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Influence of magnesium and parathyroid hormone on cisplatin-induced nephrotoxicity in esophageal squamous cell carcinoma

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Abstract. Magnesium (Mg) supplementation has previously been demonstrated to confer protective effects against nephrotoxicity induced by cisplatin. Parathyroid hormone (PTH) regulates Mg homeostasis. The aim of present study was to determine the protective effects of Mg supplementation against cisplatin-induced nephrotoxicity and its association with PTH levels in patients with esophageal squamous cell carcinoma (ESCC). A total of 55 patients with primary ESCC who received chemotherapy with high-dose cisplatin were examined. Mg was administered intravenously, and serum concentrations of PTH, parathyroid hormone-related protein (PTH-rP), creatinine and Mg were prospectively measured. Of the 55 patients, 37 received Mg supplementation. Post-chemotherapeutic creatinine concentrations were significantly increased in patients without Mg supplementation (P=0.01), with grade 1 and 2 increases of 22.2 and 5.6%, respectively, whereas these increases were suppressed by Mg supplementation (change in creatinine, P=0.21), with grade 1 and 2 increases of 8.1 and 0%, respectively. In addition, PTH and PTH-rP concentrations were high in 8 (14.5%) and 6 (10.9%) of all 55 patients, respectively. Alterations in creatinine concentrations (post-/pre-chemotherapy) due to chemotherapy were higher in patients with high levels of PTH regardless of Mg supplementation (P<0.01). Pre-therapeutic creatinine concentrations did not correlate with the alterations in creatinine concentrations due to chemotherapy. Intravenous Mg supplementation therefore conferred protective effects against cisplatin-induced nephrotoxicity in patients with ESCC. Furthermore, increases in PTH or PTH-rP may have influenced the extent of nephrotoxicity.

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Abbreviations: CRT, chemoradiotherapy; ESCC, esophageal squamous cell carcinoma; Mg, magnesium; PTH, parathyroid hormone; PTH-rP, parathyroid hormone-related protein; ULN, upper limit of normal

Key words: cisplatin-induced nephrotoxicity, magnesium, parathyroid hormone, parathyroid hormone-related protein, esophageal squamous cell carcinoma

Introduction

Esophageal carcinoma is one of the most aggressive types of malignant tumor (1). Multimodal treatments, including neoadjuvant chemotherapy and chemoradiotherapy (CRT), have been demonstrated to improve the survival rate of patients with locally advanced esophageal carcinoma (2). Cisplatin, a representative platinum-containing drug, is a key drug in the chemotherapy of esophageal squamous cell carcinoma (ESCC) and a number of other types of malignancy in Japan (3-5). Cisplatin dose-dependently exerts potent antitumor effects; however, it also induces dose-dependent nephrotoxicity. Cisplatin-induced nephrotoxicity is mild and reversible in the majority of cases, but it can also be severe and irreversible, resulting in the discontinuation of chemotherapy (3).

Hypomagnesemia and renal magnesium (Mg) wasting are established side effects of patients receiving cisplatin-containing chemotherapy (6,7). This Mg depletion has been demonstrated to further enhance renal platinum accumulation and cisplatin-induced nephrotoxicity. Therefore, oral or intravenous Mg supplementation can confer renal protective effects against cisplatin-induced nephrotoxicity (8-12).

In normal conditions, the kidney is the principal organ for regulating Mg homeostasis, and serum Mg concentrations are maintained within normal ranges by excreting excess Mg from the serum into urine, a rapid process (13). Due to this strict regulation by the kidney, no hormone is particularly associated with the maintenance of Mg homeostasis; however, large amounts of parathyroid hormone (PTH) influence serum Mg concentrations by affecting loop of Henle and bone resorption (13). Therefore, PTH or parathyroid hormone-related protein (PTH-rP), which was previously reported to be

secreted by certain types of tumor cell, including ESCC (14), may influence the physiological regulation of Mg homeostasis and cisplatin-induced nephrotoxicity in patients receiving chemotherapy.

In the present study, Mg was administered intravenously to patients with ESCC treated with a high-dose cisplatin-containing regimen, and the protective effects of Mg supplementation against cisplatin-induced nephrotoxicity were prospectively examined in relation to PTH and PTH-rP levels.

Materials and methods

Patients and treatment courses. A total of 55 patients, including 43 males and 12 females with primary ESCC receiving high-dose cisplatin-containing chemotherapy as neoadjuvant therapy (age range, 47-84 years; median, 66 years), were investigated between January 2013 and December 2014 at the University Hospital, Kyoto Prefectural University of Medicine (Kyoto, Japan). The concentrations of high sensitive PTH, PTH-rP, creatinine and Mg were measured using in-hospital biochemical tests available for clinical use in all patients before any treatments. The concentrations of creatinine and Mg were monitored until the next cycle of chemotherapy commenced (~3 weeks). No patients exhibited malnutrition or dehydration during treatment. Clinical and pathological staging were performed according to the criteria of the Japanese Classification of Esophageal Cancer, tenth edition (4), and the Tumor-Node-Metastasis Classification System of the International Union Against Cancer, seventh edition (15).

The present study was conducted in accordance with the principles of the Declaration of Helsinki, and written informed consent for the treatments and data collection was obtained from all patients. Ethical approval from the Facility of Science Committee at the Kyoto Prefectural University of Medicine was not required as the study was an observational study without interpositions with the medical practice necessary for therapeutic purpose.

Cisplatin-containing chemotherapy and Mg supplement regimens. The regimens for the majority of the patients were standard FP [5-fluorouracil (5FU; 800 mg/m^2/day, days 1-5) and cisplatin (80 mg/m^2/day, day 1)] (5) or DCF [5FU (700 mg/m^2/day, days 1-5), cisplatin (70 mg/m^2/day, day 4) and docetaxel (70 mg/m^2/day, day 1)] (16). The modified FP regimen of 5FU (700 mg/m^2/day, days 1-5) and cisplatin (70 mg/m^2/day, day 1) was combined with radiotherapy for patients treated with CRT, as previously described (17). The eligibility criteria for these chemotherapy regimens were performance status 0 or 1, creatinine level ≤1.5 mg/dl, and adequate organ function; no age criteria was imposed at the University Hospital, Kyoto Prefectural University of Medicine. Patients treated with <60 mg/m^2 of cisplatin were excluded from the study.

The regimens additionally included pre-hydration with 1,000 ml of saline, a $5HT_3$ receptor antagonist (palonosetron, 0.75 mg/day, day 1-5), aprepitant (125 mg/day, day 1; 80 mg/day, day 2-3) and dexamethasone (6.6 mg/day, day 1-5); 8 mEq of magnesium sulfate (day 1) was simultaneously administered within 2-3 h. Following these pre-treatments, high-dose cisplatin was administrated; post-hydration with 2,000 ml of electrolyte liquid, 60 g of D-mannitol and 20 mg of furosemide (day 1) were also performed. The electrolyte liquid included sodium, potassium and calcium ions in the external solution.

Mg supplementation for the patients was not determined at random; patients treated at the Division of Digestive Surgery typically received chemotherapy with Mg supplementation; however, patients treated at the Division of Gastrointestinal Medicine frequently received chemotherapy without Mg supplementation. The regimens excluding Mg supplementation, including hydration or other administrations, were confirmed to be the same between divisions. Appropriate treatments were performed for all hematological and non-hematological adverse events.

Evaluation of nephrotoxicity due to cisplatin. According to a previous study (18), the extent of nephrotoxicity was evaluated by increases in serum creatinine concentrations. A >1.1-fold increase in post-therapeutic creatinine concentrations from pre-therapeutic concentrations was defined as an increase. The grade of creatinine increase was indicated according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (19), as follows: Grade 1 indicated creatinine concentrations from above the upper limit of normal (ULN) to ≤1.5x ULN; grade 2, >1.5x and ≤3x ULN; grade 3, >3x and ≤6x ULN; and grade 4, >6x ULN. The most elevated creatinine concentration within the 3 weeks following the first chemotherapy cycle was compared with the pre-therapeutic concentration.

Statistical analysis. Statistical analyses were performed using StatView 5.0J software (SAS Institute, Inc., Cary, NC, USA). The Wilcoxon signed-rank test or Mann-Whitney U test was used to analyze the associations between various biochemical measurements. Spearman's correlation test was used to determine the correlation between pre-therapeutic creatinine concentrations and alterations in creatinine concentration. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. Patient characteristics are included in Table I. All the patients in the present study were diagnosed with SCC. A total of 37 out of the 55 patients received Mg supplementation; the remaining 18 patients did not. FP was administered to 46 patients, including 5 patients receiving CRT, whereas DCF was administered to 9 patients. FP therapy was more frequent for patients receiving Mg supplementation ($P=0.02$). The majority of the patients were clinically diagnosed with stage II or III disease. No significant differences were observed in clinicopathological features between the 2 groups with and without Mg supplementation, except for the types of chemotherapy.

Effects of Mg supplementation. Post-chemotherapeutic creatinine concentrations were significantly higher in patients without Mg supplementation ($P<0.01$; Fig. 1A) than with Mg

Table I. Characteristics of patients with esophageal squamous cell carcinoma with and without Mg supplementation.

Characteristics	Mg supplementation	
	Absent	Present
Total	18	37
Age, median (range)	65 (56-75)	67 (47-84)
Sex		
Male	15	28
Female	3	9
Performance status		
0	14	29
1	4	8
Chemotherapy		
FP alone	11	30
FP chemoradiotherapy	1	4
Docetaxel, cisplatin and 5-fluorouracil	6	3
Location		
Cervical or upper thoracic esophagus	3	6
Middle thoracic esophagus	11	21
Lower thoracic or abdominal esophagus	4	10
T stage		
1	1	1
2	1	4
3	11	28
4	5	4
Lymph node metastasis		
Absent	5	13
Present	13	24
Disease stage		
I	0	1
II	4	11
III	11	23
IV	3	2

Mg, magnesium; FP, 5-fluorouracil and cisplatin.

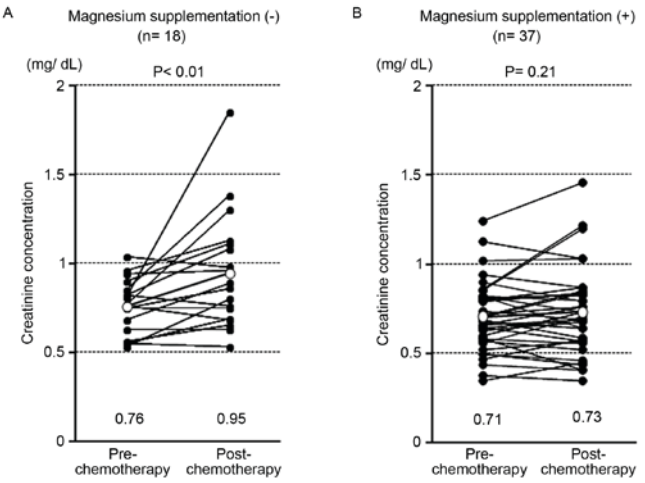

Figure 1. Increase in creatinine concentration pre- and post-chemotherapy. Alterations to creatinine concentrations prior and subsequent to chemotherapy for patients (A) without and (B) with magnesium supplementation. The mean creatinine concentrations are included. The Wilcoxon signed-rank test was used for statistical analysis.

Table II. Patients in the Mg absent and present groups experiencing an increase in creatinine.

Increase in creatinine, n (%)	Mg supplementation	
	Absent	Present
Total	18	37
Grade 1	4 (22.2)	3 (8.1)
Grade 2	1 (5.6)	0
Grade 3	0	0

Increase grade determined by the national cancer institute common terminology criteria for adverse effects version 4.0. Mg, magnesium.

Table III. Frequency of increases in PTH or PTH-rP.

PTH level, pg/ml	PTH-rP level, n (%)		Total, n (%)
	Low (<1.1 pmol/l)	High (≥1.1 pmol/l)	
Low (<520)	42 (76.4)	5 (9.1)	47 (85.5)
High (≥520)	7 (12.7)	1 (1.8)	8 (14.5)
Total	49 (89.1)	6 (10.9)	

PTH, parathyroid hormone; PTH-rP, parathyroid hormone related protein.

supplementation (P=0.21; Fig. 1B). The frequency of creatinine increases due to chemotherapy is included in Table II. In patients without Mg supplementation, 22.2% experienced grade 1 and 5.6%, grade 2 creatinine increases, whereas 8.1% of patients receiving Mg supplementation experienced grade 1 creatinine increases.

Increases in PTH or PTH-rP and the influence on creatinine concentrations. PTH and PTH-rP were high in 8 (14.5%) and 6 (10.9%) patients, respectively (Table III). Alterations in creatinine concentration following high-dose cisplatin-containing regimen tended to be higher in the high of PTH or PTH-rP level groups than in the low level groups (P=0.08 and P=0.04, respectively; Fig. 2A). These alterations were reduced in patients receiving Mg supplementation, particularly in the low PTH and PTH-rP level group and the high PTH-rP level group (Fig. 2B).

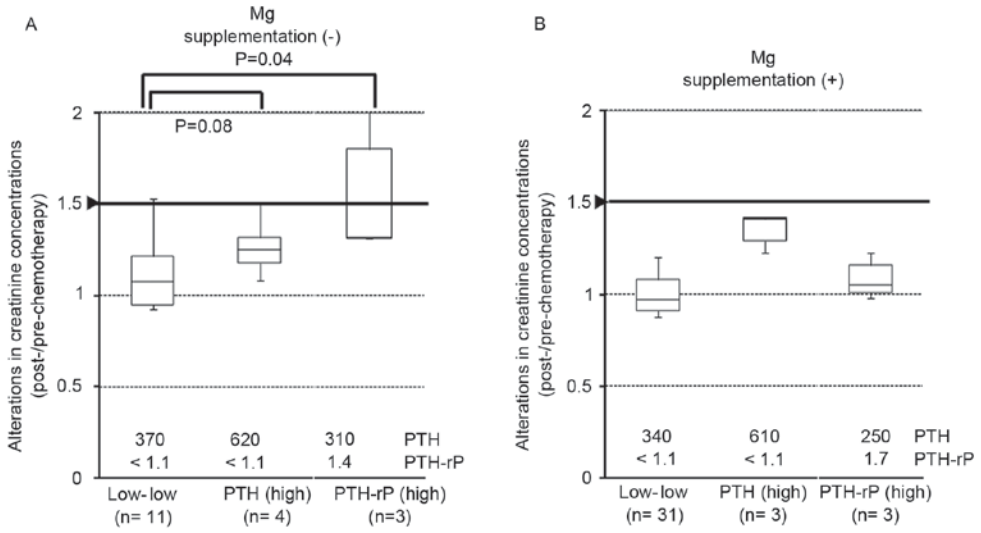

Figure 2. Alterations in creatinine concentrations between patients with low and high levels of PTH or PTH-rP. Alterations in creatinine concentrations prior and subsequent to chemotherapy for patients with low or high levels of PTH and PTH-rP without (A) or with (B) Mg supplementation. The median PTH and PTH-rP values in each group are included. The Mann-Whitney U-test was used for statistical analysis. PTH, parathyroid hormone; PTH-rP, parathyroid hormone related protein; Mg, magnesium.

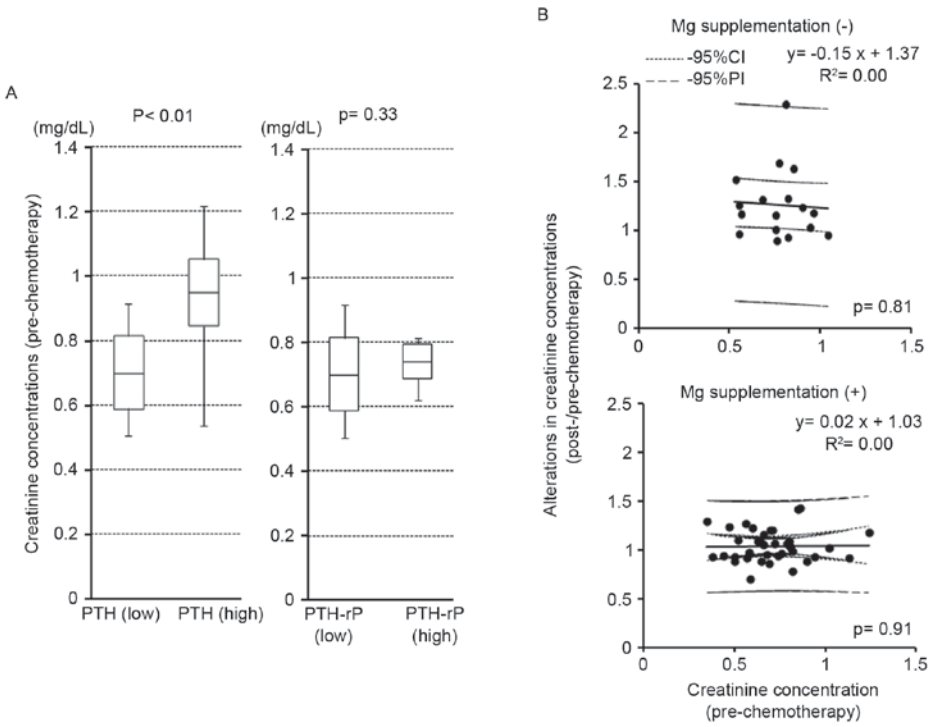

Figure 3. Influence of PTH or PTH-rP levels on pre-therapeutic creatinine concentrations. (A) Association between pre-therapeutic creatinine concentrations and PTH or PTH-rP levels. The Mann-Whitney U-test was used for statistical analyses. (B) Association between pre-therapeutic creatinine concentration and alterations to creatinine concentration were examined using Spearman's correlation test in the patients with or without Mg supplementation. PTH, parathyroid hormone; PTH-rP, parathyroid hormone related protein; Mg, magnesium.

Association of pre-therapeutic creatinine with PTH or PTH-rP levels and creatinine alterations. Pre-therapeutic creatinine concentrations were significantly higher in patients with high levels of PTH (P<0.01; Fig. 3A); however, they did not differ between high and low PTH-rP groups (P=0.33; Fig. 3A). Pre-therapeutic creatinine concentrations did not correlate with the alterations to creatinine concentrations following cisplatin-containing chemotherapy in the patients with or without Mg supplementation (P=0.81 and P=0.91, respectively; Fig. 3B).

Survival analysis of the patients with or without Mg supplementation. Mg supplementation did not affect the efficacy of high-dose cisplatin-containing chemotherapy, as the

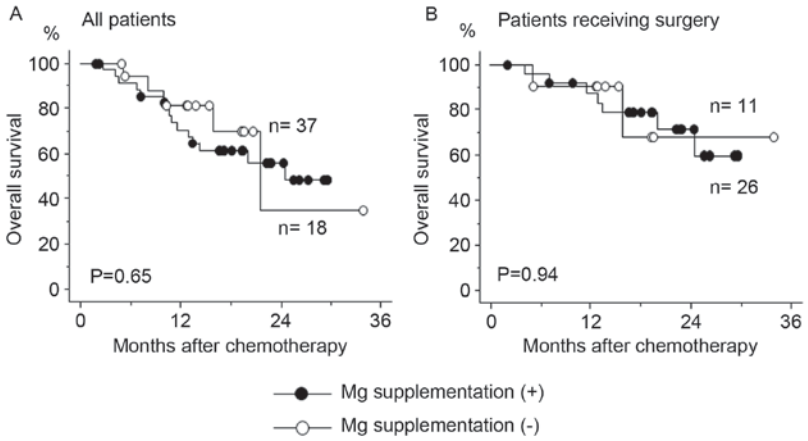

Figure 4. Survival analysis of the patients from the present study. The overall survival was analyzed with the Kaplan-Meier method, including (A) all patients with and without Mg supplementation and (B) the patients who received radical surgery following chemotherapy with and without Mg supplementation. The differences were compared by the stratified log-rank test. Mg, magnesium.

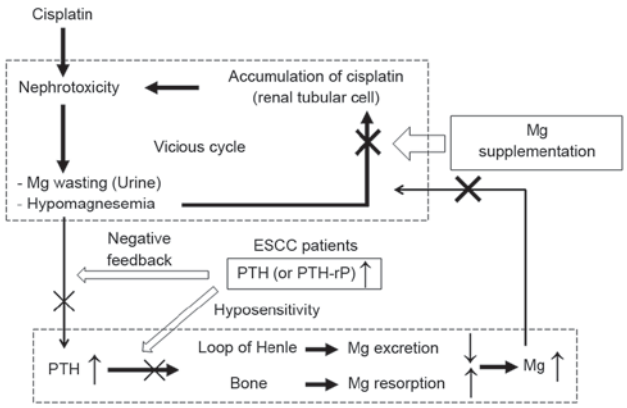

Figure 5. Schema of the present study. The vicious cycle of nephrotoxicity and expected changes in Mg and PTH levels due to cisplatin-containing chemotherapy are illustrated by dot-line boxes. Mg supplementation may interrupt this vicious cycle. Alternatively, increases in PTH or PTH-rP in patients with ESCC may disrupt the resolution of this vicious cycle as Mg increase may be interrupted by hyposensitivity or negative feedback to PTH activity. Mg, magnesium; PTH, parathyroid hormone; PTH-rP, parathyroid hormone related protein; ESCC, esophageal squamous cell carcinoma.

overall survival rate was similar between the patients with or without Mg supplementation regardless of whether surgery was performed subsequent to chemotherapy (Fig. 4).

Discussion

Cisplatin has been used in combination with other drugs as chemotherapy for various types of malignancy, including digestive tumors (3). The efficacy of administering high-dose cisplatin has been confirmed; however, severe adverse events, including hematotoxicity, anorexia, nausea and nephrotoxicity have been also reported (3,6,7). Large amounts of hydration with saline, mannitol and furosemide are accepted as the standard of care for patients treated with regimens containing high-dose (≥60 mg/m^2) cisplatin (3,10,11). Previous studies have demonstrated that Mg supplementation also confers protective effects against cisplatin-induced nephrotoxicity (10,20-22).

In the present study, the focus was on intravenous Mg supplementation for patients with ESCC treated with high-dose cisplatin. The results obtained confirmed that increases in post-chemotherapeutic creatinine concentrations were significantly suppressed by magnesium supplementation (Fig. 1 and Table II). The protective effects of oral or intravenous Mg supplementation against cisplatin-induced nephrotoxicity have been reported in various types of malignancy, including in lung (10-12), head and neck (10,23,24), digestive (8,10), testicular (25), ovarian (9,24) and bladder (24) cancer. However, just a limited number of clinical reports have demonstrated the protective effects of intravenous Mg supplementation against cisplatin-induced nephrotoxicity in ESCC (10).

PTH or PTH-rP levels in patients with ESCC were also considered; an association between increases in post-therapeutic creatinine concentrations and high levels of PTH was identified (Fig. 2). Previous studies reported that PTH-rP was expressed in a range of types of cancer, particularly ESCC and lung cancer, and mimicked the effects of PTH (14,26,27). In normal conditions, PTH is not an important physiological regulator of Mg homeostasis as renal regulation is, relatively, much more efficacious. However, it has been suggested that a large amount of PTH regulates serum Mg concentrations by decreasing urinary Mg excretion through influences on loop of Henle and bone resorption (13).

Fig. 5 is a schema for the rationale of the present study. Cisplatin induces renal Mg wasting and hypomagnesemia through its renal toxicity by directly injuring the mechanisms of Mg reabsorption (6,7,28). Hypomagnesemia reduces the expression of certain transporters in renal tubules in order to maintain serum Mg concentrations. This reduction in tubular transporters also amplifies the renal accumulation of cisplatin, which is accompanied by further nephrotoxicity (20-22). In this vicious cycle, we hypothesize that Mg supplementation protects against nephrotoxicity by blocking the augmented accumulation of cisplatin.

Alternatively, reductions in serum Mg levels due to cisplatin will induce increases in parathyroid hormone and serum Mg in order to resolve nephrotoxicity (Fig. 5). In patients with ESCC with high levels of PTH or PTH-rP, we hypothesize that rapid serum Mg increase will be disrupted by hyposensitivity to increases in PTH (29) or a negative-feedback mechanism

for lowering serum Mg (30,31), also implicated in calcium regulation. Therefore, patients with higher levels of PTH or PTH-rP may have more difficulties with hypomagnesemia and suppressing cisplatin-induced nephrotoxicity than patients with lower PTH or PTH-rP levels.

Approximately 8 mEq of Mg is excreted into the urine each day and reabsorbed during Mg deprivation (13). On this basis, 8 mEq of magnesium sulfate was administered prior to the administration of cisplatin, which was demonstrated to be similar to the volume excreted each day in a previous study (11). However, it currently remains unclear whether the volume and route of supplemented Mg was adequate.

Kidera *et al* (10) suggested that Mg supplementation was effective for protecting against renal toxicity induced by cisplatin. They also demonstrated that nephrotoxicity was more likely for patients with esophageal cancer. Although detailed tissue types were not considered in the present study, the results regarding increases in PTH or PTH-rP levels in patients with ESCC may be associated with this specificity. However, previous studies reported that Mg supplementation did not affect the tumor response to cisplatin-based chemotherapy (9,11,25). It was also concluded in the present study that Mg supplementation did not affect the efficacy of cisplatin-containing chemotherapy, as the overall survival time was similar between the patients with or without Mg supplementation (Fig. 4).

However, certain points in the present study remain undetermined. The reason why the level of PTH was increased in patients with ESCC was not identified. In addition to high sensitive PTH, the level of intact PTH was also measured, and the frequency of its increase being detected was low (data not shown). The frequency of intact PTH or PTH-rP increase was markedly lower than high sensitive PTH, although the results of high sensitive PTH may be influenced by other PTH subtypes, including PTH-rP, due to their similar structures. Although the levels of PTH and PTH-rP were analyzed separately in the present study, their effects on creatinine increases may be similar.

Alternatively, PTH levels may be influenced by chronic renal dysfunction. In the present study, pre-therapeutic creatinine concentrations were significantly higher in the patients with high levels of PTH, and not for patients with high levels of PTH-rP (Fig. 3A). The effects of Mg supplementation on creatinine alterations were also slightly different between patients with high levels of PTH and PTH-rP. These results require further investigation in order to confirm the influence of PTH or PTH-rP on cisplatin-induced nephrotoxicity.

In conclusion, although performed on a small scale, the present prospective study revealed that intravenous magnesium supplementation conferred protective effects against cisplatin-induced nephrotoxicity in patients with ESCC. Furthermore, increases in PTH or PTH-rP levels may influence nephrotoxicity.

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