Original Article

Supplementation with Oral Magnesium Oxide, 750 − 1980 mg Daily, Did Not Reduce Cisplatin-Induced Nephrotoxicity

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ABSTRACT

Introduction: Hypomagnesemia is a side effect of chemotherapy with cisplatin-containing regimens and can increase cisplatin-induced nephrotoxicity. Previous reports found that oral magnesium supplementation significantly reduced the decline in serum magnesium levels after cisplatin treatment. However, few studies have assessed the effect of magnesium oxide on serum magnesium levels after cisplatin treatment. We retrospectively evaluated the effect of supplementation with oral magnesium oxide, 750 − 1980 mg daily, for treatment of constipation on cisplatin-induced nephrotoxicity in patients receiving high-dose cisplatin therapy.

Methods: We retrospectively reviewed data from 161 patients treated with cisplatin-containing regimens between January 2011 and December 2014. Using the Common Terminology Criteria for Adverse Events, version 4.0, we compared the incidence of grade 2 or higher serum creatinine elevation in patients who did (n = 21) and did not (n = 140) receive magnesium oxide for treatment of constipation during a first course of cisplatin chemotherapy.

Results: Mean change in serum creatinine level was similar (0.29 ± 0.50 mg/dl in the control group vs 0.34 ± 0.58 mg/dl in the magnesium oxide supplementation group; p = 0.69). Nephrotoxicity was observed in 15 patients, but there was no significant difference in incidence between groups. Change in creatinine clearance after cisplatin treatment did not differ between groups.

Conclusions: Supplementation with oral magnesium oxide, 750 − 1980 mg daily, did not reduce cisplatin-induced nephrotoxicity.

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KEYWORDS: cisplatin, magnesium, nephrotoxicity

Cisplatin is widely administered for treatment of various solid tumors[1)] but is associated with nephrotoxicity and emetogenicity.[2,3)] Cisplatin treatment also increases magnesium excretion.[4,5)] A previous study implicated organic cation transporter 2 in cisplatin-induced nephrotoxicity.[6)]

Hypomagnesemia is a well-known side effect of chemo-

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Table 1 Patient characteristics

Characteristics	Control	Magnesium oxide supplementation	P value
Number of patients	140	21	
Sex			
Male	108	19	
Female	32	2	0.16
Age, years			
≥65	78	13	
<65	62	8	0.59
Tumor type			
Gastric	55	11	
Esophageal	85	10	0.25
Cisplatin dose (mg)			
Median	100	100	
(range)	(60.0-160.0)	(80.0-140.0)	0.84
Magnesium oxide dose (mg/day)			
Median	0	990	
(range)	(0-0)	(750-1980)	<0.0001
Creatinine (mg/dl)			
Median	0.73	0.75	
(range)	(0.40-1.25)	(0.52-1.06)	0.72
Creatinine clearance (ml/min)			
Median	77.8	68.2	
(range)	(37.5-139.9)	(41.1-122.8)	0.06
Hypoalbuminemia (serum albumin<3.0 g/dl)			
Yes	21	6	
No	119	15	0.12
Diabetes mellitus			
Yes	24	3	
No	116	18	0.74
Regular use of antihypertensives			
Yes	41	8	
No	99	13	0.41
Regular use of nonsteroidal anti-inflammatory drugs			
Yes	9	2	
No	131	19	0.60

Table 2 Increase to grade 2 or higher serum creatinine level

	Control	Magnesium oxide supplementation	P value
Yes	14	1	
No	126	20	0.27

therapy with cisplatin-containing regimens and can enhance cisplatin-induced nephrotoxicity.[7] In previous studies, oral magnesium supplementation significantly reduced the decline in serum magnesium levels after cisplatin treatment.[8, 9] Although the specific magnesium compounds used in these studies are not commercially available in Japan, magnesium oxide is widely used for treatment of constipation in Japan. Few studies have investigated the effect of oral magnesium oxide supplementation on serum magnesium levels after cisplatin treatment. Therefore, we retrospectively evaluated the effect of oral magnesium oxide supplementation on cisplatin-induced nephrotoxicity in patients receiving high-dose cisplatin therapy.

Patients and Methods

Eligibility criteria

We retrospectively reviewed the medical records of pa-

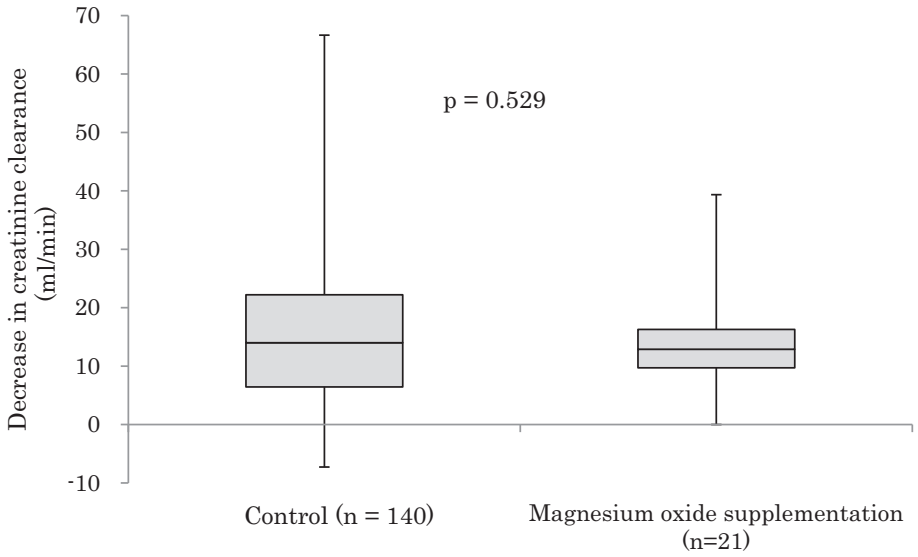

Fig. 1 Box-and-whisker plot for the relation between oral magnesium oxide supplementation and the decrease in creatinine clearance after cisplatin treatment. The difference between the two groups was analyzed with the unpaired Student's *t*-test.

tients with esophageal or gastric cancer who received high-dose (≥60 mg/m^2) cisplatin therapy at Toho University Omori Medical Center between January 2011 and December 2014. To evaluate the effect of oral magnesium oxide supplementation on cisplatin-induced nephrotoxicity, the patients were divided into those who did and did not receive oral magnesium oxide for treatment of constipation. This retrospective study was approved by the ethics committee of Toho University Omori Medical Center (No. 24-1).

Cisplatin administration

Cisplatin was administered in 500 ml of 0.9% normal saline over 1 h. Most patients were prehydrated with 1000 ml of 0.9% normal saline and posthydrated with 2000 ml of 0.9% normal saline administered over 4 − 5 h, followed by administration of 100 g of mannitol over 6 h. All patients received antiemetic prophylaxis with serotonin receptor antagonists plus dexamethasone 15 min before the start of chemotherapy. A neurokinin 1 receptor antagonist was administered as the antiemetic medication.

Nephrotoxicity evaluation

In a previous study[10] we evaluated nephrotoxicity by analyzing changes in serum creatinine level. Serum creatinine level was determined before treatment, and nephrotoxicity was evaluated by determining the increase in serum creatinine levels after the first course of chemotherapy. Creatinine clearance was evaluated by using the Cockroft-Gault equation. Nephrotoxicity was defined as a grade 2 or higher increase in serum creatinine level, according to the Common Terminology Criteria for Adverse Events, version 4.0 (2009; National Cancer Institute, Rockville, MD, USA), during the first course of cisplatin chemotherapy.

Statistical analysis

Differences in categorical outcomes were evaluated using the chi-square or Fisher exact test. Mean changes in serum creatinine level and clearance were evaluated with the unpaired Student's *t*-test. Statistical analysis was performed with the use of Statistical Package for the Social Sciences (SPSS; IBM Corp., Armonk, NY, USA). A p value of <0.05 was considered to indicate statistical significance.

Results

Patient characteristics

A total of 161 patients who received high-dose cisplatin were eligible for the analysis. The baseline characteristics of the two groups are summarized in Table 1 and were similar between groups. Neither serum creatinine concentration nor creatinine clearance significantly differed between groups before cisplatin treatment. Magnesium oxide, 250 − 660 mg three times daily, was administered to 21 patients for treatment of constipation.

Renal function after oral magnesium oxide supplementation

Cisplatin significantly increased serum creatinine levels. To determine the effect of oral magnesium oxide supplementation on cisplatin-induced nephrotoxicity, we evaluated mean change in serum creatinine levels during the first course of cisplatin treatment. Mean change in serum creatinine level was similar (0.29 ± 0.50 mg/dl in the control group vs 0.34 ± 0.58 mg/dl in the magnesium oxide supplementation group; p = 0.69).

Nephrotoxicity was observed in 15 patients, but there was no significant difference in incidence between groups (Table 2). Additionally, change in creatinine clearance after cisplatin treatment did not significantly differ between groups (Fig. 1).

Discussion

Supplementation with oral magnesium oxide, 750 − 1980 mg daily, did not have an effect on cisplatin-induced nephrotoxicity. Intravenous magnesium supplementation is another approach to reducing cisplatin-induced nephrotoxicity. Several studies reported that intravenous magnesium supplementation prevented hypomagnesemia during cisplatin treatment,[8, 11] which suggests that increased serum magnesium levels protect against cisplatin-induced nephrotoxicity. Future studies should examine the correlation between serum magnesium levels and cisplatin-induced nephrotoxicity. The incidence of nephrotoxicity in the present study was similar to that in a previous report.[12] The present cisplatin dose, proportions of patients prescribed antihypertensives, and the cisplatin administration schedule were similar to those reported in a previous study.[13]

The limitations of the present study include possible selection bias resulting from analysis of data from patients receiving magnesium treatment for constipation, which is inevitable in a retrospective study, and the small sample size. Furthermore, comorbidities relevant to inherent nephrotoxicity, such as proteinuria, hypocalcemia, and renal tubular acidosis, were not assessed in the present study.

In conclusion, this retrospective study suggests that supplementation with oral magnesium oxide, 750 − 1980 mg daily, does not reduce cisplatin-induced nephrotoxicity.

Conflicts of interest: None declared.

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