patients with malignant tumors, the GFR may have significantly decreased. Serum Cys C level can be more sensitive to monitor the renal impairment during the chemotherapy, which can replace the CCr in monitoring renal impairment in elderly cancer patients during the chemotherapy.

Recent studies have also confirmed that the Cys C is an ideal endogenous marker for monitoring GFR, and has high sensitivity for detecting early renal impairment (Khwaja, 2012), having a great value in monitoring the renal function of patients with AKI.

Cystatin C elevates in response to kidney dysfunction, often before other markers like serum creatinine rise. In our study, 18 out of 21 NGAL-positive patients had elevated Cystatin C, reinforcing the likelihood of AKI. NGAL is a sensitive marker that detects kidney stress and dysfunction long before serum creatinine rises. A positive NGAL test can suggest that the kidneys are at risk of or already experiencing injury (Pokrivčák, Poprach, 2015). Our study found that the baseline level of CysC can not only predict the occurrence of AKI in cancer patients, but is also related to the subsequent changes in renal function, independent of other risk factors. This result has important clinical significance. First, it implies that CysC can predict the risk of AKI in cancer patients. In high-risk patients, if CysC is high, it is unlikely that AKI will be resolved. These patients should be closely monitored and given intensive treatment.

Also, NGAL has been considered as an excellent biomarker predicting also early AKI occurrence in patients treated by chemotherapy (Kozan, Şare and Yılmaz, 2018; Ostermann, Zarbock, Goldstein, Kashani, Macedo, Murugan, Bell, Forni, Guzzi, Joannidis, 2020; Bunel, Tournay, Baudoux, De Prez, Marchand, Mekinda, et al.,

2017).

In this study, the elevation of NGAL is strongly correlated with AKI. In this cohort study, 21 patients were NGAL-positive, and 18 of them also had elevated Cystatin C, which confirmed kidney injury. NGAL's sensitivity as an early biomarker makes it an essential tool in detecting AKI early, especially in patients undergoing nephrotoxic chemotherapy (Akgül, Bauer, Zigrino, Storey, Mauch, Pfister, 2011).

More specifically, clinicians can avoid drugs that damage kidney function, reduce the burden on the kidneys, administer drugs that protect kidney function, and perform other related measures (Ma, Cheng, Ma, 2019). Though only about 19% patients cannot fully recover from cancer-related AKI, with the increasing absolute number and incidence of cancer cases, the CysC plays an important role in predicting the prognosis of AKI in cancer patients (Kawakami, Hirata, Mizuta, et al., 2019).

Some limitations to this study should also be addressed. First, the study included a comparatively small number of patients, thus, the statistical power of the evidence is relatively weak. Second, the follow-up time of the study was short, and the relationship between subsequent changes in renal function and CysC remains uncertain. Therefore, further multicenter, large-sample studies with longer follow-up times are needed.

5. Conclusion

The administration of nephrotoxic medication significantly elevates the risk of acute kidney injury (AKI) in cancer patients. Elevated biomarkers like NGAL and Cystatin C serve as reliable indicators of kidney injury, often occurring before clinical signs such as changes in serum creatinine. The combined use of biomarkers and clinical criteria like CKD-EPI is essential in diagnosing AKI early and preventing further renal damage in cancer patients undergoing chemotherapy.

This data emphasizes the importance of careful monitoring of AKI risk in patients receiving nephrotoxic medications and suggests the need for interventions to prevent kidney injury in these vulnerable patients.

Further clarification of risk factors is needed, and early diagnosis is essential for initiating therapeutic interventions, including dose adjustments and drug discontinuation. Addressing knowledge gaps, overcoming challenges, and incorporating emerging trends in prevention and management are essential to reduce the burden associated with AKI induced by conventional chemotherapy.

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

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted with approval from the Ethics Committee of University of Medicine, Tirana, Albania. Written informed consent was obtained from the participants in the study.

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