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Original Article

Risk analysis for cisplatin-induced nephrotoxicity during first cycle of chemotherapy

Ryo Kobayashi[1], Akio Suzuki[1], Katsuhiko Matsuura[1,2], Naomi Yamada[3], Masahiro Nakano[4], Takashi Deguchi[4], Kimio Yasuda[3], Yoshinori Itoh[1]

[1]Department of Pharmacy, Gifu University Hospital, 1-1 Yanagido, Gifu 501-1194, Japan; [2]Department of Pharmacy, Aichi Medical University Hospital, 1-1 Yazakokarimata, Nagakute, Aichi 480-1195, Japan; [3]School of Pharmacy, Kinjo Gakuin University, 2-1723 Omori, Moriyama-ku, Nagoya, Aichi 463-8521, Japan; [4]Department of Urology, Graduate School of Medicine, Gifu University, 1-1 Yanagido, Gifu City 501-1194, Japan

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Abstract: Although cisplatin is one of the most widely used anticancer drugs, nephrotoxicity remains a major dose-limiting side effect. To reduce the incidence of cisplatin-induced nephrotoxicity, we analyzed possible risk factors in 349 patients who received cisplatin (15-120 mg/m^2) for the first cycle of chemotherapy between April 2011 and March 2014. Nephrotoxicity was defined as serum creatinine elevation > 1.5 times that at baseline (grade ≥ 2) from 4 to 7 days after injection, according to the Common Terminology Criteria for Adverse Events Version 4.0. Dose of cisplatin > 20 mg/m^2 significantly increased serum creatinine concentration and caused nephrotoxicity in a dose-dependent manner, with a 13.7% incidence of nephrotoxicity (30/219) at doses > 40 mg/m^2. A multivariate logistic regression analysis revealed the following as significant risk factors for cisplatin-induced nephrotoxicity: age ≥ 65 years, low serum albumin (≤ 3.5 g/dl), high doses (≥ 80 mg/m^2) of cisplatin and the use of mannitol. Risk factors of cisplatin nephrotoxicity were old age, low serum albumin, high dose of cisplatin, and inclusion of mannitol in transfusion. Mannitol should therefore not be included in intravenous hydration. In addition, as the number of risk factors increased, so did the incidence of cisplatin-induced nephrotoxicity.

Keywords: Cisplatin, nephrotoxicity, risk factor, intravenous hydration, mannitol

Introduction

Cisplatin is an antineoplastic drug that is classified as a platinum compound and is used to treat a variety of solid tumors such as lung carcinoma, head and neck cancer, germ cell tumor, ovarian cancer and breast cancer [1-3]. However, cisplatin administration induces a number of adverse effects such as nephrotoxicity, nausea and vomiting, ototoxicity, alopecia, myelosuppression, and allergic reactions [4, 5], of which nephrotoxicity is a major dose-limiting factor [6, 7]. Nephrotoxicity is dose dependent, particularly when dose exceeds 50 mg/m^2 [3, 8]. Prevention of cisplatin-induced nephrotoxicity is therefore required to avoid discontinuation of chemotherapy.

Given that cisplatin is predominantly excreted into urine, a high concentration of this compound accumulates in the renal proximal tubules, where it causes necrosis [9]. Although the precise mechanisms underlying cisplatin-induced nephrotoxicity are unknown, reactive oxygen species are reportedly involved in cisplatin-induced renal cell injury [10]. We previously reported that generation of reactive oxygen species following exposure to cisplatin markedly increases the production of tumor necrosis factor-α (TNF-α) via phosphorylation of p38 mitogen-activated protein kinase (MAPK), which leads to renal tubular cell necrosis [11-14]. Reduced renal blood flow and the resulting decrease in glomerular filtration rate are also implicated in the pathophysiology of cisplatin-induced nephrotoxicity [15]. In addition, serum creatinine (Scr) levels reportedly peak at 6 to 7 days after cisplatin administration [16, 17]. To our knowledge, however, volume expansion with sodium chloride and diuresis remains the

Table 1. Patient demographics

Number (Male/Female)	349 (228/121)
Age (range)	62.3 (24-86)
Height (cm)	161.8 ± 8.5
Body weight (kg)	56.1 ± 10.8
Serum albumin (g/dl)	3.86 ± 0.56
Serum creatinine (g/dl)	0.70 ± 0.18
Creatinine Clearance (ml/min)	86.97 ± 29.37
Cisplatin dose (mg/m^2)	54.27 ± 20.37
Hydration volume (ml)	
Day 0	414.7 ± 621.3
Day 1	2,730.9 ± 892.5
Day 2	1,206.8 ± 914.3
Day 3	327.8 ± 567.1
Diuretuc agents (N, %)	
Furosemide	171 (49.0)
Mannitol	98 (28.1)
Magnesium (N, %)	104 (29.8)
Tumor type (N, %)	
Gastrointestinal cancer	178 (51.0)
Head and neck cancer	56 (16.0)
Uterus cancer	47 (13.5)
Lung cancer	37 (10.6)
Other	31 (8.9)

Values represent the mean ± S.D. (range) unless otherwise stated.

only means of reducing incidence of cisplatin-induced nephrotoxicity [16], although moderate increases in Scr persist in a significant proportion of patients regardless of hydration with diuresis [18, 19].

Kidera et al [20]. recently analyzed 401 patients receiving their first course of cisplatin-based chemotherapy and identified cisplatin dose, performance status, and regular use of nonsteroidal anti-inflammatory drugs as risk factors of nephrotoxicity. These authors also identified an association between magnesium supplementation and reduced risk of nephrotoxicity [20]. In the present study, we conducted a logistic regression analysis to determine risk factors for cisplatin-induced nephrotoxicity in patients receiving their first course of chemotherapy.

Patients and methods

Study design and subjects

Factors affecting the incidence of cisplatin-induced nephrotoxicity during the first course of chemotherapy were retrospectively analyzed. Data were obtained from electronic medical records. A total of 371 patients received a first course of chemotherapy containing various doses of cisplatin at Gifu University Hospital between April 2011 and March 2014. Of these patients, 22 were excluded for the following reasons: aged < 18 years (n=7), receiving daily administration of cisplatin (n=14), and creatinine clearance (Ccr) < 30 ml/min (n=1). Consequently, 349 patients were eligible for inclusion.

Evaluation of renal function and nephrotoxicity

Renal function was assessed based on Scr and Ccr estimated from Scr using the Cockcroft-Gault equation [21]. Scr was determined before (baseline) and 4 to 7 days after the first course of chemotherapy containing cisplatin. Nephrotoxicity was defined as an Scr value more than 1.5 times that at baseline (grade ≥ 2 event), according to the Common Terminology Criteria for Adverse Events (CTCAE, National Cancer Institute, MD, USA) version 4.0.

Risk analysis for cisplatin-induced nephrotoxicity

Before risk analysis, the following characteristics were statistically compared between 219 patients with and without nephrotoxicity who received > 40 mg/m^2 of cisplatin: age, height, body weight, body surface area, serum albumin level, Ccr, cisplatin dose, and use of antidiuretic agents. Cut-off values of age, serum albumin level, and cisplatin dose were determined from the Youden index maximum (sensitivity + specificity - 1) by receiver operating characteristic (ROC) curve analysis. Subsequently, any patient characteristics that significantly differed between the two groups underwent risk analysis. Univariate and multivariate logistic regression analyses were conducted to determine risk factors for cisplatin-induced nephrotoxicity.

Statistical analyses

Data were analyzed using SPSS version 11 (SPSS Inc., Chicago, IL, USA). Parametric data were analyzed using the t-test, while non-parametric data were compared using the Mann-Whitney U-test or Chi-square test. Changes in Scr were statistically analyzed before and after cisplatin injection using the paired t-test. Incidence of nephrotoxicity was compared with respect to the number of risk factors using the

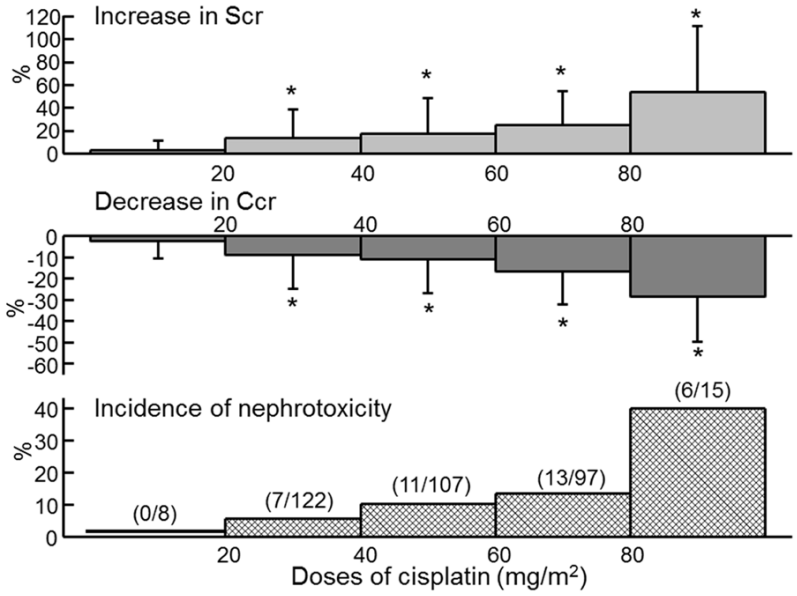

Figure 1. Dose-dependent decrease in Ccr, increase in Scr, and the incidence of nephrotoxicity in patients who received cisplatin. Ccr was calculated from Scr using the Cockcroft-Gault equation. Nephrotoxicity was defined as Scr elevated above 1.5 times as baseline (Grade ≥ 2 event) according to the Common Terminology Criteria for Adverse Events Version 4.0. *P < 0.01 compared to basal values by *paired t-test.*

Kruskal-Wallis test followed by Scheffe's test for multiple comparisons. *P*-values less than 0.05 were considered significant.

Ethical statement

The study was conducted in accordance with the guidelines for human studies determined by the ethics committee of Gifu University Graduate School of Medicine and the Government of Japan and was approved by the institutional review board (Approval No. 25-185).

Results

Changes in Scr, Ccr and the incidence of nephrotoxicity after cisplatin injection

Patient demographics are shown in **Table 1**. Gastrointestinal cancer was the most common type of tumor (n=178), followed by cancer of the head and neck (n=56), uterus (n=47) and lung (n=37). As shown in **Figure 1**, Ccr decreased but Scr increased after treatment with cisplatin in a dose-dependent fashion. Incidence of nephrotoxicity was > 10%, when the dose of cisplatin was > 40 mg/m^2. Subsequently, risk analysis for cisplatin-induced nephrotoxicity was conducted in patients who received > 40 mg/m^2 of cisplatin.

Comparison of characteristics between patients with and without renal toxicity

Characteristics of 219 patients who received > 40 mg/m^2 of cisplatin were compared between those with nephrotoxicity (30, 13.7%) and those without (189, 86.3%). Cut-off age was 64.5 years as assessed from the Youden index maximum by the ROC curve for age vs. nephrotoxicity. Significant differences between the two groups were found in proportion of patients aged ≥ 65 years (41.8% in group without nephrotoxicity vs. 66.7% in group with nephrotoxicity, P=0.019), serum albumin levels (3.90 ± 0.5 vs. 3.73 ± 0.49, P=0.043), cisplatin dose (60.3 ± 16.5 vs. 68.3 ± 22.6, P=0.001), and rate of mannitol use (32.8% vs. 56.7%, P=0.011) (**Table 2**).

Logistic regression analysis for risk of cisplatin-induced nephrotoxicity

Univariate analysis indicated that the following were associated with high incidence of nephrotoxicity (**Table 3**): age ≥ 65 years (odds ratio: 2.725; 95% confidence interval [CI]: 1.210-6.138, *P*=0.016), serum albumin level ≤ 3.5 g/dl (odds ratio: 2.428; 95% CI: 1.056-5.580, *P*=0.037), cisplatin dose ≥ 80 mg/m^2 (odds ratio: 3.486; 95% CI: 1.548-7.852, *P*=0.003), and use of mannitol (odds ratio: 2.658; 95% CI: 1.224-5.863, *P*=0.014). Multivariate analysis identified the following as significant risk factors for cisplatin-induced nephrotoxicity: age ≥ 65 years (odds ratio: 3.702; 95% CI: 1.481-9.257, *P*=0.005), serum albumin level ≤ 3.5 g/dl (odds ratio: 3.317; 95% CI: 1.324-8.311, *P*=0.011), cisplatin dose ≥ 80 mg/m^2 (odds ratio: 4.144; 95% CI: 1.591-10.793, *P*=0.004), and use of mannitol (odds ratio: 2.449; 95% CI: 1.022-5.872, *P*=0.045).

Notably, nephrotoxicity increased near linearly with number of risk factors, as follows (**Figure 2**): 4.4% for no risk factors, 3.6% for 1 factor, 19.1% for 2 factors, 38.5% for 3 factors (*P* <0.001 by Kruskal-Wallis test).

Table 2. Comparison of characteristics between patients with and without nephrotoxicity after cisplatin (> 40 mg/m^2) treatment

	Without nephrotoxicity	With nephrotoxicity	*P*-value
Number of patients (male/female)	189 (130/59)	30 (21/9)	0.937[a)]
Age (range)	61.4 (30-83)	63.5 (24-82)	0.256[b)]
Age > 65 year-old (%)	41.8	66.7	0.019[b)]
Height (cm)	162.4 ± 8.7	161.1 ± 8.0	0.455[c)]
Body weight (kg)	56.3 ± 10.3	55.7 ± 10.8	0.950[c)]
Body surface area (m^2)	1.60 ± 0.20	1.57 ± 0.16	0.195[c)]
Serum albumin (g/dl)	3.90 ± 0.50	3.73 ± 0.49	0.043[c)]
Serum creatinine (mg/dl)	0.70 ± 0.17	0.65 ± 0.12	0.062[c)]
Creatinine clearance (ml/min)	87.5 ± 28.6	89.7 ± 30.2	0.327[c)]
Cisplatin dose (mg/m^2)	60.3 ± 16.5	68.3 ± 22.6	0.001[c)]
Hydration volume (ml)			
Day 0	497.4 ± 661.9	482.0 ± 526.7	0.903[c)]
Day 1	2,926.7 ± 939.1	3,242.3 ± 983.2	0.091[c)]
Day 2	1,495.4 ± 781.6	1,531.3 ± 793.7	0.816[c)]
Day 3	415.9 ± 579.4	644.5 ± 655.4	0.053[c)]
Diuretuc agents (N, %)			
Furosemide	102 (54.0)	16 (53.3)	0.948[a)]
Mannitol	62 (32.8)	17 (56.7)	0.011[a)]
Magnesium (N, %)	71 (37.6)	10 (33.3)	0.656[a)]

[a)]*Mann-Whitney U-test*, [b)]*Chi-square test*, [c)]*t-test*.

Table 3. Univariate logistic regression analysis for risk factors involving acute renal failure after treatment with high doses of cisplatin (> 40 mg/m^2)

	Univariate analysis				Multivariate analysis			
		95% Confidence interval				95% Confidence interval		
	Odds ratio	Lower	Upper	*P*-value	Odds ratio	Lower	Upper	*P*-value
Age (> 65 years)	2.725	1.210	6.138	0.016	3.702	1.481	9.257	0.005
Serum albumin (< 3.5 g/dl)	2.428	1.056	5.580	0.037	3.317	1.324	8.311	0.011
Cisplatin dose (> 80 mg/m^2)	3.486	1.548	7.852	0.003	4.144	1.591	10.793	0.004
Mannitol	2.679	1.224	5.863	0.014	2.449	1.022	5.872	0.045
Furosemide	0.975	0.450	2.110	0.948				
Magnesium	0.831	0.368	1.876	0.656				

Discussion

In the present study, we revealed that risk factors of cisplatin nephrotoxicity were old age, low serum albumin, high dose of cisplatin and inclusion of mannitol in transfusion. Mannitol should therefore not be included in intravenous hydration. In addition, the incidence of cisplatin-induced nephrotoxicity increased along with the number of risk factors.

Nephrotoxicity is a major problem when using cisplatin in cancer chemotherapy and is a dose-limiting factor that might interfere with continuation of chemotherapy [6, 7, 18, 19]. In the present study, the incidence of nephrotoxicity associated with cisplatin was retrospectively investigated in 349 patients. Administration of cisplatin dose-dependently decreased Ccr, with a significant decrease at doses > 20 mg/m^2. The incidence of moderate to severe increases in Scr (grade ≥ 2 by CTCAE v4.0) increased with cisplatin dose, exceeding 10% when cisplatin dose was > 40 mg/m^2. The rate of cisplatin-induced nephrotoxicity at each dose level was as follows: > 40 mg/m^2, 13.7% (30/219); > 60 mg/m^2, 16.2 (23/143) and > 80 mg/m^2, 27.7 (13/47). Our data on the rate of nephrotoxicity

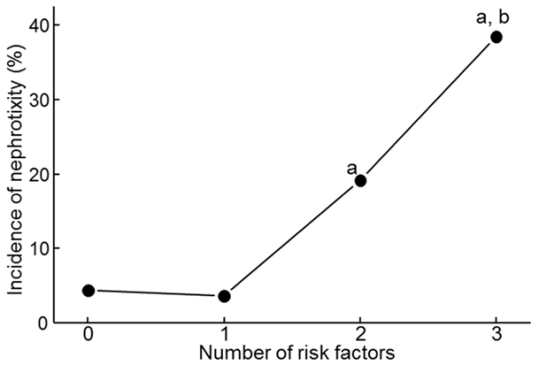

Figure 2. Relationship between number of risk factors and incidence of cisplatin-induced nephrotoxicity. [a)]*P* < 0.01 vs. 1 risk factor, [b)]*P* < 0.05 vs. 2 risk factors by Kruscal-Wallis followed by *Scheff's test.*

closely resembled findings from other reports in Japanese patients [20, 22, 23]. Ouchi et al. investigated the efficacy of a short hydration regimen and reported that the incidence of grade ≥ 2 elevation of Scr in 30 patients treated with > 60 mg/m^2 of cisplatin was 13.3% [23]. Similarly, 23.5% of patients who received 75 to 80 mg/m^2 of cisplatin exhibited increased Scr for grade ≥ 2 in a historical prospective cohort study [22]. Finally, Kidera et al. reported that 32% (127/401) of patients who received ≥ 60 mg/m^2 of cisplatin as first-line therapy exhibited increased Scr for grade ≥ 2 in a retrospective study of the efficacy of magnecium [20].

In the present study, patients with cisplatin-induced nephrotoxicity were slightly but not significantly older than those without (mean age of 63.5 vs. 61.4 years). On an ROC curve plotted for age vs. nephrotoxicity presence, the cut-off age was 64.5 years, as determined from the Youden index maximum. Notably, the percentage of patients aged ≥ 65 years old was significantly higher in those with nephrotoxicity than in those without (66.7% vs. 41.8%, *P*=0.019). Further, patients with nephrotoxicity exhibited significantly lower serum albumin levels than those without. Subsequently, both univariate and multivariate logistic regression analyses were conducted to determine the risk factors for nephrotoxicity associated with cisplatin, and the following were identified as significant risk factors: high dose of cisplatin (≥80 mg/m^2), old age (≥ 65 years), low serum albumin levels (≤ 3.5 g/dl), and use of mannitol. Multivariate analysis found the odds ratio to be highest (4.144) for high doses of cisplatin, followed by 3.702 for old age, 3.317 for low serum albumin levels, and 2.449 for use of mannitol. Interestingly, the incidence of cisplatin-induced nephrotoxicity increased with the number of risk factors.

Regarding age as a risk factor for nephrotoxicity, Sekine et al. reported that patients with nephrotoxicity are older than those without (mean age 65 vs. 59 years, *P*=0.041) [24]. In general, elderly patients carry a number of risk factors for drug-induced nephropathy, including decreased glomerular filtration rate, concentration of serum albumin and body fluid contents, and hepatic metabolic dysfunction [25].

Our finding that a higher dose of cisplatin is a risk factor for nephrotoxicity is generally consistent with other studies [9, 26, 27]. A high peak plasma concentration of free platinum is also associated with increased risk of nephrotoxicity [28, 29]. Low serum albumin concentration has also been reported as a significant risk factor for cisplatin-induced nephrotoxicity [19]. Reduction in plasma albumin concentration might be associated with elevated free platinum concentration, leading to enhanced renal toxicity.

In the present study, the incidence of cisplatin-induced nephrotoxicity was markedly high in patients receiving mannitol but not in those receiving furosemide. Further, mannitol, but not furosemide, was a significant risk factor for nephrotoxicity. The efficacy of diuretics such as mannitol and furosemide for prevention of cisplatin-induced nephrotoxicity is controversial. Hayes et al. [30] reported a protective effect of mannitol diuresis in humans, whereas Morgan et al. [31] reported that the incidence of nephrotoxicity increased following the addition of mannitol. Santoso et al. [32] also reported that hydration with saline and mannitol increased the incidence of nephrotoxicity compared to hydration with saline alone or saline and furosemide. However, the beneficial effect of furosemide is also controversial, with Sekine et al. [24] reporting that the incidence of nephrotoxicity did not significantly differ between patients who received furosemide and those who did not (8.3% vs. 4.7%, *P*=0.14). Of note: the median total dose of furosemide is significantly higher in patients with nephrotoxicity than in those without (26 mg vs. 0 mg, *P*=0.024). In addition, Sekine et al. [24] also demonstrated that total

furosemide dose is a significant risk factor for cisplatin-induced nephrotoxicity (odds ratio: 1.21, 95% CI: 1.11-1.33, $P < 0.001$).

Hypomagnesemia due to urinary magnesium wasting reportedly occurs in over half of cases of cisplatin-induced nephrotoxicity, potentially exacerbating cisplatin toxicity [33]. In addition, several investigators have reported that magnesium supplementation is effective in preventing cisplatin-induced nephrotoxicity [20, 34]. Unfortunately, we did not measure the serum magnesium concentration during the course of chemotherapy with cisplatin.

In conclusion, a retrospective chart review of 349 patients receiving the first course of cancer chemotherapy was performed to determine the risks for cisplatin-induced nephrotoxicity. A multivariate logistic regression analysis indicated that old age (≥ 65 years), low serum albumin level (≤ 3.5 g/dl), high dose of cisplatin (≥ 80 mg/m^2), and the use of mannitol were significant risk factors for cisplatin-induced nephrotoxicity. In addition, as the number of risk factors increased, so did the incidence of cisplatin-induced nephrotoxicity.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Akio Suzuki, Department of Pharmacy, Gifu University Hospital, 1-1 Yanagido, Gifu 501-1194, Japan. Tel: +81-58-230-7091; Fax: +81-58-230-7093; E-mail: akio@gifu-u.ac.jp

References

[1] Go RS and Adjei AA. Review of the comparative pharmacology and clinical activity of cisplatin and carboplatin. J Clin Oncol 1999; 17: 409-422.

[2] Gore M. Carboplatin equals cisplatin: but how do I prescribe it? J Clin Oncol 2003; 21: 3183-3185.

[3] Hotta K, Matsuo K, Ueoka H, Kiura K, Tabata M and Tanimoto M. Meta-analysis of randomized clinical trials comparing Cisplatin to Carboplatin in patients with advanced non-small-cell lung cancer. J Clin Oncol 2004; 22: 3852-3859.

[4] Hartmann JT, Fels LM, Knop S, Stolt H, Kanz L and Bokemeyer C. A randomized trial comparing the nephrotoxicity of cisplatin/ifosfamide-based combination chemotherapy with or without amifostine in patients with solid tumors. Invest New Drugs 2000; 18: 281-289.

[5] Hartmann JT and Lipp HP. Toxicity of platinum compounds. Expert Opin Pharmacother 2003; 4: 889-901.

[6] Arany I and Safirstein RL. Cisplatin nephrotoxicity. Semin Nephrol 2003; 23: 460-464.

[7] Sastry J and Kellie SJ. Severe neurotoxicity, ototoxicity and nephrotoxicity following high-dose cisplatin and amifostine. Pediatr Hematol Oncol 2005; 22: 441-445.

[8] Hartmann JT, Kollmannsberger C, Kanz L and Bokemeyer C. Platinum organ toxicity and possible prevention in patients with testicular cancer. Int J Cancer 1999; 83: 866-869.

[9] Kolb RJ, Ghazi AM and Barfuss DW. Inhibition of basolateral transport and cellular accumulation of cDDP and N-acetyl-L-cysteine-cDDP by TEA and PAH in the renal proximal tubule. Cancer Chemother Pharmacol 2003; 51: 132-138.

[10] Yao X, Panichpisal K, Kurtzman N and Nugent K. Cisplatin nephrotoxicity: a review. Am J Med Sci 2007; 334: 115-124.

[11] Mishima K, Baba A, Matsuo M, Itoh Y and Oishi R. Protective effect of cyclic AMP against cisplatin-induced nephrotoxicity. Free Radic Biol Med 2006; 40: 1564-1577.

[12] Shino Y, Itoh Y, Kubota T, Yano T, Sendo T and Oishi R. Role of poly (ADP-ribose) polymerase in cisplatin-induced injury in LLC-PK1 cells. Free Radic Biol Med 2003; 35: 966-977.

[13] Sueishi K, Mishima K, Makino K, Itoh Y, Tsuruya K, Hirakata H and Oishi R. Protection by a radical scavenger edaravone against cisplatin-induced nephrotoxicity in rats. Eur J Pharmacol 2002; 451: 203-208.

[14] Yano T, Itoh Y, Matsuo M, Kawashiri T, Egashira N and Oishi R. Involvement of both tumor necrosis factor-alpha-induced necrosis and p53-mediated caspase-dependent apoptosis in nephrotoxicity of cisplatin. Apoptosis 2007; 12: 1901-1909.

[15] Kim YK, Byun HS, Kim YH, Woo JS and Lee SH. Effect of cisplatin on renal function in rabbits: mechanism of reduced glucose reabsorption. Toxicol Appl Pharmacol 1995; 130: 19-26.

[16] Cornelison TL and Reed E. Nephrotoxicity and hydration management for cisplatin, carboplatin, and ormaplatin. Gynecol Oncol 1993; 50: 147-158.

[17] Walker RJ. Cellular mechanisms of drug nephrotoxicity. In: Seldin DW,Giebisch G, editors. The Kidney, 3rd edition. Philadelphia: Lippincott Williams & Wilkins; 2000. pp. 2836-60.

[18] de Jongh FE, van Veen RN, Veltman SJ, de Wit R, van der Burg ME, van den Bent MJ, Planting AS, Graveland WJ, Stoter G and Verweij J. Weekly high-dose cisplatin is a feasible treatment option: analysis on prognostic factors for toxicity in 400 patients. Br J Cancer 2003; 88: 1199-1206.

[19] Stewart DJ, Dulberg CS, Mikhael NZ, Redmond MD, Montpetit VA and Goel R. Association of cisplatin nephrotoxicity with patient characteristics and cisplatin administration methods. Cancer Chemother Pharmacol 1997; 40: 293-308.

[20] Kidera Y, Kawakami H, Sakiyama T, Okamoto K, Tanaka K, Takeda M, Kaneda H, Nishina S, Tsurutani J, Fujiwara K, Nomura M, Yamazoe Y, Chiba Y, Nishida S, Tamura T and Nakagawa K. Risk factors for cisplatin-induced nephrotoxicity and potential of magnesium supplementation for renal protection. PLoS One 2014; 9: e101902.

[21] Cockcroft DW and Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16: 31-41.

[22] Oka T, Kimura T, Suzumura T, Yoshimoto N, Nakai T, Yamamoto N, Matsuura K, Mitsuoka S, Yoshimura N, Kudoh S and Hirata K. Magnesium supplementation and high volume hydration reduce the renal toxicity caused by cisplatin-based chemotherapy in patients with lung cancer: a toxicity study. BMC Pharmacol Toxicol 2014; 15: 70.

[23] Ouchi A, Asano M, Aono K, Watanabe T and Kato T. Comparison of short and continuous hydration regimen in chemotherapy containing intermediate- to high-dose Cisplatin. J Oncol 2014; 2014: 767652.

[24] Sekine I, Yamada K, Nokihara H, Yamamoto N, Kunitoh H, Ohe Y and Tamura T. Bodyweight change during the first 5 days of chemotherapy as an indicator of cisplatin renal toxicity. Cancer Sci 2007; 98: 1408-1412.

[25] Rodriguez-Puyol D. The aging kidney. Kidney Int 1998; 54: 2247-2265.

[26] Madias NE and Harrington JT. Platinum nephrotoxicity. Am J Med 1978; 65: 307-314.

[27] Miller RP, Tadagavadi RK, Ramesh G and Reeves WB. Mechanisms of Cisplatin nephrotoxicity. Toxins (Basel) 2010; 2: 2490-2518.

[28] Nagai N, Kinoshita M, Ogata H, Tsujino D, Wada Y, Someya K, Ohno T, Masuhara K, Tanaka Y, Kato K, Nagai H, Yokoyama A and Kurita Y. Relationship between pharmacokinetics of unchanged cisplatin and nephrotoxicity after intravenous infusions of cisplatin to cancer patients. Cancer Chemother Pharmacol 1996; 39: 131-137.

[29] Reece PA, Stafford I, Russell J, Khan M and Gill PG. Creatinine clearance as a predictor of ultrafilterable platinum disposition in cancer patients treated with cisplatin: relationship between peak ultrafilterable platinum plasma levels and nephrotoxicity. J Clin Oncol 1987; 5: 304-309.

[30] Hayes DM, Cvitkovic E, Golbey RB, Scheiner E, Helson L and Krakoff IH. High dose cis-platinum diammine dichloride: amelioration of renal toxicity by mannitol diuresis. Cancer 1977; 39: 1372-1381.

[31] Morgan KP, Buie LW and Savage SW. The role of mannitol as a nephroprotectant in patients receiving cisplatin therapy. Ann Pharmacother 2012; 46: 276-281.

[32] Santoso JT, Lucci JA 3rd, Coleman RL, Schafer I and Hannigan EV. Saline, mannitol, and furosemide hydration in acute cisplatin nephrotoxicity: a randomized trial. Cancer Chemother Pharmacol 2003; 52: 13-18.

[33] Lajer H, Kristensen M, Hansen HH, Nielsen S, Frokiaer J, Ostergaard LF, Christensen S, Daugaard G and Jonassen TE. Magnesium depletion enhances cisplatin-induced nephrotoxicity. Cancer Chemother Pharmacol 2005; 56: 535-542.

[34] Bodnar L, Wcislo G, Gasowska-Bodnar A, Synowiec A, Szarlej-Wcislo K and Szczylik C. Renal protection with magnesium subcarbonate and magnesium sulphate in patients with epithelial ovarian cancer after cisplatin and paclitaxel chemotherapy: a randomised phase II study. Eur J Cancer 2008; 44: 2608-2614.