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Analysis of the effectiveness of different schemes of supportive therapy in the prophylaxis of cisplatin-induced nephrotoxicity

Vítor Henrique COSTA[1], Inajara ROTTA, Gisele de Paula SOUZA[3], Letícia Mastrangelo COELHO[3], Juliane CARLOTTO[3]

[1]Pharmacy Chemoterapy Sector of Pequeno Príncipe Hospital, Curitiba, Brazil; [2]Department of Pharmacy of Federal University of Paraná, Curitiba, Brazil; [3]Pharmacy Sector of the Clinics Hospital Complex of the Federal University of Paraná, Curitiba, Brazil

Corresponding author: Costa VF, vitor.costa@hpp.org.br

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Abstract

Objective: To evaluated, in the scenario of rapid infusion, the effectiveness of the different regimens of supportive therapy employed in the prevention of nephrotoxicity and electrolyte depletion induced by cisplatin (CDDP). **Methods:** Data from patients who used CDDP weekly (30 to 40mg/m^2) with an infusion time of 60-120 minutes were analyzed. The regimens evaluated were: saline solution (A), saline solution and mannitol (B), saline solution and magnesium (C) and saline solution with mannitol and magnesium (D). The following laboratory parameters were evaluated: creatinine (Cr), magnesium (Mg) sodium (Na) and potassium (K), and glomerular filtration rate (GFR). They were subsequently compiled in Microsoft Office Excel® and analyzed in Software R, using with analysis by means of descriptive statistics, developed in accordance with the recommendations of Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement. **Results:** The study population evaluated were 46 patients, who received 218 infusions of CDDP. It was observed that schemes A and B had a progressive decrease in Mg. Scheme B had decreased levels of K, Cr and increased Na. In the individual analysis of each cycle, the different schemes of supportive therapy in rapid infusion were equally effective in preventing nephrotoxicity and electrolyte depletion. The schemes used were evaluated for throughout CDDP administrations, the regimen C and D demonstrated efficacy in maintaining renal function throughout multiple administration of CDDP. **Conclusion:** In the analysis of cumulative doses, regimen C proved to be effective in preserving renal function throughout CDDP administrations. In the individual analysis of each cycle, regardless of the number of times CDDP was administered, protocols C and D, which contained Mg supplementation associated or not with mannitol, were equally effective in preventing nephrotoxicity.

Key words: Antineoplastic Agents; Cisplatin; Drug-Related Side Effects and Adverse Reactions; Electrolytes; Mannitol; Primary Prevention.

Análise da efetividade dos diferentes esquemas de terapia de suporte na profilaxia da nefrotoxicidade induzida pela cisplatina

Resumo

Objetivo: Avaliar, no cenário de infusão rápida, a eficácia dos diferentes regimes de terapia de suporte empregados na prevenção da nefrotoxicidade e da depleção de eletrólitos induzida pela cisplatina (CDDP). **Métodos:** Foram analisados dados de pacientes que usaram CDDP semanalmente (30 a 40mg/m^2) com tempo de infusão de 60-120 minutos. Os regimes avaliados foram: soro fisiológico (A), soro fisiológico e manitol (B), soro fisiológico e magnésio (C) e soro fisiológico com manitol e magnésio (D). Foram avaliados os seguintes parâmetros laboratoriais: creatinina (Cr), magnésio (Mg), sódio (Na) e potássio (K) e taxa de filtração glomerular (TFG). Posteriormente, foram compilados no Microsoft Office Excel® e analisados pelo software R, com análise por meio de estatística descritiva, desenvolvida de acordo com as recomendações da declaração *Strengthening the Reporting of Observational Studies in Epidemiology* (STROBE). **Resultados:** A população do estudo avaliada foi de 46 pacientes, que receberam 218 infusões de CDDP. Observou-se que os esquemas A e B tiveram diminuição progressiva do Mg. O Esquema B apresentou diminuição dos níveis de K, Cr e aumento de Na. Na análise individual de cada ciclo, os diferentes esquemas de terapia de suporte em infusão rápida foram igualmente eficazes na prevenção da nefrotoxicidade e da depleção eletrolítica. Os esquemas utilizados foram avaliados ao longo das administrações de CDDP, os regimes C e D demonstraram eficácia na manutenção da função renal durante a administração múltipla de CDDP**. Conclusão**: Na análise das doses cumulativas, o regime C mostrou-se eficaz na preservação da função renal ao longo das administrações de CDDP. Na análise individual de cada ciclo, independente do número de vezes que a CDDP foi administrada, os protocolos C e D, que continham suplementação de Mg associada ou não ao manitol, foram igualmente eficazes na prevenção da nefrotoxicidade.

Palavras-Chave: Antineoplásicos; Efeitos Colaterais e Reações Adversas a Medicamentos; Eletrólitos; Manitol; Prevenção Primária.

Introduction

Although cancer remains the second leading cause of death in the world, the treatment of many cancers has revolutionized thanks to the use of chemotherapy drugs, such as cisplatin (CDDP), which has activity against several types of solid tumors and hematological diseases. While CDDP is used in a variety of treatment regimens, this drug can trigger several adverse effects, most notably nephrotoxicity and electrolyte depletion, which limits the dose intensity of treatment[1,2]. About 10% to 40% of patients receiving CDDP-based chemotherapy develop nephrotoxicity as a result of drug accumulation in the proximal tubules of the kidney, resulting in cellular damage[3].

The literature recommends that CDDP should be administered over 6 to 8 hours or 1 mg per minute, with prior and subsequent hydration for a period of 2 to 4 hours, in order to limit drug exposure to tubular cells and preserve renal function[4]. However, such a scheme is not feasible for outpatient treatment, as it limits the availability of infusion chairs and the opening hours of the treatment center. Thus, in this scenario, rapid infusion schemes are used both for CDDP and for supportive therapy, which can be performed with or without the addition of mannitol and/or magnesium sulfate, in different schemes for the prevention of nephrotoxicity and electrolyte depletion[5,6]

Several strategies have been developed involving short-term, low-volume ambulatory hydration regimens, even in patients receiving treatment with intermediate or high doses, when magnesium supplementation and forced diuresis with mannitol or another diuretic are performed. Furthermore, the stimulation of oral rehydration and/or the use of a hypertonic saline vehicle may be effective in preventing nephrotoxicity. Although several studies have been performed in the last four decades, there is still no consensus on specific guidelines to avoid renal toxicity caused by cisplatin[7]. Thus, the aim of this study was to evaluate, in the context of rapid infusion and at an outpatient level, the effectiveness of different supportive therapy regimens employed in the prevention of nephrotoxicity and electrolyte depletion induced by CDDP.

Methods

A cross-sectional observational retrospective study was carried out, following the recommendations of the declaration Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[8]. The research was approved by the Research Ethics Committee of the institution (60921422.5.0000.0096).

Sample

In this study, patients aged 18 years or older who were treated at the onco-hematology outpatient clinic of a tertiary public hospital in southern Brazil, from January 2020 to June 2022, undergoing weekly infusions of cisplatin-based chemotherapy at a dose of 30 to 40mg/m², in rapid infusion (cisplatin and previous supportive therapy for 60 to 120 min) were included. The following tests were considered to assess renal function and electrolyte depletion: serum creatinine (Cr), magnesium (Mg), sodium (Na) and potassium (K), and glomerular filtration rate (GFR) determined by the CKD-EPI equation, performed before and after infusion of chemotherapy for a period of up to 28 days. Patients who did not have laboratory and/or clinical data in their medical records were excluded from the study. Due to the nephrotoxicity of the chemotherapy analyzed, patients eligible for treatment could not have previous renal dysfunction.

Nephrotoxicity prevention schemes

Based on medical prescriptions, four categories of schemes for the prevention of nephrotoxicity were defined: saline solution (A), saline solution with 20% mannitol 250ml (B), saline solution with magnesium sulphate 10% (C), and saline solution with 20% mannitol 250ml and 10% magnesium sulphate (D). The saline solution considered in the schemes was 0.9% of 1 to 2 liters, used on the same day before cisplatin administration. The analyzed patients could transition between different types of nephrotoxicity prevention regimens based on their clinical requirements.

Based on the model of the study conducted by Mach et al (2017), nephrotoxicity was evaluated by identifying the patients receiving cisplatin who exhibited declines in glomerular filtration rate (GFR), as well as reductions in serum creatinine and serum magnesium compared to baseline levels[9].

Data collection and analysis

The following data was collected using a preformatted Microsoft Office Excel® sheet: age, race, sex and patient's diagnosis, results of laboratory tests, doses of chemotherapy administered, number of chemotherapy cycles performed, treatment protocol adopted, body surface area, purpose of chemotherapy, comorbidities and pharmacotherapy in use.

Pre-cycle results were adopted as baseline values and compared with values obtained after chemotherapy infusion, which was used to classify acute nephrotoxicity. Normality was assessed using the Shapiro-Wilk test. The effectiveness of schemes for the prevention of nephrotoxicity and electrolyte depletion was evaluated using the Wilcoxon test for the difference between the results of laboratory tests obtained pre- and post-infusion of CDDP, considering the maximum and minimum values and median between the groups of patients who used as a nephrotoxicity prevention scheme A, B, C or D.

In the initial, pre- and post-chemotherapy infusion analysis, serum Cr, Mg, K and Na values and GFR were examined regardless of the number of cycles of CDDP that had been previously administered. For statistical comparison purposes, values prior to baseline CDDP infusion were used as baseline. To assess renal function over cisplatin administration cycles concomitantly with the use of prevention regimens, post-infusion laboratory variables were examined according to the number of times cisplatin was administered.

Results

During the considered period, the clinical and laboratory data of 46 patients were evaluated, 82.6% of whom were female, according to the data summarized in Table 1. A total of 218 infusions were evaluated, with a median of 3 [2; 5] cycles per patient (min/max 1 and 14). Three patients who did not have laboratory and/or clinical data were excluded, as well as laboratory tests that did not contain available values.

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Table 1. Sociodemographic and laboratory data

Sex (number, %)	Female	38 (82.6%)	
	Masculine	8 (17.4%)	
	Total	**46**	
Age (years old)	Female	Median [IQR]	54.5 [40.7; 62.2]
		Min/Max	25/77
	Male	Median [IQR]	52.5 [46.5; 71.5]
		Min/Max	36/73
Total dose of cisplatin (mg)	Mean ± SD	63.5 ± 27.5	
Body surface(m^2)	Mean ± SD	1.67 ± 0.57	
Creatinine (n=441)	Prior to cycle	Median [IQR]	0.74 [0.6;0.8]
		Min/Max	0.39/1.41
	Post cycle	Median [IQR]	0.74 [0.6;0.8]
		Min/Max	0.5/2.36
Magnesium (n=335)	Prior to cycle	Median [IQR]	1.7[1.4;1.9]
		Min/Max	1.1/2.1
	Post cycle	Median [IQR]	1.7 [1.4;1.9]
		Min/Max	0.9/2.1
Potassium (n=408)	Prior to cycle	Median [IQR]	4.3[3.9;4.5]
		Min/Max	3.1/5.6
	Post cycle	Median [IQR]	4.3 [3.9;4.5]
		Min/Max	3.1/5.3
Sodium (n=403)	Prior to cycle	Median [IQR]	138[137;140]
		Min/Max	134/144
	Post cycle	Median [IQR]	138[137;140]
		Min/Max	130/142
GFR (n=441)	Prior to cycle	Median [IQR]	95[82;105,8]
		Min/Max	83/115
	Post cycle	Median [IQR]	95[82;105,8]
		Min/Max	71/105

GFR: glomerular filtration rate; IQR: 25th quartile, 75th quartile; Min/Max: Minimum and maximum; SD: standard deviation. * In some cases, the values of laboratory parameters were not collected, which generated a different N for each exam

Groups A, B, C and D represent, respectively, 72, 61, 48 and 37 infusions (Table 2). The regimen B and D had lower Mg values than recommended in the literature[14]. Creatinine values had a statistically significant difference only in supportive therapy regimen B (p=0.02; median difference 0.02 mg/mL), without characterizing, however, acute kidney injury, according to staging criteria of KDIGO. In this criterion, the following classification into stages is utilized: 1) 1.5–1.9 times the baseline value; 2) 2.0–2.9 times the baseline value; and 3) 3.0 times the baseline value.

When evaluating the statistical alterations in the laboratory parameters of electrolytes, analyzed pre and post-cycle, in the different schemes of support therapy, significant alterations in the serum dosage of patients exposed to the scheme A were observed (Mg p=0.02 and Na p= 0.0002), which showed a median of 1.9 mg/dL and 1.8 mg/dL of magnesium and 139.0 mmol/L and 138.2 mmol/L of sodium, pre- and post-cycle, respectively.

Post-cycle laboratory values were compared, and in this context, group D was not evaluated, as the proposed model was followed with the association of only one agent to saline solution. The analysis of laboratory parameters as a function of the progressive number of doses of CDDP showed that regimens A and B had a progressive decrease in Mg (A: mean prior to cycle 1.9 and post cycle 1.8, p= 0.010; B: mean prior to cycle 1.6 and post cycle 1.4, p= 0.045). In addition, regimen B had a decrease in K (mean prior to cycle 4.3 and post cycle 4.2, p= 0.04), Cr levels (mean prior to cycle 0.77 and post cycle 0.79, p= 0.03) and a progressive increase in Na (mean prior and post cycle 138.0, p= 0.018).

The presence of comorbidities and the development of renal impairment did not present a statistically significant relationship, as can be seen in analysis considering the variation in values recorded before and after infusion in Table 3. During infusion cycles, the prescriber's clinical perception may imply the choice of each supportive therapy scheme, which generates the possibility of changing schemes between CDDP doses.

Table 2. Analysis of laboratory parameters of CDDP cycles according to the supportive therapy scheme

Parameter	MED [IQR] prior to cycle	MED [IQR] post cycle	P-value
Scheme A (72 cycles evaluated)			
Creatinine (mg/dL)	0.8 [0.7;0.8]	0.8 [0.7;0.8]	0.7
Magnesium (mg/dL)	1.9 [1.7; 2.0]	1.8 [1.6;1.9]	0.02*
Potassium (mmol/L)	4.3 [4.1;4.6]	4.3 [4.0;4.6]	0.2
Sodium (mmol/L)	139.0 [138.0;140.1]	138.2 [135.8; 140.0]	0.0002*
GFR (mL/min/1.73m^2)	92.0 [83.0;101.6]	93.5 [85.0;102.4]	0.9
Scheme B (61 cycles evaluated)			
Creatinine (mg/dL)	0.77 [0.63;0.91]	0.79 [0.64;0.91]	0.02*
Magnesium (mg/dL)	1.6 [1.0;1.8]	1.4 [0.9;1.7]	0.2
Potassium (mmol/L)	4.3 [4.0;4.7]	4.2 [3.9;4.5]	0.3
Sodium (mmol/L)	138.0 [136.0;139.8]	138.0 [136.0;140.0]	0.7
GFR (mL/min/1.73m^2)	91.0 [71.0;102.0]	85.5 [70.8;97.5]	0.02*
Scheme C (48 cycles evaluated)			
Creatinine (mg/dL)	0.7 [0.6; 0.8]	0.7 [0.7;0.8]	0.5
Magnesium (mg/dL)	1.8 [1.6; 2.0]	1.8 [1.5; 2.0]	0.1
Potassium (mmol/L)	4.1 [3.7;4.5]	4.1 [3.7;4.4]	0.6
Sodium (mmol/L)	139.0 [138.0;140.0]	139.0 [138.0;140.0]	0.1
GFR (mL/min/1.73m^2)	100.3 [91.5;115.0]	101.7 [89.2;113.8]	0.6
Scheme D (37 cycles evaluated)			
Creatinine (mg/dL)	0.7 [0.6; 0.8]	0.7 [0.6; 0.8]	0.1
Magnesium (mg/dL)	1.4 [1.3;1.7]	1.4 [1.2;1.7]	0.09
Potassium (mmol/L)	4.2 [3.8;4.4]	3.9 [3.8;4.3]	0.1
Sodium (mmol/L)	138.5 [137.0;139.6]	138.0 [136.0;139.2]	0.4
GFR (mL/min/1.73m^2)	95.5 [89.8;106.4]	95.0 [89.0;109.3]	0.2

GFR: glomerular filtration rate; IQR: 25th quartile, 75th quartile.* p value with statistical significance (p < 0.05)

Table 3. Analysis of the effect of the presence of comorbidities in laboratory tests considering the variation in values recorded before and after infusion.

Parameter	Variable	With comorbidity (n=31)	Without comorbidity (n=15)	Total	P-value
Creatinine (mg/dL)	Min/Max Med [IQR]	-0.1 / 0.4 0.01 [-0.03;0.1]	-0.1 / 0.1 0.01 [-0.009;0.03]	-0.1 / 0.4 0.01 [-0.02;0.04]	0.9626
Magnesium (mg/dL)	Min/Max Med [IQR]	-1.0 / 0.9 0.01 [-0.3;0.3]	-0.6 / 0.8 0 [-0.04;0.1]	-1.0 / 0.9 0 [-0.2;0.2]	0.8234
Potassium (mmol/L)	Min/Max Med [IQR]	-2.4 / 2.2 -0.1 [-0.5;0.1]	-0.3 / 0.7 -0.04 [-0.1;0.04]	-2.4 / 2.2 -0.05 [-0.2;0.1]	0.5346
Sodium (mmol/L)	Min/Max Med [IQR]	-23.0 / 17.5 0 [-3.0;1.2]	-5.4 / 10.7 0.4 [-0.3;3.0]	-23.0 / 17.5 0 [-2.2;2.3]	0.2273
GFR (mL/min/1.73m^2)	Min/Max Med [IQR]	-14.7 / 10.4 -0.8 [-4.9;1.9]	-7.0 / 2.0 -1.0 [-4.0;0.5]	-14.7 / 10.4 -0.9 [-4.5;0.8]	0.6362

GFR: glomerular filtration rate; IQR: 25th quartile, 75th quartile; Min/Max: Minimum and maximum *post infusion- before infusion = analyzed value

Discussion

A retrospective observational study conducted by Williams Jr et al (2017) showed patients who received treatment with cisplatin-based regimens, 9.2% developed acute kidney injury and 37.9% developed chronic kidney injury. One of the strategies indicated in some studies is forced diuresis with the objective of potentiating the elimination effect of cisplatin accumulated in the renal tubules[10]. In comparation of hydration therapy alone with the addition of mannitol to hydration therapy, found that the addition of mannitol resulted in lower levels of nephrotoxicity[11]. In contrast, the analysis of the comparison of the creatinine clearance rate before and after cisplatin administration, suggests that mannitol hydration is associated with more nephrotoxicity and the study was terminated prematurely due to nephrotoxicity in the mannitol group[12]. This result was also observed in our study, where only the hydration scheme with mannitol showed a difference in creatinine and GFR.

The electrolyte depletion observed in schedule A was also evidenced in the non-randomized intervention study, participants who did not receive supplementation were 2.6 times more likely to develop nephrotoxicity compared to those who received it, in addition to electrolyte depletion[13]. Hypomagnesemia was also similar in another retrospective observational study, who evaluated the choice of diuretics for the prevention of cisplatin-induced nephrotoxicity[9]. The analysis of the individuals who received the diuretics furosemide and mannitol showed that for the effects of cumulative dose as a function of the number of times cisplatin was administered, progressive hypomagnesemia occurred from the third infusion of cisplatin regardless of the forced diuresis scheme adopted.

Impairment of renal function with electrolyte depletion and increased Cr and/or GFR was related to the presence of comorbidities such as diabetes mellitus, ischemic heart disease, and risk factors such as advanced age and female gender[11]. These results were not found in our study, since the presence of comorbidity may have influenced the prescriber in choosing the supportive therapy regimen.

Some studies indicate that in addition to nephrotoxicity, cumulative doses of cisplatin can lead to increased serum creatinine and urea, hypomagnesemia, hypocalcemia, hypophosphatemia and hypokalemia[12]. In this study the scheme was most effective in preserving renal function over the progressive administration of CDDP doses. Although cisplatin-induced nephrotoxicity limits its dose and intensity, a systematic review of strategies to prevent cisplatin-induced nephrotoxicity recommends regimens with Mg supplementation, use of mannitol for high-dose CDDP and for patients with preexisting hypertension, in addition to hydration[7].

This study is a non-randomized retrospective study in which it was not possible to collect laboratory samples from all infusions. Also, it should be considered that this study may not have enough statistical power to detect specific relationships between demographic characteristics and clinical outcomes of comorbidities, due to the low sample of patients. The diseases studied comprised a diverse array, and information on disease staging was not reported. This absence may limit the comprehension regarding the severity of the conditions among the patients included in the study. Additionally, there was a lack of documentation regarding the cessation of treatment due to toxicities.

Internal and external validation

The data presented in the study are essential for aiding in the institutional prevention and management of cisplatin-induced nephrotoxicity. International guidelines such as EVIQ from the Cancer Institute NSW government[16] and the Guideline for Management of Hydration During Systemic Anti-Cancer Therapy Containing Cisplatin from the Wales Cancer Network[17] differ in their recommendations regarding supportive therapy for cisplatin. The Australian guideline recommends the administration of 10 mmol of intravenous magnesium as pre-hydration for regiments containing cisplatin at any dose, and the use of mannitol only for high doses of cisplatin schedules (≥100 mg/m²) or in patients with pre-existing hypertension. In contrast, the British guideline recommends the infusion of 10 mmol of magnesium as post-hydration, combined with 20 mmol of potassium for cisplatin doses above 40 mg/m², and does not mention the use of mannitol in any schedules. These discrepancies in approach highlight how each institution may internally validate their prevention and management strategies based on the patient profiles and the conflicting published data.

Currently, the institution where this study was conducted proposed pre-hydration with 10 mmol of magnesium in cisplatin-containing regimens, regardless of dosage. The addition of mannitol is only recommended for cisplatin doses above 50 mg/m². The findings corroborate with the existing practices and may influence the actual necessity of incorporating mannitol into prevention therapies, aligning with international guidelines.

Conclusion

In this study, in the individual analysis of each cycle, regardless of the number of times CDDP was administered, protocols C and D, which contained Mg supplementation associated or not with mannitol, were equally effective in preventing nephrotoxicity and not worsening of renal function was observed with the progressive increase in administration of doses or oscillations of electrolytes for scheme C. In addition, in the analysis of cumulative doses, the serum regimen associated with magnesium supplementation proved to be effective in preserving renal function over the progressive administration of CDDP doses.

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Collaborators:

Conception and project (VHC, IR and JC); Data analysis (VHC); Data interpretation (VHC, IR and JC); Article writing (VHC, LCC, JC and IR); Critical review of content (VHC, LCC, GPS, JC and IR).

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Declaration of conflict of interests:

The authors declare that there are no conflicts of interest in relation to this article.

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