Risk factors for renal alterations in patients with hematological cancer undergoing antineoplastic treatment

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Abstract

Purpose Antineoplastic treatments, mainly chemotherapy, affect the kidneys, causing toxicity, and can trigger acute and long-term chronic kidney injury. The objective of this study was to analyze the prevalence of renal disorders in patients with oncohematological neoplasms under antineoplastic treatment.

Methods This is a retrospective cohort study involving 75 patients affected by hematological cancer who underwent chemotherapy between 2012 and 2108 in the Hematology Sector of the Walter Cantídeo University Hospital of the Federal University of Ceará. Sociodemographic and clinical data, blood biochemical assessment, and Glomerular Filtration Rate (GFR) were analyzed using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. The data were tabulated, transferred to the Statistical Package for the Social Sciences software, version 20.0, and analyzed using Fisher's exact test or Pearson's chi-square test, followed by the Mann-Whitney test. Additionally, the variables were treated using a multinomial logistic regression model ($p < 0.05$).

Results The prevalence of renal disorders was 52.4%, considering the episodes of GFR through the CKD-EPI equation. There was an association between the reduction in GFR and the variables: female gender ($p = 0.002$), diagnosis of multiple myeloma ($p = 0.008$), start of treatment within 40 days ($p = 0.005$), protocol Cyclophosphamide, Oncovin, Prednisone ($p = 0.026$), Idarubicin ($p = 0.032$), Vidaza protocol, Dexamethasone, Cyclophosphamide ($p < 0.001$), Zoledronate ($p < 0.001$) and Pamidronate ($p = 0.012$). It was also observed that the Cancer and Leukemia Group B protocol ($p < 0.001$) is inversely associated with a reduction in GFR.

Conclusions The prevalence of renal disorders is high in the service evaluated, requiring periodic monitoring of the evaluation of renal function, since the reduction in GFR is statistically associated with different protocols used.

Introduction

Hematological cancers, among the most common, are classified into leukemias, lymphomas, and multiple myeloma. These neoplasms affect about 22,780 thousand people a year, being more incidents in men than in women. Among them, the most frequent is non-Hodgkin lymphoma, with 10,240 thousand cases, soon followed by leukemias with 10,070 thousand cases in Brazil [1].

The options for the antineoplastic treatment plan consist of Chemotherapy (CT), radiation therapy, gene therapy, pharmacological therapy, and surgical resection. However, it usually consists of a combination of these modalities [2]. The toxicity of therapeutic modalities, mainly CT, affects the kidneys, which are the preferred elimination pathway for chemotherapeutic drugs. Nephrotoxic drugs cause kidney damage due to the delay or interruption of treatment, or due to excess chemotherapy and its difficulty in removing it from the body [3].

In association with cancer, renal involvement is evident with an incidence of 18% only in the first year of diagnosis, revealing to affect this sick population more when compared to the general population, which is approximately 1,000 per year. Five years after diagnosis, this rate increases to 43% in patients with solid tumors and bone metastases [3, 4].

In lymphomas, renal impairment reaches about 33% in myeloid leukemia, in myelodysplastic syndrome, this number is 36%, and in multiple myeloma, it happens in about 30 to 40% of the patients, and, during the progression of the disease, this index increases to 50% [5–9].

Once installed, renal dysfunction causes the breakdown of homeostasis leading to the appearance of edema, systemic arterial hypertension, accumulation of sodium chloride, hyperkalemia, hyponatremia, hypophosphatemia, anemia, change in coagulation, suppression of the immune system, metabolic acidosis and, in its consequence, pulmonary hyperventilation as a compensatory mechanism, azotemia, and uremic encephalopathy [10].

Despite therapeutic advances, patients with hematological cancers are more vulnerable to kidney changes, Acute Kidney Injury (AKI), and Chronic Kidney Disease (CKD), when opposed to patients with other types of malignancies, in addition to having worse prognosis [11, 12].

Therefore, we sought to analyze the prevalence of renal disorders in patients with hematological neoplasms under antineoplastic chemotherapy treatment in the Hematology Sector of the Walter Cantídeo University Hospital of the Federal University of Ceará, from 2012 to 2018.

Methods

This is a retrospective cohort study, with a descriptive and analytical approach developed in a reference hospital (HUWC-UFC), in the Hematology Sector, located in the city of Fortaleza-CE.

The sample consisted of 75 patients, over 18 years old, with hematological neoplasia, who underwent or were still undergoing chemotherapy in the period from 2012 to 2018 at the hematology service.

Data were collected by consulting printed medical records, digital records, and other documents of the institution. The following variables were tabulated: A) sociodemographic data: name, age (considering up to 50 and over 50 years), sex (male and female), education (illiterate, elementary, middle, upper), race (white, brown or black), marital status (with a partner or without a partner), place of birth; B) clinical aspects: presence of comorbidities, weight, height, Body Mass Index (BMI), BMI classification, dental care, type of neoplasia, remission, time of treatment initiation after diagnosis, type of antineoplastic treatment, type of conditioning, previous transplantation and what type of transplantation, medications in use, place of chemotherapy application, protocol, number of cycles, medications in use, kidney injury relapse, duration of antineoplastic treatment; C) Glomerular Filtration Rate: using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

For the basal creatinine value, the first measurement found in the medical records of each patient was adopted, following the recommendations of KDIGO, and to estimate GFR, the formula CKD-EPI was used because of its accuracy is more effective than when compared with the others [13], and thus the outcome variable was determined.

Categorical data were expressed as absolute frequency, considering the patient as the sample unit. The clinical evaluation event was adopted as the sample unit for the assessment of CKD risk factors, which were crossed using Fisher's exact test or Pearson's chi-square test. Examination data were expressed as means and standard deviations and analyzed using the Mann-Whitney test (non-parametric data).

After identifying the clinical variables significantly associated with increased risk of CKD-EPI, these were divided into two levels: clinical-epidemiological variables and therapeutic variables. At each level, these variables were analyzed using a multinomial logistic regression model, and after that, the variables independently associated with CKD-EPI were selected at each level for multilevel analysis using the same model. For all analyzes, $p < 0.05$ was considered statistically significant.

The research is in accordance with ethical principles, and the Ethics Committee for Research on Human Beings of the Faculty of Medicine (UFC) was firstly approved with CAAE 87952818.7.0000.5054 and then by the Ethics Committee of the Walter Cantídeo University Hospital (UFC)) under CAAE number 87952818.7.3001.5045.

Results

Sociodemographic profile of the sample and influence on the incidence of CDK-EPI episodes

Sociodemographic characteristics revealed that of the 75 patients included in the study, the majority (n = 47) were in the age group above 50 years old, representing 62.7%, 39 were female (52.0%), 44 brown (95.7%), 29 had a partner (53.7%), and 46 lived in Fortaleza or the metropolitan area (61.3%). Regarding the level of education, it is emphasized that 10 (31.3%) patients had incomplete higher education, seven incomplete high school (21.9%), and six complete elementary school (18.8%) (Table 1).

Table 1
Sociodemographic profile and its influence on the reduction of CKD-EPI in patients undergoing chemotherapy under analysis of renal function at the Hospital Universitário Walter Cantídio from 2012 to 2018.

	CDK-EPI (n = 450)[b]						
	Sample		**Normal**		**Reduced**		**p-value**
Age							
Up to 50	28	37.3%	153*	71.5%	30	12.7%	<0.001
> 50	47	62.7%	61	28.5%	206*	87.3%	
Sex							
Female	39	52.0%	105	49.1%	147*	62.3%	0.005
Male	36	48.0%	109*	50.9%	89	37.7%	
Race							
White	1	2.2%	0	0.0%	15*	7.9%	< 0.001
Brown	44	95.7%	155*	100.0%	172	90.5%	
Black	1	2.2%	0	0.0%	3	1.6%	
Marital status							
With partner	29	53.7%	77	49.4%	79	46.7%	0.638
Without partner	25	46.3%	79	50.6%	90	53.3%	
Education							
Illiterate	1	3.1%	0	0.0%	10*	9.5%	< 0.001
Incomplete elementary school	2	6.3%	1	0.9%	3*	2.9%	
Complete elementary school	6	18.8%	21	19.3%	35*	33.3%	
Incomplete high school	7	21.9%	10	9.2%	17*	16.2%	
Complete high school	1	3.1%	11*	10.1%	1	1.0%	
Incomplete higher	10	31.3%	44*	40.4%	26	24.8%	
Graduated	5	15.6%	22*	20.2%	13	12.4%	
Place of Birth							
Fortaleza/Metropolitan area	46	61.3%	113	52.8%	153*	64.8%	0.010

Data expressed as absolute frequency and percentage. * p < 0.05, Fisher's exact test or Pearson's chi-square. [a]Sample unit = patient; [b]Sample unit = episodes of CDK-EPI assessment.

			CDK-EPI (n = 450)[b]			
Countryside	29	38.7%	101*	47.2%	83	35.2%

Data expressed as absolute frequency and percentage. * $p < 0.05$, Fisher's exact test or Pearson's chi-square. [a]Sample unit = patient; [b]Sample unit = episodes of CDK-EPI assessment.

Patients over the age of 50 had a more significant number of episodes with reduced CKD-EPI ($p < 0.001$) as well as female ($p = 0.005$), being from Fortaleza or metropolitan region ($p = 0.010$) and being patients of white color ($p < 0.001$). Education is inversely associated with these episodes ($p < 0.001$) (Table 1).

Sample comorbidity profile and influence on the incidence of CDK-EPI episodes

There was a prevalence of Systemic Arterial Hypertension (SAH) as comorbidity, affecting 29 patients (38.7%), the classification of pre-obesity according to the Body Mass Index (BMI) was present in 30 patients (40.0%) and obesity I in 27 patients (36%). Non-dental follow-up was present in 62 patients (82.7%), the diagnosis of Multiple Myeloma (MM) affected about 33 (44.0%) and, concerning remission, chemotherapy as a type of treatment and not transplantation accounted for 63 (84.0%), 72 (96.0%) and 66 (88.0%) respectively (Table 2).

Table 2
Clinical and admission profile and its influences on the reduction of CKD-EPI in patients undergoing chemotherapy under analysis of renal function at the Hospital Universitário Walter Cantídio from 2012 to 2018.

	CKD-EPI (n = 450)[b]						
	Sample		Normal		Reduced		p-value
Comorbidities							
Systemic Arterial Hypertension	29	38.7%	33	15.4%	143*	60.6%	< 0.001
Diabetes Mellitus	12	16.0%	10	4.7%	62*	26.3%	< 0.001
Coronary disease	1	1.3%	0	0.0%	10*	4.2%	0.002
Chronic Obstructive Pulmonary Disease	1	1.3%	0	0.0%	4	1.7%	0.056
Others	12	16%	11	5.1%	75*	31.8%	< 0.001
Body mass index							
Normal	5	6.7%	27*	12.6%	10	4.2%	< 0.001
Pre-obese	30	40.0%	90*	42.1%	59	25.0%	
Obesity I	27	36.0%	51	23.8%	127*	53.8%	
Obesity II	10	13.3%	27	12.6%	27	11.4%	
Obesity III	3	4.0%	19	8.9%	13	5.5%	
Dental care							
No	62	82.7%	172	80.4%	171	72.5%	0.056
Yes	13	17.3%	42	19.6%	65	27.5%	
Diagnosis							
Multiple myeloma	33	44.0%	33	15.4%	183*	77.5%	< 0.001
Lymphoid leukemia	10	13.3%	58*	27.1%	7	3.0%	
Myeloid leukemia	17	22.7%	91*	42.5%	38	16.1%	

Data expressed as absolute frequency and percentage. * $p < 0.05$, Fisher's exact test or Pearson's chi-square. [a]Sample unit = patient; [b]Sample unit = episodes of CDK-EPI assessment.

			CKD-EPI (n = 450)[b]				
Lymphoma	15	20.0%	32*	15.0%	8	3.4%	
Remission							
No	63	84.0%	203*	94.9%	193	81.8%	< 0.001
Yes	12	16.0%	11	5.1%	43*	18.2%	
Treatment type							
CT	72	96.0%	200	93.5%	236*	100.0%	< 0.001
CT + RDT	3	4.0%	14*	6.5%	0	0.0%	
Transplant							
No	66	88.0%	205*	95.8%	199	84.3%	< 0.001
Yes	9	12.0%	9	4.2%	37*	15.7%	
Medications in use							
Acyclovir	33	44.0%	120*	56.1%	105	44.5%	0.014
Bactrim	41	54.7%	117	54.7%	177*	75.0%	< 0.001
Fluconazole	4	5.3%	30*	14.0%	12	5.1%	< 0.001
Levofloxacin	3	4.0%	25*	11.7%	12	5.1%	0.011
Others	32	42.7%	54	25.2%	143*	60.6%	< 0.001
Initial renal function							
Normal	70	93.3%	207*	96.7%	208	88.1%	0.003
Acute renal failure	1	1.3%	2	0.9%	5*	2.1%	
Chronic kidney disease	4	5.3%	5	2.3%	23*	9.7%	
Hemodialysis							
No	74	98.7%	214*	100.0%	231	97.9%	0.032
Yes	1	1.3%	0	0.0%	5*	2.1%	

Data expressed as absolute frequency and percentage. * $p < 0.05$, Fisher's exact test or Pearson's chi-square. [a]Sample unit = patient; [b]Sample unit = episodes of CDK-EPI assessment.

			CKD-EPI (n = 450)[b]				
Place of application							
Outpatient	67	89.3%	130	60.7%	212*	89.8%	< 0.001
Inpatient	8	10.7%	84*	39.3%	24	10.2%	
Time to start treatment							
Up to 40 days	37	49.3%	134*	62.6%	126	53.4%	0.048
> 40 days	38	50.7%	80	37.4%	110*	46.6%	

Data expressed as absolute frequency and percentage. * $p < 0.05$, Fisher's exact test or Pearson's chi-square. [a]Sample unit = patient; [b]Sample unit = episodes of CDK-EPI assessment.

According to the additional medications, Bactrim stood out among the others. Forty-one patients used it (54.7%). Thirty-three patients used acyclovir (44.0%). Thirty-two patients (42.7%) used other drugs (amitril, atenolol, omeprazole, metformin, simvastatin, atorvastatin, enalapril, aspirin, carvedilol, itraconazole, captopril, thalidomide, glibenclamide, propranolol, amlodipine, allopurinol, hydrochlorothiazide, gliclazide, Puran, nifedipine, furosemide, folic acid, Tazocin, dexamethasone, insulin, pregabalin, prednisone) (Table 2).

Almost the entire population had a normal initial renal function, 70 patients (93.3%), and 74 did not use hemodialysis (98.7). Regarding the place where the treatment was applied, the vast majority of patients were administered at the outpatient clinic, 67 (89.3%) and concerning the start of medications, part of the patients started after 40 days after diagnosis, representing 38 (50, 7%) (Table 2).

Regarding the clinical and admission profile of the patients, it was observed that SAH ($p < 0.001$), DM ($p < 0.001$), coronary disease ($p = 0.002$), other comorbidities ($p < 0.001$) of the most varied, grade I obesity ($p < 0.001$) are directly associated with a reduction in CKD-EPI. Although the lack of dental follow-up did not show statistical significance ($p = 0.056$), there is a trend when associated with a decrease in GFR (Table 2).

Patients diagnosed with multiple myeloma ($p < 0.001$) revealed more GFR reduction events as well as those who presented remission ($p < 0.001$), exclusive treatment with chemotherapy ($p < 0.001$) and transplantation ($p < 0.001$) (Table 2).

Acyclovir ($p = 0.014$), fluconazole ($p = 0.001$) and levofloxacin ($p = 0.011$) were inversely associated with a decrease in CKD-EPI whereas, the use of bactrim ($p < 0.001$) and other drugs ($p < 0.001$) showed a direct relationship with this change. According to renal function, patients who started treatment with AKI or CKD ($p = 0.003$) also had more episodes of reduced GFR as well as hemodialysis ($p = 0.032$) and progression to CKD ($p < 0.001$) (Table 2).

Patients who underwent treatment at the outpatient clinic ($p < 0.001$) were directly associated with renal dysfunction. It should be noted, however, that the sample studied consisted almost entirely of outpatients. There was also a higher number of dysfunctional episodes ($p = 0.048$) in patients who started treatment within 40 days after diagnosis (Table 2).

Therapeutic profile of the sample and influence of the scheme on the incidence of CDK-EPI episodes

The 75 patients participating in the research totaled 985 episodes of analysis (data collection), with a mean of 6.6 ± 6.8 and a median of 4 events per patient with a minimum and maximum of 1 to 46 events, respectively. Most patients underwent 1 to 2 cycles of CT, totaling 302 (30.7%) (Table 3).

Table 3
Clinical and admission profile of patients undergoing chemotherapy under analysis of renal function at Hospital Universitário Walter Cantídio from 2012 to 2018. Fortaleza / CE, Brazil. 2018.

	n	%
Total number of episodes evaluated	985	100
Evaluation cycle		
1st or 2nd cycle	302	30.7
3rd or 4th cycle	224	22.7
5th to 10th cycle	297	30.2
11th or higher	162	16.4
CKD-EPI (n = 450)		
Normal	214	47.6
Reduced	236	52.4
GFR classification (n = 450)		
Normal	212	47.1
Mild decrease	123	27.3
Mild to moderate	49	10.9
Moderate to severe	39	8.7
Severe decrease	21	4.7
Kidney failure	6	1.3

Data expressed as absolute frequency and percentage. * $p < 0.05$, Fisher's exact test or Pearson's chi-square. TGF = Glomerular filtration rate

When the estimate of GFR was assessed using the CKD-EPI formula, a result of 450 analyzes was obtained, since not all patients had a creatinine value. Of these, 236 (52.4%) had reduced GFR and categorizing the GFR determined by the result of the CKD-EPI formula; it was found that 212 (47.1%) episodes were considered normal. This variable was used for association with the other sociodemographic, clinical, and therapeutic variables (Table 3).

Analyzing the therapeutic profile, it was possible to dichotomize groups: inversely associated with a reduction in GFR (Cyclophosphamide, Oncovin, Prednisone (COP) $p = 0.004$, Transretinoic Acid (ATRA) $p < 0.001$, Idarubicin $p < 0.001$, Daunorubicin $p < 0.001$, Filgrastim $p = 0.003$, Cancer and Leukemia Group B (CALGB) $p < 0.001$, Cytarabine $p = 0.004$, Procarbazine, Oncovin, Mecloretamine, Prednisone (POMP) $p = 0.003$, Imatinib $p = 0.027$, other drugs $p = 0.003$) and those directly related the decrease in GFR (Vidaza, Dexamethasone, Cyclophosphamide (VDC) $p < 0.001$, Zoledronate $p < 0.001$, Pamidronate $p < 0.001$, Talcidex $p < 0.001$) (Table 4).

Table 4
Influence of the therapeutic profile on the reduction of CKD-EPI in patients undergoing chemotherapy under analysis of renal function at Hospital Universitário Walter Cantídio from 2012 to 2018.

	CKD-EPI (n = 450)				
	Normal		Reduced		p-Value
Cycle					
1st or 2nd cycle	67	31.3%	91	38.6%	0.129
3rd or 4th cycle	41	19.2%	52	22.0%	
5th to 10th cycle	66	30.8%	64	27.1%	
11th or higher	40	18.7%	29	12.3%	
Therapeutic schemes					
Anti CD20	7	3.3%	2	0.8%	0.067
COP	10*	4.7%	1	0.4%	0.004
CHOP	1	0.5%	4	1.7%	0.215
Anti CD21	0	0.0%	1	0.4%	0.340
Anti CD22	0	0.0%	0	0.0%	1.000
ATRA	48*	22.4%	9	3.8%	< 0.001
Idarubicin	25*	11.7%	2	0.8%	< 0.001
Daunorubicin	10*	4.7%	0	0.0%	0.001
Mitoxantrone	0	0.0%	0	0.0%	1.000
Filgrastim	8*	3.7%	0	0.0%	0.003
CalgB	51*	23.8%	5	2.1%	< 0.001
Mabthera	1	0.5%	0	0.0%	0.293
Cytarabine	12*	5.6%	2	0.8%	0.004
Daunoblastin	1	0.5%	1	0.4%	0.945
VDC	5	2.3%	76*	32.2%	< 0.001

Data expressed as absolute frequency and percentage. *p < 0.05, Fisher's exact test or Pearson's chi-square. Sample unit = event. CHOP: Cyclophosphamide, Hydroxidoxorubicin, Oncovin, Prednisone. CalgB: Cancer and Leukemia Group B. POMP: Procarbazine, Oncovin, Mecloretamina, Prednisone. VDC: Velcade, Cyclophosphamide, and Dexamethasone. ATRA: Trans-retinoic acid. FLAG: Fludarabine, ARA-C, and Idarubicin. **Rituximab, GVD, ICE, ABVD, Hydroxyurea, Vesanoid, 6mercaptopurine, methotrexate, MADIT, PVAB, GVM, FC Lite, FCR, Hipercvad cycle A.

	CKD-EPI (n = 450)				
Zoledronate	12	5.6%	74*	31.4%	< 0.001
Pamidronate	4	1.9%	25*	10.6%	< 0.001
POMP	8*	3.7%	0	0.0%	0.003
Talcidex	9	4.2%	34*	14.4%	< 0.001
Nivolumab	0	0.0%	0	0.0%	1.000
Imatinib	11*	5.1%	3	1.3%	0.027
FLAG	13	6.1%	12	5.1%	0.647
Vidaza	0	0.0%	0	0.0%	1.000
Brentuximab	3	1.4%	0	0.0%	0.068
Other drugs **	22*	10.3%	8	3.4%	0.003

Data expressed as absolute frequency and percentage. *p < 0.05, Fisher's exact test or Pearson's chi-square. Sample unit = event. CHOP: Cyclophosphamide, Hydroxidoxorubicin, Oncovin, Prednisone. CalgB: Cancer and Leukemia Group B. POMP: Procarbazine, Oncovin, Mecloretamina, Prednisone. VDC: Velcade, Cyclophosphamide, and Dexamethasone. ATRA: Trans-retinoic acid. FLAG: Fludarabine, ARA-C, and Idarubicin. **Rituximab, GVD, ICE, ABVD, Hydroxyurea, Vesanoid, 6mercaptopurine, methotrexate, MADIT, PVAB, GVM, FC Lite, FCR, Hipercvad cycle A.

When the multivariate analysis of the variables that showed significant relevance of the sociodemographic and clinical admission aspects was performed, it was found that being female increased the chance of episodes with a reduction in the CKD-EPI index by 18.75 times. Also, the diagnosis of MM increased this prevalence by 4,111.01 times, as well as the initiation of treatment within 40 days after the diagnosis increased the risk by 103.25 times (Table 5).

Table 5
Multivariate and multilevel analysis of sociodemographic, clinical admissions, and pharmacotherapies modifying the prevalence of CKD-EPI and multilevel analysis of independent factors associated with increased prevalence of CKD-EPI in patients undergoing chemotherapy under analysis of renal function at Walter Cantídio University Hospital in the period from 2012 to 2018.

	Multivariate		**Multilevel**	
	p-Value	**Adjusted OR**	**p-Value**	**Adjusted OR**
Reduced CKD-EPI				
Age (> 50)	0.972	-	-	-
Sex (Female)	0.002	18.75 (2.83-124.01)	0.010	2.26 (1.12–4.21)
Race (White)	1.000	-	-	-
Education (Illiterate / Elementary)	0.963	-	-	-
Place of birth (Fortaleza / metropolitan area)	0.973	-	-	-
SAH (Yes)	0.980	-	-	-
Diabetes Mellitus (Yes)	0.988	-	-	-
CD (Yes)	0.981	-	-	-
Others (Yes)	1.000	-	-	-
BMI (Obese)	0.084	-	-	-
Diagnosis (Multiple myeloma)	0.008	4111.01 (9.06–1.865.992)	< 0.001	5.75 (2.86–11.53)
Remission (Yes)	0.997	-	-	-
Treatment type (CT)	0.989	-	-	-
Transplant (Yes)	0.988	-	-	-
Initial kidney function (Normal)	0.932	-	-	-
Hemodialysis (Yes)	1.000	-	-	-
Evolution (Normal)	1.000	-	-	-
Application location (Inpatient)	0.060	-	-	-

* $p < 0.05$, multinomial logistic regression. Sample unit = event. SAH: Systemic Arterial Hypertension; CD: Coronary disease; BMI: Body Mass Index; CT: Chemotherapy; COP: Cyclophosphamide, Oncovin, Prednisone. ATRA: Transretinoic acid. CalgB: Cancer and Leukemia Group B. VDC: Velcade, Cyclophosphamide, Dexamethasone. POMP: Procarbazine, Oncovin, Mecloretamina, Prednisone.

	Multivariate		Multilevel	
Time to start treatment (Up to 40 days)	0.005	103.25 (4.16–2.559.69)	0.059	-
COP	0.026	0.09 (0.01–0.75)	0.116	-
ATRA	0.122	-	-	-
Idarubicin	0.032	0.12 (0.02–0.84)	0.134	-
Daunorubicin	0.988	-	-	-
Filgastrin	0.989	-	-	-
CalgB	< 0.001	0.09 (0.03–0.26)	0.005	0.23 (0.08–0.64)
Cytarabine	0.765	-	-	-
VDC	< 0.001	11.7 (4.09–33.85)	< 0.001	10.64 (3.78–29.86)
Zoledronate	< 0.001	4.42 (1.97–9.92)	0.006	3.20 (1.41–7.29)
Pamidronate	0.012	4.60 (1.40-15.12)	0.032	3.86 (1.12–13.32)
POMP	0.989	-	-	-
Talcidity	0.052	-	-	-
Imatinib	0.136	-	-	-
Granulokine	1.000	-	-	-
Others	0.025	0.32 (0.12–0.87)	0.21	-

* $p < 0.05$, multinomial logistic regression. Sample unit = event. SAH: Systemic Arterial Hypertension; CD: Coronary disease; BMI: Body Mass Index; CT: Chemotherapy; COP: Cyclophosphamide, Oncovin, Prednisone. ATRA: Transretinoic acid. CalgB: Cancer and Leukemia Group B. VDC: Velcade, Cyclophosphamide, Dexamethasone. POMP: Procarbazine, Oncovin, Mecloretamina, Prednisone.

When performing the same procedure with the variables involved in the treatment, it was found that the use of COP, Idarubicin, CalgB, and others were inversely associated, reducing by 0.09, 0.12, 0.09 and 0.32 times, in this order, the prevalence of episodes with decreased CKD-EPI, independently of the others. However, the use of VDC, Zoledronate, Pamidronate increased, respectively, 11.77, 4.42, 4.60 the chances of occurring the renal dysfunction event (Table 5).

Finally, another analysis of the variables described above was made, highlighting that, independently, the female gender and the diagnosis of MM are associated with a greater probability of occurring episodes

with renal dysfunction in 2.26 and 5.75 times, respectively. This fact also happened with the use of Vidaza, Zoledronate, and Pamidronate, increasing the chances by 10.64, 3.20, and 3.86 times, respectively. On the other hand, the use of CalgB was inversely associated with the occurrence of episodes with low GFR, reduced by 0.23 times (Table 5).

Discussion

Renal impairment in patients with oncological hematology mainly comes from nephrotoxicity caused by the excretion of chemotherapy drugs. The dysfunctionality of this organ relates to the suspension of antineoplastic treatment, increased costs, reduced quality of life, and, among others, the increase in mortality [14, 11, 15, 16].

The present research, evaluated in episodes, found that 52.4% of the participants had reduced GFR according to the result of the CKD-EPI formula. One study showed that, in patients with CLL, approximately 15% of the patients developed some degree of renal dysfunction [17].

The significance of females with a higher number of episodes of reduced GFR may be associated with MM, and this fact is reaffirmed by other studies in which women are predominant with this disease [18–20] and patients with MM are more prone to kidney injury [21, 22]. Research shows that, in developing countries, this scenario is visualized, but when it comes to first world countries, there is a balance between the sexes in the diagnosis of MM [23].

The influence of the diagnosis of MM with renal impairment has a broad scientific basis since 20 to 40% of patients with MM have renal dysfunction at the time of diagnosis. There are reports that the chemotherapy plan can reverse this dysfunctionality even in patients with low GFR rates [24]. However, the interaction of MM with renal dysfunction impacts on the survival time of affected patients, presenting an average of two years when renal function is normal and, in the presence of failure, the time is reduced by 50% [25–27].

The CalgB protocol is applied in hematological neoplasms, mainly in leukemias and their various aspects. The scheme in question in the present study is composed of oncovin, dexamethasone, and doxorubicin showing relation with GFR. Oncovin is a chemotherapy that has the main adverse effect on neurotoxicity [28, 29]. Dexamethasone is a potent anti-inflammatory used in the treatment of numerous diseases whose mechanism of action is aimed at minimizing the inflammatory state (attenuating chemokines and cytokines) and increasing vascular permeability [30–32]. It has been reported that its activity decreases the breakdown of the glycocalyx and improves renal perfusion, thereby reducing renal dysfunction [33, 34]. Doxorubicin, on the other hand, is a versatile and effective anticancer used in several types of neoplasms. However, it triggers cardiotoxicity, hepatotoxicity, nephrotoxicity, pulmonary, and hematological toxicity [35, 36]. After performing the multivariate and multilevel analysis, it was found that the therapeutic set is inversely associated with a reduction in GFR, that is, its use is less harmful to the kidneys, causing mild protection. This fact can occur due to the beneficial action of dexamethasone in

protecting and recovering from kidney damage. There is still a deficit of scientific findings specifically about this protocol. However, when drugs are analyzed separately, there is a greater collection.

The VCD protocol was statistically relevant in the analyses, being independently related to the decrease in GFR, causing an impact more than ten times. The proteasome inhibitor antineoplastic, such as Vecalde present in the VCD protocol, is widely used for the treatment of MM and mantle cell lymphoma. Its action consists of the degradation of proteins, essential for cell hemostasis, and the accumulation of these fragments triggers the process of cell death [37]. In addition, it also has the effect of minimizing the action of the immune system [38, 39]. There are reports of its benefits in the kidney, causing an improvement in renal function. Another study points out that there is a need for further analysis about the dosage of the drug to verify its efficiency [40]. The second member of the scheme is dexamethasone, whose beneficial action on the renal system reduces the possibilities of dysfunction and progression to the installation of CKD [35]. Cyclophosphamide is the last component of the VCD protocol, being conceptualized as an immunosuppressive and antineoplastic drug that has ample potential for nephrotoxicity. This research showed a direct association between renal dysfunction and the use of this protocol (VCD), which, despite comprising a drug considered nephroprotective, has more dominant characteristics of the action of the two drugs that are harmful to the kidneys. The properties of Vecalde support the findings in which most patients are in the first and second chemotherapy cycles.

The use of bisphosphonates stands out as harmful to the kidneys with a decrease in GFR, and this risk can vary between 3 to almost 4 times. Bisphosphonates, zoledronate, and pamidronate are used to restore bone mineral density, minimizing the possibility of fractures and treating malignant hypercalcemia [41]. In the context of cancers, bisphosphonates hinder malignant osteolysis, neoplastic growth, and bone destruction, and, in particular, zoledronate has antitumor and antiangiogenic characteristics [42]. This pharmacological group can be used in patients with MM and bone metastases due to breast, prostate, lung, and other soft tissue cancer [43]. It should be noted that nitrogenous bisphosphonates do not have specific enzymes that recognize and metabolize them, causing an accumulation of bisphosphonates in the cortex and renal medulla [44]. When the drug cannot be absorbed, it is excreted unchanged by the kidney, damaging it, a fact that can be modified according to the dose administered [45]. About 63% of patients with MM developed renal dysfunction due to the use of this drug [46]. The literature largely reinforces the present research above, confirming the harmful action of bisphosphonates in the kidneys. Its use must be accompanied by more rigorous monitoring of renal function at each cycle and/or application with verification of serum creatinine, urea, electrolyte values, in addition to the calculation of GFR.

In oncohematological patients, the prevalence of renal disorders is high, affecting women more, increasing the probability of the event by more than two times, and the diagnosis of MM has an independent influence, increasing the chance of episodes with reduced GFR by 5.75 times. The pharmacological protocol CalgB is inversely associated with GFR reduction events, minimizing the chances of renal dysfunction by 0.23 times. On the other hand, the VDC, zoledronate and pamidronate

therapeutic regimens are related to higher chances of episodes of reduced GFR, and specifically, the VDC protocol increases the chances of occurring this change by more than ten times.

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Helena Pitombeira and Jacqueline Holanda de Sousa designed the model, conducted the research, revised the text and read and approved the final version.

Ana Paula Negreiros Nunes Alves designed the study. She read and approved the final version.

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