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DYNAMICS OF NEUTROPHIL GELATINASE-ASSOCIATED LIPOCALIN SERUM IN MALIGNANT SUBJECTS TREATED WITH CHEMOTHERAPY

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ABSTRACT Background: Acute kidney injury in malignant subjects can be caused by the process of the malignant itself or its therapy, in this case, chemotherapy. Neutrophil Gelatinase-Associated Lipocalin detects acute renal injury earlier than creatinine. This study measures the dynamics of Neutrophil Gelatinase-Associated Lipocalin serum in malignant subjects treated with chemotherapy. **Method:** Analytical research with a cohort design. The research subjects were subjects aged > 18 years treated with chemotherapy at Dr Wahidin Sudirohusodo Hospital, Makassar, Indonesia. Serum level of Neutrophil Gelatinase-Associated Lipocalin measured before and 24 hours after chemotherapy. **Results:** Post-chemotherapy Neutrophil Gelatinase-Associated Lipocalin serum level was significantly higher than pre-chemotherapy (280,330 ng / ml vs. 204,453 ng / ml, p <0,001). The increased percentage of Neutrophil Gelatinase-Associated Lipocalin serum level was significantly higher in subjects with a serum creatinine level > 1.3 mg/dl compared to subjects with serum creatinine level < 1.3 mg/dl (185% vs 52%, p <0, 05). The increased percentage of Neutrophil Gelatinase-Associated Lipocalin serum level was found to be higher in subjects with diabetes and hypertension than those without diabetes and hypertension (160% vs 48%, p <0.05). **Discussion:** This study found overall increased of Neutrophil Gelatinase-Associated Lipocalin serum level in malignant patients 24 hours after chemotherapy, especially in patients with serum creatinine > 1.3 mg/dl and with diabetes and hypertension. A possible explanation is previous kidney injury, hypertension, and diabetes Mellitus makes kidney vulnerable to nephrotoxic substances.

KEYWORDS Neutrophil Gelatinase-Associated Lipocalin, acute kidney injury, malignancy, chemotherapy

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Introduction

Acute kidney injury (AKI) in malignant subjects can be caused by the process of the malignancy itself or its therapy, in this case, chemotherapy. [1] Risk factors for acute kidney injury are older age (> 65 years), previous chronic kidney disease (CKD), comorbidity (diabetes mellitus and hypertension), decreased intravascular volume, type and dose of chemotherapy. [2]

Traditionally, the parameters for diagnosing AKI are decreased urine volume and increased level of serum creatinine (SCr). However, increased SCR occurs 24-48 hours after injury. Therefore, some markers such as Neutrophil Gelatinase-

Table 1 Subjects Characteristics (n=40)

Variable		n	%
Sex	Man	26	65,0
	Woman	14	35,0
Age	≤60 years	26	65,0
	>60 years	14	35,0
Creatinine serum	≤1,3	36	90,0
	>1,3	4	10,0
Type of chemotherapy	Non-Platinum Based	30	75,0
	Platinum Based	10	25,0
Comorbid	Yes	6	15,0
	No	34	85,0
Chemotherapy Cycle	First	15	37,5
	Advanced	25	62,5

Table 2 Subjects Descriptive Statistics (n=40)

Variable	Min	Max	Mean	SD
Age	26	78	52,43	14,72
sCr (mg/dl)	0,45	3,78	1,02	0,60
NGAL serum pre-chemotherapy (ng/ml)	28,850	517,526	204,442	134,905
NGAL serum post-chemotherapy (ng/ml)	35,735	503,137	280,330	150,955

Associated Lipocalin (NGAL) is used to detect the injury earlier, because this marker can detect injury 2-4 hours after exposure. [3]

This study aims to measure the dynamics of NGAL in malignant subjects treated with chemotherapy.

Materials and Methods

Analytical research with a cohort design was conducted at Dr Wahidin Sudirohusodo Hospital in Makassar, Indonesia from August to October 2018. It was approved by the ethics committee of the Faculty of Medicine with reference number: 842 / H4.8.4.5.31 / PP 36-KOMETIK / 2018.

A. Population

Subjects > 18 years old with malignancy and treated with chemotherapy. A biopsy or bone marrow puncture make the diagnosis of malignancy and confirmed by an anatomical pathologist while the exclusion criteria are subjects with kidney tumours.

Table 3 Percentage of Increase in NGAL Serum Level

Variable		N	Mean	SD	p
Age	≤60 years	26	57,0	108,0	0,576
	>60 years	14	80,0	148,0	
Type of Chemotherapy	Non Platinum Based	30	70,0	137,0	0,679
	Platinum Based	10	51,0	61,0	
Comorbid	Yes	6	160,0	194,0	0,035
	No	34	48,0	99,0	
Chemotherapy Cycle	First	15	72,0	137,0	0,786
	Advanced	25	61,0	115,0	
sCr	≤ 1,3	36	52,0	99,0	0,036
	>1,3	4	185,0	241,0	

B. Methods and data collection

All subjects underwent history taking, physical examinations and additional laboratory test including SCR and NGAL serum. These subjects will be examined for NGAL serum before chemotherapy and 24 hours after chemotherapy. After data is complete from all samples, then a retrospective analysis is performed to identify risk factors that can affect changes in NGAL serum level after chemotherapy.

C. Statistical analysis

Data analyzed with SPSS version 22. The statistical analysis performed was descriptive statistic calculation, frequency distribution and Paired-t, Independent-t and Chi-Square test. Test results are significant if p <0.05.

Results

Of the 40 subjects, aged between 26-78 years with an average of 52.4 ± 14.7 years. Subjects consisted of men (65.0%) aged < 60 years (65.0%). Based on the result of laboratory tests, it was found that most of the subjects had a level of SCR < 1.3 mg/dl (90.0%). Based on the type of chemotherapy, the majority used non-platinum chemotherapy (75.0%) and advanced cycles (62.5%). Before chemotherapy, NGAL serum level were 204,442 + 134,905 ng / mL, whereas after chemotherapy, NGAL serum level were 280,330 + 150,955 ng / ml. The increased percentage of NGAL serum level was higher at age> 60 years (80%) than at <60 years (57%) but statistically insignificant (p> 0.05). It was found that the increased percentage of NGAL serum level was significantly higher in subjects with a level of sCr > 1.3 compared to subjects with a level of SCR <1.3 mg/dl (185% vs 52%, p <0.05). The increased percentage of NGAL serum level was higher in non-platinum chemotherapy (70%) than in platinum (51%), but statistically insignificant (p> 0.05). The increased percentage of NGAL serum level was found to be significantly higher in subjects with diabetes mellitus and hypertension compared to those without diabetes mellitus and/or hypertension (160% vs 48%, p <0.05). The increased percentage of NGAL serum level was higher in the first chemotherapy cycle (72%) than in the

advanced cycle (61%), but statistically insignificant (p> 0.05).

Discussion

The progress of chemotherapy has improved the prognosis of malignant subjects. Nevertheless, the side effect of chemotherapy including nephrotoxicity is still a problem, because it can reduce the quality of life for the malignant subjects.[4] Nephrotoxicity of chemotherapy drugs depends on its pharmacokinetics and pharmacodynamics. Elderly age, the presence of comorbidities such as diabetes mellitus and hypertension, the presence of CKD, and hypovolemia, are risk factors for AKI in a malignant subject treated with chemotherapy.[5] Increased NGAL serum level due to chemotherapy can be caused by several mechanisms such as thrombotic microangiopathy, acute glomerular disease, acute tubular necrosis, crystalline nephropathy, or interstitial nephritis, depending on the chemotherapy drug used.[6,7]

In this study, NGAL serum level after chemotherapy increased compared to before chemotherapy. Kos et al. [8] in 34 subjects who received chemotherapy with cisplatin found an average NGAL serum level increased after chemotherapy compared to before chemotherapy (139.4 vs 125.5 ng/ml).

In this study, we found a significant increase in post-chemotherapy subjects with sCr> 1.3 mg/dl. Maghsoudi et al. [9] compared ten subjects with CKD and five subjects without CKD gave cisplatin chemotherapy, found that NGAL serum level and NGAL urine level were higher in subjects with CKD compared with those without CKD (p 0.024; p 0.011). Peres et al. [10] measured NGAL serum level in 50 subjects with head and neck malignancies, found that an increase in NGAL serum level was higher in subjects with CKD than without CKD, and although without CKD, NGAL serum level could be detected to increase earlier (3 hours after exposure compared to SCR, which increased after 48-72 hours).

In this study, there was a significant increase in NGAL serum in subjects with comorbid diabetes mellitus and hypertension compared to those without diabetes mellitus and hypertension. In uncontrolled hypertension, increased renin-angiotensin-aldosterone system (RAAS) activity results in chronic vasoconstriction of renal afferent arteries, which results in kidney hypoperfusion, leading to kidney damage.[11] Advanced glycation end products (AGEs) formed in subjects with diabetes mellitus can damage podocyte cells, resulting in proteinuria and increased intraglomerular pressure which will cause fibrosis in the kidney. Both are risks for the occurrence of AKI even with minimal triggers. Lacquaniti et al. [12] studied the correlation of NGAL with the incidence of diabetic nephropathy. In this study, 56 subjects with type 2 diabetes mellitus were collected, then categorized into three groups (normoalbuminuria, microalbuminuria and diabetic nephropathy). Neutrophil Gelatinase-Associated Lipocalin serum increases in line with the severity of diabetic nephropathy. Hypertension and diabetes mellitus make the kidney susceptible to injury because this chronic disease decreases the number of healthy nephrons, which makes even the slightest exposure to the injury can manifest into acute kidney injury. [13,14]

This study concluded that there was an increase in NGAL serum level in malignant subjects 24-hour after treated with chemotherapy, especially in subjects with level sCr> 1.3 mg/dl and those with diabetes mellitus and hypertension.

Conflict of interest

The author states that there is no conflict of interest in this study. The personal funds of the authors covered all funds in this study.

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