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The efficacy of magnesium in preventing renal dysfunction due to high-dose cisplatin for treatment of thoracic tumor

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Objective Cisplatin is well known for producing severe adverse events, including renal dysfunction. To prevent renal dysfunction caused by cisplatin, routine magnesium supplementation is recommended. However, few reports exist about the efficacy of magnesium in preventing renal dysfunction. Therefore, the purpose of this study was to retrospectively survey the efficacy of magnesium in preventing renal dysfunction after administration of cisplatin.
Methods We evaluated patients who received first-line cisplatin-based chemotherapy from May 2008 to June 2013.
Results Data from 146 patients and a total of 394 treatments was analyzed. Elevation of serum creatinine was detected in 77 / 394 treatments (19.5%). Statistical significance was found between prevention of elevation of serum creatinine and magnesium supplementation. The other significant parameters were serum creatinine and eGFR levels before treatment and patient age. In multivariate analysis, magnesium and eGFR before treatment were statistically significant.
Conclusions The study results suggest that magnesium supplementation might reduce nephrotoxicity caused by cisplatin. The eGFR level before treatment might be an important factor associated with nephrotoxicity after cisplatin administration.

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Key words: cisplatin, renal dysfunction, magnesium, eGFR

Introduction

Cisplatin is one of the most widely used drugs as part of a combination chemotherapeutic regimen for treating lung cancer and other solid tumors. Chemotherapy with cytotoxic agents plays an important role in the treatment of lung cancer. Several trials have documented the efficacy of adjuvant cisplatin-based chemotherapy [1, 2] ; therefore, the tendency has been increasing for chemotherapy to be used as adjuvant therapy after surgery.

Cisplatin demonstrates an anti-tumor reaction that binds the drug to DNA and creates platinum–DNA adducts. Although cisplatin produces a good anti-tumor reaction, it is well known for producing severe adverse events such as renal dysfunction, vomiting, etc. To treat chemotherapy-induced nausea and vomiting (CINV), various anti-emetic drugs have been developed, such as 5-hydroxytryptamine type 3 (5-HT_3) receptor antagonists [3] and neurokinin-1 receptor antagonists [4]. Antiemetic guidelines were established, and the control of CINV was improved.

To prevent renal dysfunction caused by cisplatin, hydration and evaluation of renal function before chemotherapy have been recommended [5]. In addition, monitoring of the magnesium level and routine magnesium supplementation have also been recommended [6, 7]. Some reports have indicated that the administration of magnesium before adminis-

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tration of cisplatin prevents the development of renal dysfunction [8, 9].

Recently, some indicate the possibility that the renal dysfunction after high-dose cisplatin-based chemotherapy can be prevented by a short hydration regimen that includes magnesium [10]. However, previous studies have not provided sufficient evidence regarding the prevention of renal dysfunction because the clinical trials were small and not aimed at treating thoracic tumors [8, 9]. Therefore, the purpose of the present study was to survey the efficacy of magnesium in preventing renal disfunction after administration of high-dose cisplatin for treatment of thoracic tumors.

Method and patients

Patients and treatment

Information was collected on patients who had been pathologically diagnosed with thoracic malignancies and treated with cisplatin-based chemotherapy as first-line therapy between May 2008 and June 2013 at Nagasaki University School of Medicine and Japanese Red-Cross Nagasaki Atomic Bomb Hospital. All patients were administered cisplatin at a dose of more than 50 mg/m^2 in each cycle, and received sufficient hydration and antiemetic agents. The following variables before treatment were collected: sex, age, weight, body surface area, performance status (PS) according to the Eastern Cooperative Oncology Group scale, pathological type of cancer, and clinical staging. Serum creatinine level and estimated glomerular filtration rate according to the Japanese Society of Nephrology (eGFR) were obtained just before each chemotherapy cycle. In accordance with the previous report [10], we defined the patients who were intravenously administered magnesium at a dose of ≥ 8 mEq during the chemotherapy as the study group, and defined the patients who did not receive magnesium or who were intravenously administered magnesium at a dose of < 8 mEq during the chemotherapy as the control group. The study protocol was reviewed and approved by the institutional review board.

Renal function

The evaluation of renal function in each patient was performed by estimating the serum creatinine level and eGFR. We used eGFR because it has come to be recognized as the most accurate eGFR in Japanese cancer patients. In Japan, the eGFR is calculated using the Cockcroft–Gault formula, creatinine clearance measured by 24-h urine collection, the 0.808 × Modification of Diet in Renal Disease study equation, and the 0.813 × Chronic Kidney Disease Epidemiology Collaboration equation [11].

The eGFR formula is as follows:

eGFR (ml/min/ 1.73 m^2) = 194 × (serum creatinine)$^{-1.094}$ × (age)$^{-0.287}$ (× 0.739 if female) [12]. We defined elevation of serum creatinine level as higher than the institutional upper limit of the normal level, and low serum creatinine level as lower than the institutional lower limit of the normal level.

Statistical analysis

Differences between the study group and the control group were evaluated using the chi-square test. In this analysis, renal dysfunction was defined as elevation of serum creatinine level beyond the upper limit of the institutions. Additional hydration due to renal dysfunction was also evaluated using the chi-square test. Relationships between renal dysfunction and various parameters were evaluated by the Mann–Whitney U test and the chi-square test. In multivariate analysis, we used the logistic regression method. Statistical significance was determined by using two-tailed P values and was reported at $P < 0.05$. All of the statistical analyses were performed using SPSS (SPSS for Windows, version 22.0, SPSS, Chicago, IL, USA).

Results

Patients

Data was analyzed for 146 patients who were treated between June 2008 and June 2013. There were 77 patients who were treated with platinum-based chemotherapy without magnesium (control group), and 69 patients who received magnesium (study group). Table 1 shows the characteristics of both groups. There were no significant differences between both groups in terms of age, sex, and PS. Eight patients with malignant pleural mesothelioma (MPM) were treated with magnesium-containing regimens, and 8 patients with MPM were treated with magnesium-free regimens. No patients with thymic tumors were treated with magnesium-containing regimens, and 6 patients with thymic tumors were treated with regimens containing magnesium of doses < 8 mEq. There was no statistically significant difference in the serum creatinine and eGFR just before the administration of cisplatin-containing regimens.

Table 1. Patient characteristics and renal function before cisplatin-based chemotherapy

Characteristics	Non-Mg	Mg	*P* value
Age (n), Median (range)	64 (33-77)	62 (31-74)	0.0846
Men : Women (n)	59 : 18	58 : 11	0.3028
Performance Status (n) 0 : 1 : 2	15 : 60 : 2	9 : 55 : 5	0.2763
Disease (n)			
NCSLC			
Stage III, IV	32	29	
Neoadjuvant	3	6	
Adjuvant	11	16	
SCLC			
Limited disease	7	4	
Extended disease	8	6	
MPM			
Stage II, III	5	6	
Stage IV	3	2	
Thymic tumor	6	0	
Sarcoma	2	0	
Cr (mg/dl), Mean ± SD	0.74 ± 0.15	0.75 ± 0.14	0.6040
eGFR (ml/min/1.73m^2), Mean ± SD	80.4 ± 16.2	81.8 ± 16.6	0.6274

NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; MPM, malignant pleural mesothelioma; Cr, serum creatinine; eGFR, estimated glomerular filtration rate.

Treatment

A total of 394 treatments were evaluated in the analysis of the present study: 193 treatments in the study group and 201 treatments in the control group. The median number of chemotherapy cycles was 3 in both groups. Seventeen patients (23%) in the control group and 23 patients (31%) in the study group received more than 4 cycles. The mean dose of cisplatin in the study group and the control group was 68.3 mg/m^2 and 70.9 mg/m^2, respectively (P = 0.1105). In the control group, irinotecan, etoposide and gemcitabine were mainly used with cisplatin. In the study group, pemetrexed, S-1 and vinorelbine were the main drugs that were used. The frequency of combined thoracic radiotherapy was 22% and 17% in the control and study group, respectively.

Renal function

Figure 1 shows the fluctuations in serum creatinine and eGFR just before each treatment. The mean serum creatinine level and mean eGFR for all cycles were stable at around 0.8 mg/dl and 80 ml/min/1.73m^2 in both groups. Figure 1 also indicates that the elevation of serum creatinine and the reduction of eGFR were mild in the study group compared with the control group after three cycles, although this observation was not statistically significant.

In the 394 treatments, 77 treatments produced an elevation in serum creatinine (19.5%). Of these, 24 (12.4%) were in the control group (n = 193), and 53 (26.3%) were in the study group (n = 201); this difference was statistically significant (P = 0.006). In other parameters, the serum creatinine level and eGFR level before treatment and patient age were statistically associated with elevation in serum creatinine (Table 2). In multivariate analysis, magnesium and eGFR before treatment were found to be statistically significant, but the other parameters were not statistically significant (Table 3).

Additional infusions to protect renal function were administered in a total of 35 treatments (8.9%); 21 treatments in the control group and 14 in the study group, with no statistically significant differences. In addition, there were no grade 3 or 4 neuromuscular or cardiovascular adverse events recorded in either group that might have been related to hypermagnesemia, although the serum magnesium level had failed to be checked in most treatments.

Eight patients (10.4%) in the control group and 4 patients (5.7%) in the study group did not experience recovery of renal dysfunction. Seven patients (9.1%) in the control group

Table 2. Result of univariate analysis of risk factors for the elevation of serum creatinine level caused by cisplatin

Factors	Above normal level	Within normal level	*P* value
Cr (mg/dl), Mean ± SD	0.891 ± 0.170	0.747 ± 0.139	<0.0001
eGFR (ml/min/ 1.73 m^2), Mean ± SD	65.7 ± 12.2	80.7 ± 15.8	<0.0001
Age, Median (range)	67 (37-77)	63 (31-77)	0.0015
Men : Women (n)	63 : 14	252 : 65	0.7517
Body surface area (m^2), Mean ± SD	1.676 ± 0.171	1.640 ± 0.162	0.0667
Dose of cisplatin (mg/m^2), Mean ± SD	68.8 ± 9.57	67.0 ± 9.83	0.1292

Mg, magnesium; Cr, serum creatinine; eGFR, estimated glomerular filtration rate.

Table 3. Result of multivariate analysis of risk factors for the elevation of serum creatinine level caused by cisplatin

Factors	Odds Ratio	95% CI	*P* value
Mg	0.490	0.275-0.873	0.016
eGFR	0.735	0.601-0.899	0.003
Cr	1.085	0.928-1.269	0.307
Age	1.045	0.890-1.227	0.591

Mg, magnesium; Cr, serum creatinine; eGFR, estimated glomerular filtration rate.

and four patients (5.7%) in the study group required dosage reduction of cisplatin. Neither the recovery of renal function nor dosage reduction of displatin were statistically significant between the study group and the control group.

Discussion

The results of this analysis support that renal dysfunction induced by a cisplatin-based chemotherapeutic regimen might be prevented by the intravenous infusion of magnesium before the administration of cisplatin. Recently, Yoshida et al. [13] retrospectively analyzed the role of magnesium in patients with thoracic malignancy who were treated with cisplatin-based combination chemotherapy. According to this report, the elevation of serum creatinine in the magnesium group was significantly lower during all cycles than in the non-magnesium group, and, in a multivariate analysis, magnesium preloading significantly reduced cisplatin-induced nephrotoxicity throughout the entire period from after the first administration. The investigators concluded that magnesium preloading before cisplatin administration significantly reduced cisplatin-induced nephrotoxicity. The results of the present study also indicate that magnesium preloading significantly prevented the elevation of serum creatinine levels.

Measurement of eGFR is a new method for estimating the glomerular filtration rate in the Japanese population [14]. This method can evaluate the glomerular filtration rate exactly according to age, sex, and serum creatinine levels without measuring the amount of urine creatinine. Thus, eGFR can evaluate renal function exactly even after the administration of cisplatin. In the present study, we evaluate the eGFR just before each cycle of cisplatin. Although not statistically significant, the reduction in eGFR was mild in the magnesium-preloading group compared with the non-magnesium-preloading group after three chemotherapy cycles (Fig 1). This led to the hypothesis that magnesium preloading might prevent renal dysfunction induced by repeated administrations of cisplatin.

The present retrospective analysis regarding the prevention of renal dysfunction induced by cisplatin by magne-

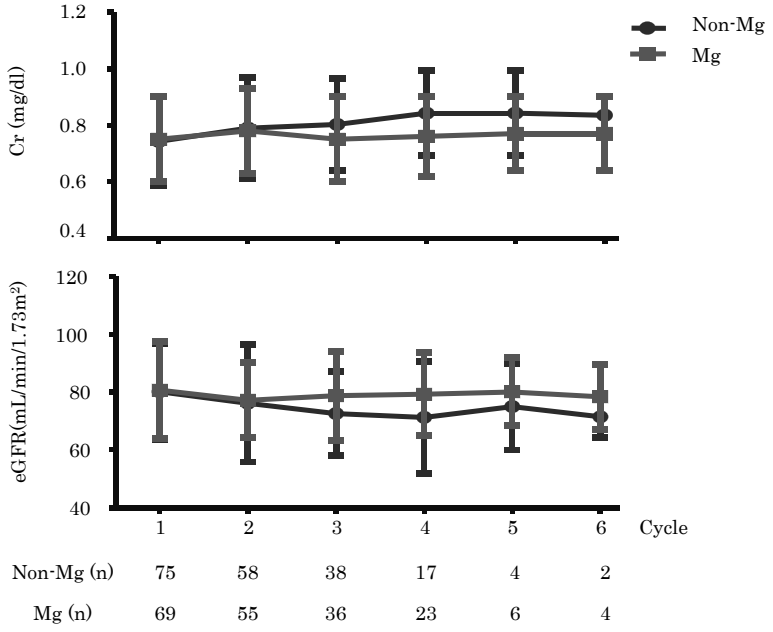

Fig.1 Graphs showing the fluctuations of the level of serum creatinine (Cr) and estimated glomerular filtration rate (eGFR) just before each treatment. The red line indicates the magnesium-preloading group (Mg), and the blue line indicates the magnesium non-preloading group (Non-Mg).

sium preloading had some limitations. First, the method for determing eGFR has only been established relatively recently; therefore, few prospective analyses have been conducted that evaluate the relationship between eGFR and cisplatin-induced renal dysfunction. Second, we could not evaluate the timing and dose of magnesium preloading. On these two points, a further prospective trial is needed to evaluate the relationship between eGFR and cisplatin-induced renal dysfunction, and the adequate timing and dose of magnesium preloading.

In conclusion, the present study retrospectively revealed that intravenous administration of magnesium prevented elevation in the serum creatinine level in patients with thoracic tumor treated with cisplatin-containing regimens. This suggests that administration of magnesium might reduce nephrotoxicity caused by cisplatin. Although few prospective trials exist, and adequate dosing and timing remains unclear, magnesium might be considerably useful in cisplatin-based chemotherapy for patients with non-small cell lung cancer. Further investigations are needed to confirm that magnesium preloading prevents nephrotoxicity, which includes reduction of eGFR, caused by cisplatin.

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