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Evaluation of Acute Kidney Injury and Hypomagnesemia in Patients with Head and Neck Cancer Treated With Cisplatin and Radiotherapy

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ABSTRACT

Hypomagnesemia is one of the most common side effects for patients who receive cisplatin in chemotherapy. However, the relative importance between Hypomagnesemia and cisplatin nephrotoxicity has not been thoroughly discussed. Acute Kidney Injury (AKI) in patients who get cisplatin is frequent, and the evaluation of kidney functions in patients taking nephrotoxic drugs is critical. The objective is to evaluate AKI incidence based on the AKIN scale and Hypomagnesemia in patients with head and neck cancer (HNC) who have taken cisplatin. 50 patients with HNC treated with three cycles of cisplatin (100mg/m2/dose) were evaluated. Blood and urine samples were collected 24h before taking the cisplatin, 24h after infusion, 48h after each application, and 35 days after finishing the treatment (C-reactive protein, creatinine, glomerular filtration rate (GFR), Lactic dehydrogenase, plasma magnesium). AKI was observed in 78% of the patients. There was an increase in creatinine, urea and a decline in GFR after each cisplatin cycle. An increase in creatinine, CRP, and reduction of GFR were evidenced in AKI patients compared to non-AKI patients. AKI was observed in 78% of patients with HNC patients treated with cisplatin, as well as a correlation of creatinine and GFR while showing a kidney injury. There was a decrease in plasma magnesium even in the samples of patients who did not have any kidney injury. However, there was no significant statistical distinction in the AKIN groups, which shows that Hypomagnesemia is an essential effect of cisplatin even in patients without kidney injury.

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KEYWORDS:

Head and Neck Neoplasms, Acute Kidney Injury, Hypomagnesemia, Cisplatin, Radiotherapy.

INTRODUCTION

Kidney impairment is common among patients with cancer due to the illness or drugs used for the treatment, usually chemotherapeutic drugs. Kidney function evaluations are essential in managing a safe treatment and accompanying chemotherapeutic effects, especially in subjects with head and neck cancer, who are treated predominantly with cisplatin; the main dose-limiting side effect is nephrotoxicity [1].

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The kidney stores cisplatin to a higher degree than other organs and is the primary route for excretion. The cisplatin concentration in proximal tubular epithelial cells is about five times the serum concentration. The drug´s kidney toxicity depends on the dose taken and consequently limits the increase of the quantities, which might affect the efficiency of the treatment. Toxic effects occur primarily in proximal tubules, especially in segment S-3, and the glomeruli and distal tubules are involved in a later process. Chronic nephrotoxicity is rare because, in general, patients recover from acute toxicity caused by the drug. Cisplatin nephrotoxicity can exhibit in several ways. However, the most serious and one of the more typical presentations is AKI which occurs in 20–30% of patients, and Hypomagnesemia is also common (40–100%), particularly after repeated doses of

cisplatin, even in the absence of a fall in the glomerular filtration rate[1, 2].

Hypomagnesemia results in other modifications in renal tubular function in keeping the electrolytic balance; frequently, it is observed in conjunction with other electrolyte imbalances, including hypokalemia and hypocalcemia, as well as metabolic acid-base disturbances[2,3].

Antineoplastic drugs are believed to influence magnesium absorption when acting in the ascendant portion of the thick segment of the loop of Henle (AEAH)[4]. In hypomagnesemia states, the mineral is reabsorbed in AEAH; in this situation, the urine eliminates less than 2% of the filtered. Other researchers report that cisplatin performs toxic effects also in distal tubules by depolarizing the apical membrane, which increases magnesium and potassium excretion.

Magnesium depletion also raises the nephrotoxicity induced by cisplatin, which agrees that hydration with this ion supplement reduces the nephrotoxicity induced by the drug[1]. Besides, recent multivariate analysis studies have shown that hypomagnesemia is an independent risk factor for maintaining kidney collapse[5] and is associated with mortality in the final phases of kidney diseases. It is essential to highlight that cisplatin might have a cumulative effect bringing hypomagnesemia persistence for many years.[3]

Although hypomagnesemia represents a common side effect in patients who take chemotherapy with cisplatin, since this is part of the group of drugs that interfere in tubule magnesium resorption[3], the relevance between hypomagnesemia and nephrotoxicity induced by cisplatin has not been wholly discussed[6,7,8]. No research data specifies the incidence or proportion of hypomagnesemia in HNC patients treated with radiotherapy and chemotherapy. This is the first study using a homogeneous cancer population to raise such information.

This paper aims to evaluate the incidence of AKI through the AKIN scale and hypomagnesemia in patients with head and neck cancer who took cisplatin.

METHODOLOGY

This research was approved by UNIOESTE Research Ethic Committee, according to document number 272/2012-CEP. The study was observational and prospective; the data were collected between October 2012 and November 2013. All patients who understood the treatment and its conditions signed the term of free and informed consent and allowed the collection and use of information for the study.

Data from 50 patients were analyzed. All of them were more than 18 years old, diagnosed with Head and neck cancer, and under a treatment protocol of three cycles of chemotherapy based on a dose of 100 mg/m2 of cisplatin associated with radiotherapy (70 Gy).

Patients previously treated with cisplatin, patients with GFR < 60ml/min/1,73m2, with non-controlled hypothyroidism or hyperthyroidism, and those who did not want to submit to blood or urine collection were excluded from the study.

Blood and urine samples were collected 24h before the chemotherapy (D0, D21 e D42), 24h after it (D1, D22 e D43), 48h after it (D3, D24 e D45), and also 35 days after the last section of cisplatin (D78). Lab exams collected were: C-reactive protein, creatinine, GFR, Lactic dehydrogenase (LDH), and plasma magnesium. Other exams collected 24h before each application of chemotherapy were: Blood cell analysis, urea, sodium, potassium, albumin, glycemia, alkaline phosphatase, glutamic-pyruvic transaminase, and urine I.

The dose of chemotherapy was calculated using Du Bois Formula, adjusted to the body surface[9]. Creatinine was dosed in mg/dL by Jaffé methods without deproteinization, and afterward, GFR was calculated in ml/min/1,73m2 by aMDRD formula[10, 11].

AKIN classification[12] was used as defining criterion and AKI staging in all the observations cycles, as follows: AKIN 1: increase in creatinine higher than 0,3mg/dL, AKIN 2: increase ≥100% and <200%; AKIN 3: increase ≥200% to baseline creatinine considering a segment of 48h. Another AKI criterion used for the comparison analysis between patients with and without AKI throughout the study was the increase of 0,3mg/dl in the value of baseline creatinine (D0). Residual renal dysfunction was considered when GFR <60 ml/min/1,73m2 in D78. Serum concentration considered normal for PCR was from zero to 1,0 mg/dL[13] and for magnesium was from 1,6 to 2,3 mg/dL[14].

For the statistical analysis, the quantitative variables were expressed as average ± standard deviation or median according to normal or non-normal data. Fisher exact test or chi-square was applied to compare categorical variables. For the comparison of independent groups, the Student T-test was used when data showed normality; the Mann-Whitney non-parametrical test when the data normality hypothesis was rejected; nonparametric analysis of variance (Kruskal-Wallis) was used in the comparison between two or more groups. They were analyzed by treatment cycle (three in each) and throughout the research to evaluate lab exams.

The spearman coefficient was used to evaluate the correlation among continuous variables with non-normal distribution. Variables from the groups with and without AKI were compared. A significance level of 5% ($p < 0,05$) was adopted. Data was stored in a Microsoft Excel database and analyzed in R Software (SPSS version 13.0).

RESULTS AND DISCUSSION

Clinical characteristics

A total of 50 patients with HNC were elected to the study, and they were aged medium 58,5 years old, and 80% of them were male. As for the histopathological exams, 94% of the tumors were classified as squamous cell carcinoma,

44% originated in the oropharyngeal area, 20% larynx, and 14 % oral cavity. The most frequent clinical stage was IV in 70% of the cases. Regarding comorbidities, seven patients were hypertensive, four were diabetic, and those were without CKD. Table 1 shows the initial clinical and laboratory characteristics of patients included in the study.

It was detected a decreased GFR, increased serum creatinine, and urea in the samples collected 48h after applying cisplatin (D3-TFG: 70.75 ml/min/1, 73m2, creatinine 1.11 mg/dL, BUN: 46 mg/dL), GFR-D24: 52,84 ml/min/1, 73m2; creatinine 1.4 mg/dL; BUN: 54.05 mg/dL) and D45 - GFR: 54.2 ml/min/1, 73m2; creatinine 1.21 mg/dL; BUN: 60.25 mg/dL) and D78 (GFR: 71.02 ml/min/1, 73m2, creatinine 1.11 mg/d; BUN: 40.95 mg/dL) compared to D0 (TFG: 100.7 ml/min/1, 73m2, creatinine 0.81 mg/dL, BUN: 30.05 mg/dL), as well as compared to the previous use of cisplatin (D0 - D21 GFR days: 76 10 ml/min/1, 73m2, creatinine: 1.01 mg/dL; BUN: 37.7 mg/dL) and D42-TFG: 75.24 ml/min/1, 73m2; creatinine: 1.03 mg /dL; BUN: 54.05 mg/dL) and 24h followed cisplatin use (D1 - TFG: 90.01 ml/min/1, 73m2, creatinine 0.84 mg/dL, urea: 26.0 mg/dL), D22 - GFR: 80.6 ml/min/1, 73m2; creatinine 0.99 mg/dL; BUN: 30.9 mg/dL) and D43 - GFR: 85.7 ml/min/1, 73m2; creatinine 0.95 mg/dL; BUN: 34.7 mg/dL) ($p < 0.05$).

Also, a reduction in the levels of serum magnesium was observed to baseline (D0), and this difference was statistically significant only from the D22 ($p <0.05$). PCR increased on days D22, D42, and D43 concerning D3 ($p <0.05$), as described in Table 2.

The incidence of AKI

From the total of the patients analyzed (n = 50), 78% developed AKI during the study. According to AKIN classification in Cycle 1, 26% of patients developed ARF, 17% of them AKIN 1 and 9% AKIN 2; in cycle 2, 42% developed AKI, 21% AKIN 1, 19% AKIN 2, 2% AKIN 3; in cycle 3, there was an incidence of AKI in 29% of the patients, 20% AKIN 1, 6% AKIN 2 and 3% AKIN 3 (data not shown). There was a need to reduce the dose of the drug in nine patients (18%), and such use was suspended in D43 in two of the patients (4%) because of febrile neutropenia and in three of them (6%) because of AKI, according to the institution protocol.

Comparison of groups with and without AKI

When clinical and baseline lab exams from the patients with and without AKI were compared, it was not observed a significant statistical difference between the groups ($p>0,05$). When evaluating laboratory tests in three cycles comparing groups with and without AKI, it was observed an increase in CRP and creatinine and a decrease in GFR, which was statistically significant only in the levels of creatinine and GFR for patients with AKI compared with patients without ARF from D21 ($p <0.05$). In contrast, CRP was significantly increased only at D42 ($p <0.05$), and serum magnesium was not significantly different in both groups over the study. These data are presented in Table 3.

In the Spearman correlation analysis among the creatinine, GFR, CRP, DHL, and magnesium levels, a negative correlation between creatinine and GFR in all cycles ($p = 0.000$) was observed. Also, a positive correlation was noticed between creatinine and magnesium in cycle 2 ($p=0.020$) 48h after the application of the cisplatin.

Residual dysfunction after treatment

At the end of the study (D78), 32% (n = 16) still had GFR below 60 ml/min, statistically significant compared to patients without renal dysfunction (Table 4). All other variables showed no statistically significant difference between the groups with and without residual renal dysfunction.

The use of chemotherapy and radiotherapy increases the risk of acute toxicity compared with isolated radiotherapy[15], [16]. Throughout the study, 78% of the analyzed patients increased more than 0.3 mg/dL baseline creatinine and, for the AKIN scale, 62% developed ARF during the observation of the study, 26% of them developed ARF in the first cycle, 42% in 2nd Cycle 2 and 29% in the third cycle. The incidence of ARF by cisplatin in scientific studies is around 20% -40%, which is observed by using criteria such as creatinine and GFR data isolated[17]. At the end of the study (D78), 32% (n=16) still had GFR below 60ml/min with the potential for progression to chronic kidney disease, which contradicts the scientific literature that reports that there is a normalization of renal function of most patients who use cisplatin[18].

The criteria AKIN[12] or RIFLE[19] has tried to redefine and prevent ARF, which parameters are based on serum creatinine and urine output. Many studies have shown that elevation of serum creatinine alone is not parallel to kidney damage, and following this criterion could delay the clinical diagnosis[26]. The classification of the risk of AKIN with an increase of 0.3 mg/dL from baseline creatinine within 48h indicates subclinical renal damage (AKIN 1), which clinicians and oncologists often overlook since it is a scale used especially in critically ill patients, and this could interfere with a higher incidence of drug-related ARF, particularly cisplatin, than when using only the value of GFR or creatinine. The study revealed that there was a decrease in GFR and an increase in serum creatinine and urea 48h after each session with cisplatin, which shows the equivalence to demonstrate the change in renal function on these tests, but only after and not previous to a new exposure to the drug (2nd and 3rd cycles).

Hypomagnesemia is one of the side effects common in patients who are under chemotherapy treatment containing cisplatin. The study has shown decreased serum magnesium levels even in samples from patients who did not have a renal

injury, despite not having a statistically significant difference according to the AKIN groups, which shows that hypomagnesemia is an essential effect of cisplatin even in those patients without renal injury[17,18]. However, the importance of observing hypomagnesemia and nephrotoxicity induced by cisplatin has yet to be completely discussed[20,21].

A recent study by Alves et al. (2013) showed that hypomagnesemia was higher in patients who did not recover renal function (70% vs. 31%). Also, with multivariate analysis, the research identified hypomagnesemia as an independent risk factor for non-recovery of renal functions[22]. Studies in mice suggest that hypomagnesemia could cause dehydration and up-regulation of the cisplatin receptor, the organic cation transport (OCT2), which increases the renal accumulation of cisplatin and makes ARF worse[23].

Biomarkers of acute kidney injury have been extensively studied in the definition of ARF[24], especially in ischemic ARF, either experimentally or in clinical scenarios in which ischemia is expected (e.g., sepsis and cardiopulmonary bypass). Although few clinical studies in cancer patients have been done, there are several publications on the cellular mechanism of cisplatin nephrotoxicity and a considerable amount of biomarkers studies on ARF with a nephrotoxic origin, mainly in preclinical research, which include nephrotoxicity to cisplatin[25].

There are few scientific reports evaluating the cisplatin clinical toxicity and its objective measures by biomarkers that detect early kidney injury in patients with head and neck cancer, where the use of high doses of cisplatin significantly increases the incidence of ARF and its nephrotoxicity, which is a significant limitation to the drug use in the cancer treatment, including head and neck tumors.

Our study has a few limitations. First, it was an observational study and is likely to be affected by several biases, including the absence of a control group and possible confounding through unmeasured variables. Finally, the simple group and single-center design may interfere with its external validity and generalizability.

CONCLUSIONS

This study has demonstrated an increased rate of ARF in 78% of patients with head and neck cancer who used three cycles of cisplatin and equivalence of creatinine and GFR in demonstrating renal injury 48h after the sessions with cisplatin application. There was a decrease in serum magnesium levels even in samples from patients who did not have a renal injury, despite not showing a statistically significant difference according to the AKIN groups, which shows that hypomagnesemia is an essential effect of cisplatin even in patients without renal injury. These data allow us to conclude that identifying patients at risk for acute renal injury induced by cisplatin could stimulate strategies for treatment and prevention of nephrotoxicity or even forbidding the drug. These data need to be replicated and validated in prospective, randomized studies.

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TABLES

Table 1. Initial clinical and laboratory characteristics (D0) of patients with head and neck cancer treated with cisplatin and radiotherapy*.

Variable		**n (%)**
Gender	Male	40 (80%)
	Female	10 (20%)
Histopathological	Adenocarcinoma	2 (4%)
	Adenoid cystic carcinoma	1 (2%)
	Squamous cell carcinoma	47 (94%)
Local of the tumor	Oral cavity	7 (14%)
	Oropharynx	22 (44%)
	Other	11 (22%)
Clinical staging	III	15 (30%)
	IV	35 (70%)
Variable		**Mean ± standard deviation**
Age		58,5 ± 9,1
Creatinine (mg/dL)		0,83 ± 0,23
GFR (mL/min/1,73m^2)		108,3 ± 35,5
Urea (mg/dL)		30,1 ± 8,9
Magnesium		2,0 ± 0,2
Sódium (mEq/L)		136,4 ± 3,7)
Potassium (mEq/L)		4,4 ± 0,4
Cálcium (mg/dL)		9,2 ± 0,6

CRP (mg / dL)	2,3 ± 4,0
LDH (U / L)	199,8 ± 70,4
Hemoglobin (g / dL)	13,0 ± 1,6
Lymphocytes (cells/mm3)	1898,1 ± 691,1
Albumin (g / dL)	5,2 ± 6,2
SGPT (U / L)	84,8 ± 32,4
Alkaline phosphatase (U / L)	9,2 ± 0,5)

*Laboratory evaluation in samples collected throughout the study

Table 2. Results of laboratory tests (median) on all days studied in patients with head and neck cancer treated with cisplatin

Variáveis	D0	D1	D3	D21	D22	D24	D42	D43	D45	D78
Mg (mg/dL)	1,99	1,84	1,92	1,77	1,64†	1,72†	1,49†	1,44†	1,49†	1,43†
Cr (mg/dL)	0,81	0,84	1,11•	1,01	0,99	1,40•	1,03	0,95	1,21•	1,11†
GFR (mL/min/1,73m^2)	100,7	90,01	70,75•	76,10	80,60	52,84•	75,24	85,07	54,20•	71,02†
Urea (mg/dL)	30,05	26,00	46,00•	37,70	30,90	54,05•	40,60	34,70	60,25•	40,95†
PCR (mg/dL)	0,98	0,93	1,08	1,91	3,00	1,68	4,74†	4,55†	2,64	2,37

!! p<0,05 (Kruskal-Wallis-Method Dunn) related to D1

† p<0,05 (Kruskal-Wallis- Method Dunn) related to D0 and D1

‡ p<0,05 (Kruskal-Wallis- Method Dunn) related to D0 and D1 and days during 24h of cisplatin (D22 e D43)

• p<0,05 (Kruskal-Wallis- Method Dunn) related to the baseline values before each cycle (D0, D21 e D42) and in 24h after cisplatin (D1, D22 e D43)

ABBREVIATIONS: Mg: magnesium, Cr: creatinine, GFR: glomerular filtration rate, NGAL: lipocalin associated to neutrophil gelatinase, CRP: C-reactive protein

Table 3. Clinical and laboratory data of D78 of patients treated with cisplatin for head and neck cancer according to the occurrence of Residual ARF

Variable	ARF (n=39)	No ARF (n=11)	p value
Age	58,1±8,9	60,3±9,5	0,725†
Male gender (n)	31 (79%)	10 (90%)	0,807*
Body surface area (m2)	1,6±0,3	1,56±0,16	0,325‡
Creatinine (mg/dL)	0,80±0,18	0,88±0,35	0,914†
GFR (mL/min/1,73m2)	109,2±34,5	103,7±38,9	0,350‡
Urea (mg/dL)	29,93±9,1	30,4±7,9	0,476†
Magnesium (mg/dL)	1,96±0,25	2,02±0,20	0,085†
Sodium (mEq/L)	136±3,4	136,88±4,7	0,865‡
Potassium (mEq / L)	4,3±0,37	4,76±0,37	0,848†
Calcium (mg/dL)	9,1±0,52	9,6±0,72	0,200‡
CRP (mg/dL)	2,23±3,92	2,6±4,4	0,982‡
LDH (U/L)	202,7±76,1	196,6±35,5	0,742‡
Hemoglobin (g/dL)	13,1±1,6	12,3±1,2	0,326†
Lymphocytes (cells/mm3)	1819,8±733,5	1821,4±521,37	0,370†
Albumin (g/dL)	4,2±0,39	3,9±0,32	0,400†
SGPT (U/L)	26,9±15,8	22,27±16,7	0,394‡
Alkaline phosphatase (U/L)	87,8±33,5	66,51±15,3	0,063‡

* p value in Fisher exact test; † p value in Student T test; ‡ p value in Mann-Whitney test.

Table 4. Clinical and laboratory data of D78 of patients treated with cisplatin for Head and Neck cancer according to the occurrence of Residual ARF

Variable	With residual disfunction (n=16)	Without disfunction (n=11)	p value
Age (years)	59,3±9,6	60,8±9,5	0,342†
Males (n)	11 (68%)	10 (90%)	0,771*
Body surface area (m2)	1,71±0,23	1,5±0,16	0,126‡
Creatinine (mg/dL)	1,60±0,48	0,8±0,2	<0,0001‡
GFR (mL/min/1,73m2)	46,38±10,28	104,6±40,1	0,0010†
Urea (mg/dL)	65,6±35,0	50,48±38,03	0,135‡
Magnesium (mg/dL)	1,63±0,31	1,5±0,2	0,316‡
Sodium (mEq/L)	132,7±4,8	133,2±3,9	0,891‡
Potassium (mEq/L)	4,8±0,9	4,4±0,38	0,640‡
Calcium (mg/dL)	9,0±0,7	8,7±0,4	0,427†
CRP (mg/dL)	5,2±5,0	2,5±1,8	0,192‡
LDH (U/L)	188,4±43,1	195±85,7	0,841‡
Hemoglobin (g/dL)	10,19±1,46	10,8±0,68	0,420†
Lymphocytes (cells/mm3)	852,1±359,3	745±438	0,438†
Albumin (g/dL)	3,7±0,4	3,6±0,4	0,828†
SGPT (U/L)	23,9±18,0	17,1±9,0	0,473†
Alkaline phosphatase (U/ L)	100,4±30,8	85,6±28,0	0,150†

* p value in Fisher exact test; † p value in Student T test; ‡ p value in Mann-Whitney test.