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# Correlation between magnesium pre-loading and cisplatin-induced nephrotoxicity in 5-fluorouracil/cisplatin combination therapy for esophageal cancer

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The use of cisplatin may cause nephrotoxicity in patients. Hydration solutions supplemented with magnesium could reduce cisplatin-induced nephrotoxicity. In this study, we evaluated the preventive effect of magnesium pre-loading on cisplatin-induced nephrotoxicity in patients with esophageal cancer. We retrospectively evaluated the prevalence of, and risk factors for, nephrotoxicity in 160 patients with esophageal cancer treated with the 5-fluorouracil/cisplatin regimen from 2014 to 2016 with and without magnesium supplementation. Significant differences were observed between the magnesium and non-magnesium groups in terms of frequency of estimated creatinine clearance of grade 2 or higher that was at 4% (n = 3) and 13% (n = 10) ($p$ = 0.027), respectively. The logistic regression analysis revealed that eCcr of grade 2 or higher was significantly associated with the non-magnesium regimen (odds ratio (OR), 4.175; 95% confidence interval (CI) = 1.061–16.430; $p$ = 0.041) and age ≥ 65 years (OR, 13.951; 95% CI = 1.723–112.974; $p$ = 0.014). This study suggests that 20 mEq magnesium pre-loading significantly reduces the prevalence of cisplatin-induced nephrotoxicity. Furthermore, when cisplatin is administered to individuals older than 64 years, a close observation for the onset of cisplatin-induced nephrotoxicity is crucial.

## 1. Introduction

Cisplatin is an important chemotherapeutic agent that is highly effective in various cancers, including lung, bladder, ovarian, gastric, and esophageal cancers. However, cisplatin-induced nephrotoxicity (CIN) is a well-known adverse effect leading to dose-limiting toxicity, manifesting as acute or chronic impairment of renal function in most patients receiving a cisplatin-containing regimen (Higby et al. 1974).

Some mechanisms through which cisplatin causes renal cell injury have been reported. Tumor necrosis factor receptor family members, such as the Fas receptor and tumor necrosis factor receptor 1, seem to induce renal tubular cell apoptosis and renal dysfunction (Tsuruya et al. 2003). Cisplatin induces proximal tubule cell apoptosis *via* the activation of mitochondrial signaling pathways (Park et al. 2002). The major electrolyte imbalance resulting from tubular reabsorption defects and urinary waste accumulation is called hypomagnesemia, which is observed in more than 50% of patients treated with cisplatin-containing regimens (Schilsky and Anderson 1979; Lam and Adelstein 1986). Nephrotoxicity and Mg-depletion are well-known adverse effects of cisplatin treatment. Lajer et al. (2005) reported a substantial additive effect of Mg-depletion on cisplatin-induced renal toxicity, as evidenced by significant changes in plasma creatinine and urea levels, renal failure-induced mortality, and a loss of renal transporters.

Hydration solutions supplemented with Mg have been reported to reduce CIN (Muraki et al. 2012; Yamamoto et al. 2016; Aoyama et al. 2020; Bodnar et al. 2008; Yoshida et al. 2014; Yamamoto et al. 2015; Saito et al. 2017; Hamroun et al. 2019; Casanova et al. 2020; Hase et al. 2020). Only one randomized controlled trial has studied the effect of Mg pre-loading on CIN (Bodnar et al. 2008); however, this trial was short-scaled, and did not use a standardized acute kidney injury (AKI) classification. In addition, the dose of Mg in each hydration solution differs among studies, ranging from 8 to 40 mEq in pre-hydration solutions; thus, the adequate dose required to prevent CIN remains unclear. Hodgkinson et al. (2006) reported a significant association between cisplatin (dose, frequency, and number of cycles) and the degree of hypomagnesemia; a high dose of cisplatin is a risk factor for the development of hypomagnesemia. A Mg dose of 15 mEq was reportedly not sufficient to counteract cisplatin-induced Mg depletion.

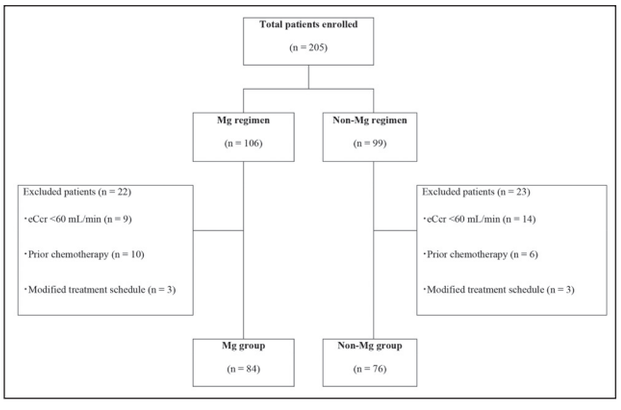


Fig.: CONSORT diagram. The diagram shows the number of participants evaluated for eligibility, those excluded and included in the statistical analysis. CONSORT: Consolidated Standards of Reporting Trials; eCcr: estimated creatinine clearance.

**Table 1: Baseline characteristics of patients**

| | Mg group | Non-Mg group | *p*-Value[a] |
|---|---|---|---|
| *Number of patients* | 84 | 76 | |
| *Age (years)* | | | |
| *Median (range)* | 64 (40–80) | 64 (43–82) | 0.95 |
| < 65, n (%) | 45 (54) | 38 (50) | 0.652 |
| ≥ 65, n (%) | 39 (46) | 38 (50) | |
| *Sex* | | | |
| Male, n (%) | 74 (88) | 60 (79) | 0.117 |
| Female, n (%) | 10 (12) | 16 (21) | |
| *ECOG performance status* | | | |
| 0–1, n (%) | 83 (99) | 75 (99) | 0.726 |
| 2, n (%) | 1 (1) | 1 (1) | |
| *Cardiovascular disease* | | | |
| Yes, n (%) | 33 (39) | 26 (34) | 0.506 |
| No, n (%) | 51 (61) | 50 (66) | |
| *Diabetes mellitus* | | | |
| Yes, n (%) | 9 (11) | 4 (5) | 0.208 |
| No, n (%) | 75 (89) | 72 (95) | |
| *Smoking* | | | |
| Yes, n (%) | 70 (83) | 63 (83) | 0.941 |
| No, n (%) | 14 (17) | 13 (17) | |
| *NSAIDs* | | | |
| Yes, n (%) | 10(12) | 6(8) | 0.398 |
| No, n (%) | 74(88) | 70(92) | |
| *Baseline serum albumin (g/dL)* | | | |
| Median (range) | 4 (2.3–4.7) | 4 (2.6–4.8) | 0.425 |
| < 3.5, n (%) | 13 (15) | 11 (14) | 0.859 |
| ≥ 3.5, n (%) | 71 (85) | 65 (86) | |
| *Baseline eCcr (mL/min)* | | | |
| Median (range) | 83.5 (60.4–212.4) | 87.6 (60.1–140.9) | 0.872 |
| *Baseline SCr (mg/dL)* | | | |
| Median (range) | 0.73 (0.32–1.17) | 0.70 (0.31–1.0) | 0.678 |
| *Baseline eGFR (mL/min/1.73 m²)* | | | |
| Median (range) | 76.4 (51.4–135.4) | 78.3 (53.7–125.6) | 0.863 |
| *Concurrent radiation therapy* | | | |
| Yes, n (%) | 32 (38) | 33 (43) | 0.493 |
| No, n (%) | 52 (62) | 43 (57) | |
| *Dose of cisplatin (total mg/m²)* | | | |
| Median (range) | 140 (70–160) | 160 (56–160) | 0.142 |
| 140–160, n (%) | 73 (87) | 60 (79) | 0.18 |
| 56–139, n (%) | 11 (13) | 16 (21) | |

ECOG: Eastern Cooperative Oncology Group; NSAIDs: non-steroidal anti-inflammatory drugs; eCcr: estimated creatinine clearance; SCr: serum creatinine; eGFR: estimated glomerular filtration rate.
[a] Mann–Whitney *U* test / Fisher's exact test.

The aim of this study was to evaluate the correlation between pre-loading with 20 mEq Mg and CIN in patients with esophageal cancer treated with the 5-fluorouracil/cisplatin (FP) regimen.

## 2. Investigations and results

### *2.1. Patient characteristics*

A Consolidated Standards of Reporting Trials diagram of the study is displayed in the Fig. Among the shortlisted 205 patients, 160 (84 in the Mg group and 76 in the non-Mg group) were included in the analysis; 22 and 23 patients were excluded from the Mg and non-Mg groups, respectively, as they did not meet the criteria for study eligibility. Baseline characteristics of the included patients are shown in Table 1. No significant differences were detected in age, sex, Eastern Cooperative Oncology Group performance status, cardiovascular disease, diabetes mellitus, smoking, regular use of non-steroidal anti-inflammatory drugs, baseline serum albumin, baseline eCcr, baseline SCr, baseline eGFR, concurrent radiation, and cisplatin dose. In total, 6 and 10 patients received only one course of chemotherapy in the Mg and non-Mg groups, respectively.

### *2.2. CIN evaluation*

Renal function evaluation results of the patients in both the Mg and non-Mg groups following chemotherapy are shown in Table 2. Significant differences were observed between the Mg and non-Mg groups in terms of the prevalence of eCcr of grade 2 or higher that was at 4% (n = 3) and 13% (n = 10) ($p = 0.027$), median eCcr level at 83.7 mL/min (range 25.5–166.7) and 75.9 mL/min (range 9.3–144) ($p = 0.037$), and median eGFR level at 78.2 mL/min/1.73 m² (range 23.8–135.1) and 69.7 mL/min/1.73 m² (range 7.2–144) ($p = 0.009$) after chemotherapy, respectively. The prevalence of AKI (KDIGO criteria) (1% in both groups, $p = 0.179$) and median SCr levels (0.74 and 0.79 mg/dL, $p = 0.076$) after chemotherapy did not differ significantly between the groups.

**Table 2: Evaluation of renal function after chemotherapy**

| | Mg group | Non-Mg group | *p*-Value[a] |
|---|---|---|---|
| *Number of patients* | 84 | 76 | |
| *KDIGO criteria* | | | |
| Yes, n (%) | 1 (1) | 1 (1) | 0.179 |
| No, n (%) | 83 (99) | 75 (99) | |
| *eCcr (mL/min)* | | | |
| ≥ Grade 2, n (%) | 3 (4) | 10 (13) | 0.027 * |
| < Grade 2, n (%) | 81 (96) | 66 (87) | |
| *eCcr (mL/min)* | | | |
| Median (range) | 83.7 (25.5–166.7) | 75.9 (9.3–144) | 0.037 * |
| *SCr (mg/dL)* | | | |
| Median (range) | 0.74 (0.38–2.07) | 0.79 (0.4–6.4) | 0.076 |
| *eGFR (mL/min/1.73 m²)* | | | |
| Median (range) | 78.2 (23.8–135.1) | 69.7 (7.2–144) | 0.009 * |

KDIGO criteria: Kidney Disease: Improving Global Outcomes criteria; eCcr: estimated creatinine clearance; SCr: serum creatinine; eGFR: estimated glomerular filtration rate. Grade: National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0.
[a] Mann–Whitney *U* test / Fisher's exact test. *Statistically significant

**Table 3: Univariate and multivariate analyses of risk factors for the prevalence of eCcr of Grade 2 or higher**

| Factors | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | OR (95% CI) | *p*-Value | OR (95% CI) | *p*-Value |
| *Regimen (non-Mg)* | 4.091 (1.081–15.476) | 0.027 * | 4.175 (1.061–16.430) | 0.041 * |
| *Age (≥ 65 years)* | 15.138 (1.918–119.467) | 0.001 * | 13.951 (1.723–112.974) | 0.014 * |
| *Sex (female)* | 1.617 (0.413–6.332) | 0.355 | | |
| *Baseline serum albumin (< 3.5 g/dL)* | 1.8 (0.457–7.087) | 0.305 | | |
| *NSAIDs (yes)* | 1.727 (0.347–8.591) | 0.382 | | |
| *Cardiovascular disease (yes)* | 2.131 (0.681–6.675) | 0.153 | | |
| *Diabetes mellitus (yes)* | 2.248 (0.442–11.440) | 0.285 | | |
| *Smoking (yes)* | 2.579 (0.321–20.713) | 0.318 | | |

OR: odds ratio; CI: confidence interval; NSAIDs: non-steroidal anti-inflammatory drugs.
*Statistically significant.

### 2.3. Risk factors for the prevalence of eCcr of grade 2 or higher

Based on the univariate analysis, the risk factors for the prevalence of eCcr of grade 2 or higher are shown in Table 3. The non-Mg regimen (odds ratio [OR], 4.091; 95% confidence interval [CI] = 1.081–15.476; $p = 0.027$) and age ≥ 65 years (OR, 15.138; 95% CI = 1.918–119.467; $p = 0.001$) marginally correlated with the prevalence of eCcr of grade 2 or higher. The logistic regression analysis revealed that the risk factors for the prevalence of eCcr of grade 2 or higher were significantly associated with the non-Mg regimen (OR, 4.175; 95% CI = 1.061–16.430; $p = 0.041$) and age ≥ 65 years (OR, 13.951; 95% CI = 1.723–112.974; $p = 0.014$).

## 3. Discussion

In this study, we evaluated the correlation between Mg pre-loading and CIN in patients with esophageal cancer who were treated with the FP regimen. We observed that pre-loading with 20 mEq Mg significantly reduced CIN. The proportion of patients with eCcr of grade 2 or higher after chemotherapy in the Mg group was significantly lower than that in the non-Mg group. Our study also indicated that age ≥ 65 years was a risk factor for the presence of grade 2 or higher eCcr.

Although both groups showed a similar AKI prevalence, the eCcr and eGFR values measured after chemotherapy indicated a significant reduction in the prevalence of CIN in the Mg group compared with the non-Mg group. The number of patients with eCcr of grade 2 or higher after chemotherapy was significantly lower in the Mg than in the non-Mg group. When the eCcr is < 60 mL/min, a reduced dose of cisplatin is recommended (1995). Therefore, the CIN preventive effect of Mg pre-loading is considered clinically important.

Yajima et al. (2013) reported a reliability of predicted renal function in Japanese patients on cisplatin therapy. The Japanese Society of Nephrology states the following: "the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) requires a coefficient correction of ×0.813 when applied to Japanese patients." In addition, the CKD-EPI formula is not suitable for Japanese patients, because its estimation error is larger than that of the Japanese GFR estimation formula when the GFR is < 60 mL/min/1.73 $m^2$, even if the coefficient is corrected. Therefore, we used the Cockcroft formula rather than the CKD-EPI.

CIN studies have primarily focused on lung cancer (Muraki et al. 2012; Yoshida et al. 2014; Hase et al. 2020); thus, there are only a few reports on CIN in esophageal cancer (Kubo et al. 2019). Patients with esophageal cancer have a significantly higher risk of CIN than that in patients with lung cancer, although the mechanism remains unknown (Kidera et al. 2014). We hypothesized that the renal protective effect of Mg pre-loading in esophageal cancer was similar to that observed in lung cancer.

Risk factors reported to predict CIN include hypoalbuminemia, smoking, female sex, old age, concomitant use of other anticancer drugs, serum potassium level, cardiovascular disease, diabetes complications, advanced cancer, and the total cisplatin dose (de Jongh et al. 2003; Steward et al. 1997; Mizuno et al. 2013). However, the CIN definition in these studies varies, and the thresholds for the risk factors are not clear. In our study, the multivariate analysis revealed that the non-Mg group, and elderly patients over 64 years of age, had an increased prevalence of eCcr of grade 2 or higher, which is similar to the results of a previous study (de Jongh et al. 2003). We summarized our results at patients aged over 64 years based on two factors-first, significantly different results observed in this age group in our study and, second, another study that defined patients aged 65 years and older as the "elderly" (Yancik and Ries 2000). Elderly patients have inadequate physiological functions and reduced ability to metabolize drugs (Ginseng et al. 2005; Mühlberg and Platt 1999). Therefore, elderly patients should be carefully monitored for the occurrence of CIN.

There were some limitations in this study. First, to date, the exact dose of Mg required to efficiently ameliorate CIN has not been investigated; therefore, our dose selection may have been suboptimal even though it produced a positive effect. Second, we did not validate the association between CIN and serum or urinary Mg levels. Thus, a future study to measure serum Mg level is warranted. Nevertheless, it is important to identify therapeutic strategies that can contribute to the practicality of prospective studies.

In conclusion, we evaluated the correlation between Mg pre-loading and CIN in patients with esophageal cancer. The results of the current study suggested that 20 mEq Mg pre-loading significantly reduced the prevalence of CIN. Furthermore, when cisplatin is administered to individuals older than 64 years of age, a close observation for the onset of CIN is crucial.

## 4. Experimental

### 4.1. Patients

We retrospectively evaluated the clinical data of patients with esophageal cancer treated with the FP regimen in the Department of Gastroenterological Chemotherapy, Cancer Institute Hospital, Japan, from August 1, 2014 to July 30, 2016. The patients were divided into two groups: a control or non-Mg group treated with a non-Mg premedication FP regimen from August 1, 2014 to June 30, 2015, and an Mg group treated with an intravenous Mg premedication FP regimen from July 1, 2015 to July 30, 2016. Patients were eligible if they had esophageal cancer and an Eastern Cooperative Oncology Group performance status of 0–2. Patients were excluded from the study if their estimated creatinine clearance (eCcr) was less than 60 mL/min or if they had previously received chemotherapy.

### 4.2. Treatment methods

Patients received two regimens of FP (5-fluorouracil 700–800 mg/$m^2$ on days 1–4 or 1–5 and cisplatin 70–80 mg/$m^2$ on day 1; every 3–4 weeks). For the Mg group, hydration was performed with a total volume of 3000 mL (pre-cisplatin, 1500 mL; at cisplatin, 500 mL; post-cisplatin, 1000 mL). In addition, Mg sulfate at a dose of 20 mEq (2.46 g) and 20 mg of furosemide were administered before cisplatin. For the non-Mg group, hydration with a total volume of 3500 mL (pre-cisplatin, 1300 mL; at cisplatin, 300 mL; post-cisplatin, 1900 mL) was performed. In addition, 20 mg of furosemide was administered before cisplatin. In both groups, on days 2–4, 1000–2000 mL of hydration fluid was administered intravenously. Chemotherapy and radiation therapy were administered concurrently. For patients requiring concomitant radiation therapy, the treatment field ranged from the neck to upper abdomen, and the dose was 40–60 Gy.

### 4.3. CIN evaluation

CIN was evaluated by measuring the serum creatinine (SCr) level, eCcr (using the Cockcroft-Gault formula), and estimated glomerular filtration rate (eGFR = $194 \times Cre^{-1.094} \times age^{-0.287}$; for women, × 0.739). Each CIN parameter was evaluated before the first course of chemotherapy (baseline value) and after the two FP cycles. Patients who could receive only one course of treatment were evaluated after the first course. To evaluate CIN, renal function post-chemotherapy was measured at the initial blood sampling point post-treatment (after drug washout). We investigated eCcr level of grade 2 or higher according to the Common Terminology Criteria for Adverse Events (version 5.0), Chronic Kidney Disease. To assess AKI, we used the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 criteria (Khwaja 2012).

### 4.4. Statistical analyses

Continuous variables were compared using the Mann–Whitney *U* test, and categorical variables, using Fisher's exact test. To evaluate the risk factors for eCcr of grade 2 or higher following the FP regimen, univariate and multivariate logistic regression analyses were conducted. All analyses were carried out using SPSS version 24.0 (IBM, Armonk, NY, USA). A significance level of $p < 0.05$ was employed. Factors with $p < 0.05$ or less in the univariate analysis were included in the multivariate analysis to explore any confounding factors.

These analyses were conducted in accordance with the World Medical Association Declaration of Helsinki, and were independently reviewed and approved by the Clinical Research Ethics Review Committee of the Hospital (approval no. 2019-1168). Patients were not solicited for informed consent given the retrospective nature of the study. All patient data were processed in anonymity and de-identified before analysis.

Disclosure of interest: K.Y. received speaking honoraria from Taiho, Eli Lilly, Ono ,BMS, Yakult ,Sanofi, Chugai, Takeda, Bayer, Daiichi-Sankyo, Dainippon-Sumitomo, MSD, and Gilead Sciences Squibb; research grants from Taiho, Eli Lilly Japan, Ono, Bristol-Myers Squibb, Yakult Honsha, Sanofi, Chugai. K.C. received speaking honoraria from Ono, Chugai; research grants from Taiho. The other authors have no conflicts of interest to declare.

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