Magnesium Supplementation and Cisplatin-Induced Renal Impairment in Cancer Patients

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Cisplatin-induced renal dysfunction represents a limiting complication in patients receiving chemotherapy. Various preventive strategies have been implemented and various guidelines recommend magnesium supplementation. Twenty-four patients receiving cisplatin regimens and magnesium supplementation were assessed before, during and at the end of chemotherapy cycles. Renal impairment is generally expected to occur in up to 75% of the patients; our study reports this side effect in 20.8%, with a median decrease in the creatinine clearance of 11.2%.

Keywords: renal dysfunction, cisplatin, hypomagnesemia, cancer

Cisplatin is a platinum-based alkylating compound used in a broad spectrum of malignancies, improving both survival and cure in various settings. However, due to its renal excretion and accumulation in the proximal tubes, it frequently leads to dose-limiting toxicity such as nephrotoxicity [1]. The mechanisms involved in cisplantin-induced renal dysfunction include DNA damage, mitochondrial dysfunction, increased tumor necrosis factor (TNF) and oxidative stress [2-4].

Hypomagnesaemia is a frequently reported in patients undergoing chemotherapy with cisplatin [5], as a consequence of renal tubular cell damage and alterations induced in Ca^{2+}/Mg^{2+} receptors. In preclinical models, cisplatin treatment increased Mg^{2+} excretion through a down-regulation of transient receptor potential subfamily Melastatin (TRPM6) and epidermal growth factors (EGF), suggesting a possible role of EGFR pathway in cisplatin-induced nephrotoxicity and hypomagnesaemia [6]. Yokoo et al. reported that hypomagnesaemia could induce the up-regulation of the organic cation transporter 2 (rOCT2), expressed in the proximal tubules, favoring the renal accumulation of cisplatin and thus, inducing acute renal injury [7]. The same authors also suggest that decreased Mg^{2+} levels reduce the expression of multidrug and toxin extrusion protein 1 (rMate1), a protein involved in cisplatin transport from the proximal tubule into the urine.

Another mechanism involved in cisplatin-induced nephrotoxicity is through the toxic generation of reactive oxygen species (ROS) that bind to various molecules, including anti-oxidant gluthatione [8]. Genetic predisposition to platinum-induced renal dysfunction include individuals with polymorphisms in genes for DNA repair enzymes such as ERCC2 and XPC [9, 10].

In clinical practice, the use of platinum agents is limited to patients with a good performance status and a creatinine clearance (CrCl) > 60mL/min. The use of anti-inflammatory drugs, as well as older age are associated with increased rated of cisplatin-induced renal dysfunction. Moderate to severe nephrotoxicity has been reported in up to 75% of patients who received various administration schedules, with higher incidence in those receiving more than 75mg/m^2 [11]. Various approaches to prevent cisplatin-induced kidney injury include various hydration regimens, which reduced cisplatin half-life and proximal tubule transit time [12], as well as magnesium supplementation as it can decrease tubular damage [13]. Although magnesium intake can be suggested, it is not systematically included as a preventive measure against cisplatin-induced nephrotoxicity.

The current study aims to evaluate the incidence of renal dysfunction in patients undergoing chemotherapy with cisplatin using magnesium supplementation alongside standard hydration regimen.

Experimental part

Material and methods

A retrospective study was conducted at Victoria Hospital Iasi that included patients with metastatic non-small cell lung cancer and hepato-billiary cancers treated between 2010-2018 with cisplatin-based regimens and undergoing magnesium supplementation. Twenty-four patients were included in the study. Hospital charts were reviewed in detail and blood tests that included serum creatinine, serum albumin and serum electrolytes including magnesium levels were documented before each cycle and at day 8 after chemotherapy. Creatinine clearance was calculated according to Cockroft–Gault formula, taking into account patient's body weight in each chemotherapy cycle, apart from patient's age and gender. Nephrotoxicity was defined as renal function decline characterized by a creatinine clearance < 60mL/min.

Patients were treated in first line with Cisplatin 75mg/m^2 and Gemcitabine administered every three weeks for their cancers. None of the patients have previously received platinum agents as part of their treatment. Blood tests that included serum creatinine, serum albumin and serum electrolytes including magnesium levels were documented before each cycle and at day 8 after chemotherapy. Creatinine clearance was calculated according to Cockroft–Gault formula, taking into account patient's body weight in each chemotherapy cycle, apart from patient's age and gender. Nephrotoxicity was defined as renal function

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decline characterized by a creatinine clearance < 60mL/min.

All patients received pre-hydration of 1 liter of 0.9% sodium chloride and 8mEq (1g) of magnesium sulfate infused intravenously over 1 hour prior Cisplatin and a minimum of 500 mL of 0.9% sodium chloride solution infused over 2 hours following Cisplatin administration. In case of decreased magnesium levels below 1.8mg/dL, patients were instructed to use oral magnesium supplementation.

Results and discussions

Twenty-four patients were included in the present study, between 59 and 79 years old. The mean age of the population was 68 years old. Six patients (25%) were female and eighteen patients (75%) were men, with a mean age of 68.08 years old. Ten patients were diagnosed with advanced biliary tract tumors and twenty-four patients had advanced non-small cell lung carcinoma (table 1).

Although with a good performance status (PS 0-1), most patients had associated comorbidities such as arterial hypertension (66.5%), diabetes (29.12%), myocardial infarction that occurred earlier than 6 months (16.64%) and pulmonary comorbidities such as chronic obstructive pulmonary disease (COPD) or asthma.

Most patients (83.3%) underwent chemotherapy for six or more cycles, as four patients experienced dissuade progression under treatment and so, chemotherapy protocol needed to be changed. Disease progression was documented by imaging evaluations such as computer tomography. Nephrotoxicity occurred in 5 patients (20.8%) at the end of chemotherapy.

Table 2 shows the incidence of renal function and serum magnesium levels decline induced by chemotherapy with Cisplatin before chemotherapy and at the end of the treatment. There was an 11.2% median decrease in creatinine clearance and a 22.3% decrease in serum magnesium level in our group of patients. Paired T-test showed significant difference between creatinine clearance levels ($n=24$, $p=0.032$) and also between serum magnesium levels ($n=24$, $p=0.000$) before first cycle and at the end of the treatment.

In order to assess if the decrease in renal function was correlated with the occurrence of hypomagnesemia, we performed Spearman correlation analysis. The test showed a moderate correlation that was not statistically significant ($n=24$, $r^2=0.352$, $p= 0.092$).

Patients' characteristics	Number of patients (Percentage %)
Gender	
Female	6 (25%)
Male	18 (75%)
Age	
<65 years old	6 (25%)
65-75 year old	15 (62.5%)
>75 years old	3 (12.5%)
Performance status	
PS 0	15 (62.5%)
PS 1	9 (37.5%)
Comorbidities	
Arterial hypertension	16 (66.5%)
Atrial fibrillation	2 (8.32%)
Myocardial infarction	4 (16.64%)
Diabetes	7 (29.12%)
Chronic obstructive pulmonary disease (COPD)	2 (8.32%)
Asthma	3 (12.48%)
Other	4 (16.64%)
None	2 (8.32%)
Tumor type	
Biliary tract cancer	10 (41.7%)
Non-small cell lung cancer	14 (58.3%)
Completed chemotherapy cycles	
<6 cycles	4 (16.7%)
6-7 cycles	14 (58.3%)
8 cycles	6 (25%)

Table 1
PATIENTS' CHARACTERISTICS

	First chemotherapy cycle	Last chemotherapy cycle
Creatinine clearance (CrCl) Mean (ml/min)	83.91±27.24	74.55±20.72
Creatinine clearance (CrCl) decrease %	-	11.2
Serum magnesium levels mean	1.80±0.20	1.40±0.28
Serum magnesium levels decrease %	-	22.3

Table 2
DECREASED CREATININE CLEARANCE AND SERUM MAGNESIUM LEVELS DURING CHEMOTHERAPY ADMINISTRATION

The ROC-AUC values of serum magnesium levels associated with renal function deterioration during chemotherapy lacked sensitivity or specificity, as seen in figure 1 (AUC <0.7 and p=0.1).

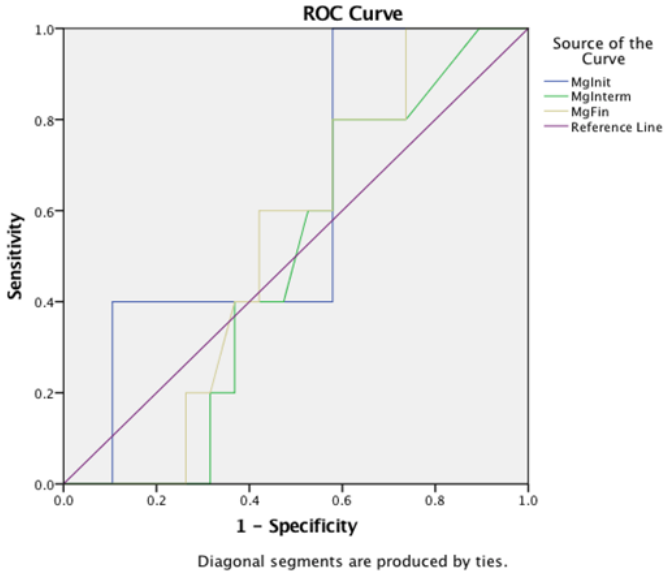

Fig. 1. ROC curve for serum magnesium levels during treatment in predicting creatinine clearance decrease

Renal dysfunction during chemotherapy with cisplatin remains a restrictive factor for its clinical use in the treatment of various solid tumors [14]. The incidence of cisplatin nephrotoxicity varies between 25 to 75% of patients receiving platinum based chemotherapy and in some patients this occurs after the first chemotherapy cycle [11]. Reduction in creatinine clearance is also linked to the number of treatment cycles, as cisplatin therapy can induce progressive and permanent nephrotoxicity despite various preventive strategies [15].

Even when recommended hydration for preventing renal dysfunction is provided, patients receiving cisplatin may develop nephrotoxicity. Hypomagnesemia is frequently reported in patients undergoing chemotherapy with cisplatin and magnesium supplementation is recommended [16]. However, it is not a universally used approach and the adequate dose of magnesium for preventing nephrotoxicity is still unknown.

Although we did not find a statistically significant correlation between hypomagnesemia and renal dysfunction, we should take into account that magnesium supplementation was performed in all patients prior to chemotherapy and also during the treatment cycles if magnesium levels were found lower than the normal value. In patients treated with cisplatin, hypomagnesemia can contribute to renal impairment as a consequence of renal tubular cell damage and alterations induced in Ca^{2+}/Mg^{2+} receptors. However, other mechanism are also involved in cisplatin-induced nephrotoxicity such as DNA damage, mitochondrial dysfunction, increased tumor necrosis factor (TNF) and oxidative stress [2-4].

The incidence of renal dysfunction reported in our study is 20.8%, whereas other authors reported it as a limiting side-effect in 25-75% of the patients [11, 17]. None of the patients interrupted chemotherapy due to nephrotoxicity; the four patients that only completed less than six cycles experienced early disease progression and were offered another line of treatment. Limitations of the study include the low number of patients that were assessed and the retrospective design that limited the statistical interpretation and value of the findings.

Moreover, patient selection in terms of comorbidities and baseline renal evaluation is important, as cardiovascular disease could be a contributing factor [18, 19]. Addressing patients with moderate renal dysfunction to specialized evaluation should be considered, as renal impairment after cisplatin treatment can occur progressively.

Conclusions

Further prospective trials comparing prevention strategies that include magnesium supplementation on a larger cohort are needed in order to confirm the findings. However, we suggest that magnesium supplementation is beneficial as a preventive strategy in patients undergoing chemotherapy with cisplatin and serum magnesium levels should be systematically assessed before treatment.

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