Magnesium supplementation therapy to prevent cisplatin-induced acute nephrotoxicity in pediatric cancer: A protocol for a randomized phase 2 trial

Atsushi Makimoto, Motohiro Matsui, Motoaki Chin, Katsuyoshi Koh, Masako Tomotsune, Tetsuji Kaneko, Yoshihiko Morikawa, Yuki Yuza

Abstract

Although cisplatin is one of the most effective agents against various pediatric cancers, it is sometimes difficult to manage due to its dose-limiting nephrotoxicity. Magnesium sulfate (Mg) showed a kidney-protective effect against cisplatin-induced nephrotoxicity (CIN) by regulating renal platinum accumulation both in vitro and in vivo, and the body of clinical data demonstrating the efficacy of this drug in adult cancer patients is increasing.

In this open, multicenter, phase-2, randomized trial, patients under age 18 years who are scheduled to receive cisplatin-containing chemotherapy will be enrolled and randomly allocated either to an Mg supplementation arm in even-numbered chemotherapy courses (arm AB) or to another arm in odd-numbered courses (arm BA), with a 1:1 allocation. Analysis objects will be reconstructed into two groups depending on whether the chemotherapy course has Mg supplementation (group B) or not (group A). The primary endpoint is the proportion of chemotherapy courses resulting in elevated serum creatinine equal to or greater than 50% of the pre-chemotherapy value. For the secondary endpoints, various parameters for measuring kidney function, such as serum cystatin-C, B2M, L-FABP, NGAL, and urinary NAG in the two groups will be compared. A sample size based on alpha = 5% and 80% power requires at least 40 samples per group (ideally, 60 samples per group).

If Mg demonstrates efficacy, a phase-3 study to confirm the prophylactic effect of Mg supplementation in both acute and chronic CIN will be developed using novel and better biomarkers.

Trial registration: UMIN-CTR (http://www.umin.ac.jp/icdr/index.html) Identifier UMIN000029215.

1. Introduction

Cisplatin is one of the most active chemotherapeutic agents in the treatment of pediatric cancers, including neuroblastomas, hepatoblastomas, medulloblastomas, osteosarcomas, malignant germ cell tumors, etc. [1]. Long-term survival recently increased to 50-90% per disease, making countermeasures against acute and chronic toxicity increasingly important for young survivors [2].

Cisplatin exerts its cytotoxic effects by platination of DNA, which damages the DNA template and induces cellular apoptosis. The dose limiting nephrotoxicity of cisplatin involves a reduction in renal blood flow, glomerular filtration rate (GFR), and renal tubular function [1]. Although the exact mechanism of cisplatin-induced nephrotoxicity (CIN) is not understood, various processes, including local inflammation, oxidative stress, DNA damage, and tubular epithelial cell apoptosis have been suggested [3,4].

The incidence of CIN is 30-60% in pediatric cancer patients who receive cisplatin [5]. Although intravenous hydration and diuresis with mannitol during cisplatin administration can decrease CIN, randomized studies have failed to show any clear benefit from these supportive treatments [6].

In a rat model, magnesium (Mg) supplementation showed a kidney-
protective effect against CIN by regulating renal platinum accumulation via changes in cisplatin efflux transporter expression in the tubular epithelial cells [7]. In humans, the efficacy of Mg supplementation for CIN prevention was evaluated in several clinical trials in adults and showed promising results [8–12], but its efficacy in pediatric patients has not been thoroughly evaluated. Prior to designing the current study, we performed a retrospective study which suggested that Mg supplementation had a kidney-protective effect in a pediatric cancer cohort [13].

The current study is designed to investigate prospectively whether Mg supplementation can reduce the incidence of CIN in children with cancer who are scheduled for treatment with cisplatin-containing chemotherapy in a randomized phase-2 setting. For the primary endpoint, CIN will be evaluated by the increase in serum creatinine. Furthermore, this study will use the values for serum cystatin-C, beta-2 microglobulin (B2M), L-type fatty acid binding protein (L-FABP), neutrophil gelatinase-associated lipocalin (NGAL), and urinary N-acetyl-β-D-glucosaminidase (NAG) to assess CIN in detail.

In the proposed study, a single course of chemotherapy will be regarded as one sample. Each patient will be randomly allocated to two arms with different patterns of Mg supplementation. Because a pediatric cancer patient usually undergoes 3–8 courses of chemotherapy, Mg supplementation will be administered alternately with chemotherapy in each patient to facilitate the recruitment of samples and to minimize selection bias between two the randomized groups.

2. Methods

2.1. Study design

This study is an open, multicenter, phase-2, randomized trial aimed at determining whether Mg supplementation during cisplatin-containing chemotherapy reduces CIN. As described above, a single chemotherapy course will be regarded as one sample. Participants will be randomly allocated either to an arm in which Mg supplementation is administered only during the odd-numbered courses (arm BA) or to another arm in which Mg supplementation is administered alternately with chemotherapy in a randomized phase-2 setting. For the primary endpoint, CIN will be evaluated by the increase in serum creatinine. Furthermore, this study will use the values for serum cystatin-C, beta-2 microglobulin (B2M), L-type fatty acid binding protein (L-FABP), neutrophil gelatinase-associated lipocalin (NGAL), and urinary N-acetyl-β-D-glucosaminidase (NAG) to assess CIN in detail.

In the proposed study, a single course of chemotherapy will be regarded as one sample. Each patient will be randomly allocated to two arms with different patterns of Mg supplementation. Because a pediatric cancer patient usually undergoes 3–8 courses of chemotherapy, Mg supplementation will be administered alternately with chemotherapy in each patient to facilitate the recruitment of samples and to minimize selection bias between two the randomized groups.

2.2. Participants

Subjects who fulfill all the inclusion criteria and none of the exclusion criteria which are described in Table 1 will be enrolled.

2.3. Interventions

In this study, participants will be randomly allocated equally to two arms. As shown in Fig. 1, one arm will receive cisplatin-containing chemotherapy without Mg in the first course, then start Mg supplementation in the second and subsequent, even-numbered courses (arm AB). The other arm will receive cisplatin-containing chemotherapy with Mg supplementation from the first course; thereafter, Mg will be administered only during the odd-numbered courses (arm BA).

In group B, intravenous Mg sulfate will be administered concomitantly with intravenous fluid 2,400–3,000 ml/m²/day. The Mg supplementation dosage will be 15 mEq/m²/day (allowance: 13.5–16.5) starting at least 12 h prior to the initiation of the cisplatin infusion and continuing until at least 24 h after termination of the infusion. In group A, Mg administration will be allowed in patients who present hypomagnesemia < 1.5 mg/dl only when cisplatin is not being administered.

2.4. Outcomes

The primary endpoint will be calculated based on the serum creatinine value, and the secondary endpoints will be calculated based on the serum cystatin-C, B2M, L-FABP, NGAL, and urinary NAG values. The baseline of these parameters will be examined at least 12 h before starting cisplatin in each group. In group B, Mg administration will be started after the base line samples are taken. The parameters will subsequently be measured at 48 (± 24) hours, 7 (± 2) days, 14 (± 2) days, and 21 (± 2) days after starting cisplatin administration.

For the primary endpoint, the highest serum creatinine value will be
Table 2
Definition of nephrotoxicity in terms of the various parameters.

| Parameters        | Definition of nephrotoxicity                                                                 |
|-------------------|---------------------------------------------------------------------------------------------|
| Cystatin-C (serum) | Greater than 50% increase from pretreatment value                                           |
| Beta-2 microglobulin (urine) | Equal to or below 0.5 μg/mg creatinine (0–5 yo).                                               |
| L-FABP (urine)    | Equal to or below 0.35 μg/mg creatinine (> 5 yo).                                            |
| NGAL (urine)      | Equal to or below 8.4 μg/g creatinine                                                       |
| NAG (urine)       | Equal to or below the 95 percentile per age                                                  |

L-FABP: L-type fatty acid binding protein.
NGAL: neutrophil gelatinase-associated lipocalin.
NAG: N-acetyl-β-D-glucosaminidase.

selected from the sequential data. A serum creatinine value exceeding 1.5-fold the baseline value will be considered a sign of complication by CIN. The proportion of CIN will then be compared between groups A and B. With respect to the secondary endpoints, the definition of CIN in terms of each parameter is shown in Table 2. The proportion of CIN between groups will be compared as with the primary endpoints. Furthermore, the kinetics of the parameters as well as the serum Mg will be assessed and compared between the groups using one-way analysis of variance (ANOVA). Adverse events will be listed and graded as per the common terminology criteria for adverse events (CTCAE) v4.03 [14]. Causality with respect to Mg will be judged mainly by the investigators, and their judgments will be validated by the data monitoring committee (DMC).

3. Statistical analysis

3.1. Sample size

This randomized phase-2 study is not strictly confirmatory because a single chemotherapy course rather than a single participant will be regarded as one sample. To minimize the effect of this limitation, the sample size will be calculated conservatively to detect a difference of 5% between groups using alpha = 0.05 (two-tailed). Assuming two scenarios in which the proportion of non-CIN patients in group A (Mg-) is 85 and 90%, respectively. The statistical power to determine the required sample size was calculated as shown in Table 3. In order to guarantee 80% power, we estimated that a minimum of 40 samples per group would be required (ideally, 60 samples). When the total number of samples reaches 40 per group, the investigators will consult the DMC about terminating recruitment.

3.2. Data analysis

Clinical and demographic factors, treatment details, and study outcomes will be described using standard statistical methods; frequencies and percentages will be used for categorical data; the mean and standard deviation or the median and range will be used for continuous data. To compare the two groups, the chi-square test or Fisher’s exact test will be used for categorical data and the t-test or one-way ANOVA will be used for continuous data, as appropriate. All analyses of efficacy will be conducted on an intention-to-treat basis for the randomized arm, regardless of the treatment actually received.

4. Discussion

So-called “late adverse effects” of cancer therapy are becoming an increasingly serious problem in pediatric oncology because approximately 80% of children with cancer are able to survive longer than 5 years [1]. Chemotherapy at an early age can produce serious complications resulting from repetitive, acute damage to developing organs. The glomerular filtration rate (GFR) starts to increase at the gestational age of 34 weeks and continues to increase gradually until age 3 years when it reaches the absolute GFR (120 mL/min/1.73 m²) [15]. Considering the vulnerability of developing renal tissue, younger patients may be at greater risk of CIN.

CIN consists of glomerular and renal tubular damage, both of which can be cumulative. The former may be reversible when cisplatin is used in a low dose regimen (less than 360 mg/m² in total) while the latter may persist years after the completion of chemotherapy [16]. Because CIN is one of the typical late effects which may become fatal if exacerbated, an effective prophylactic treatment is worth pursuing [17].

The exact mechanism of CIN is unknown. In an analogy to intoxication by heavy metals, cisplatin can be seen as inducing renal tubular cell death by binding to proteins with an SH-base, resulting in increased intracellular lysosome enzyme secretion. Pathological changes are observed primarily in the proximal and distal renal tubular epithelium and collecting ducts [1]. In a rat model, magnesium (Mg) supplementation showed a kidney-protective effect against CIN by regulating renal platinum accumulation via changes in cisplatin efflux transporter expression in tubular epithelial cells [7]. The increased efflux of cisplatin did not reduce its cytotoxic effect either in vitro or in vivo.

The efficacy of Mg supplementation has been demonstrated in several studies of adult patients. Wilcox et al. [11] reported that supplementation with 16 mEq Mg was effective in reducing renal tubular damage in 16 patients with testicular cancer who received a cisplatin-containing regimen (20 mg/m² i. v. for 5 days). Bodnar et al. [8] revealed in a double-blind, placebo-controlled, randomized study that 40 mEq Mg supplementation had kidney-protective effects against CIN in 41 patients with epithelial ovarian cancer receiving paclitaxel (135 mg/m²/24 h) plus cisplatin (75 mg/m²) every three weeks. All other adult studies also showed the efficacy of Mg supplementation for CIN [9,11,12]. In terms of safety, high serum Mg levels can cause cardiac arrhythmia and respiratory depression. However, in adult studies, grade III and IV adverse events resulting from Mg supplementation have never been reported.

The current study aims to investigate the efficacy of Mg supplementation in preventing CIN in pediatric patients with cancer. The rationale for this study is based on our retrospective study, which strongly suggested a kidney-protective effect of Mg supplementation in children with cancer, and on the adult studies described above. In pediatric oncological practice, Mg supplementation is often used to treat chemotherapy-induced hypomagnesemia and rarely causes adverse effects such as hypermagnesemia. We retrospectively investigated two groups, one of which included chemotherapy courses containing cisplatin with concomitant Mg supplementation (Mg+ group; 92 courses) and another which did not receive Mg supplementation (Mg- group; 66 courses). The incidence of CIN in the Mg+ group was significantly lower than in the Mg- group 9.8% vs 22.7%, p = 0.025 [13]. No Mg-related adverse event was observed. The rationale for the current prospective randomized study was based on these findings.

Pediatric cancers are rare and heterogeneous. Thus, in view of the rarity of these diseases, we focused on acute nephrotoxicity and evaluated it per individual course of chemotherapy, which was generally
repeated every 21–28 days. As a rule, each course of chemotherapy was begun when organ function achieved the normal range. With regard to this rule and the retrospective data described above, a course of single chemotherapy was treated as one sample to facilitate the recruitment of subjects.

Randomization was based on the patients. Because each patient usually repeats chemotherapy three to eight times, Mg supplementation is administered only alternately with chemotherapy per patient. Analysis objects will be reconstructed into two groups depending on whether or not the chemotherapy regimen included Mg supplementation. Then, the two groups will be analyzed for comparison. Therefore, samples from a single patient will be allocated roughly into two equal groups. This procedure will allow us further to minimize bias secondary to the cumulative toxicity of cisplatin because the sum of the number of courses in each chemotherapy regimen will theoretically be similar between the analysis groups (A and B). In view of the heterogeneity of the disease, this procedure will minimize any possible selection bias.

The chief limitation of this study design is the subject pool. If the mean number of chemotherapy courses per patient is four, only 30 patients will be enrolled in the study for a maximum sample number of 120, which may be insufficient to verify the efficacy of Mg supplementation therapy for pediatric cancer. However, the sample number in this phase 2 study is likely to have enough power to determine whether a phase 3 study using a larger population should be planned. The second limitation of this study is that it is not designed to detect the efficacy of Mg supplementation therapy in chronic nephrotoxicity. This point will be explored in a post-hoc analysis of long-term follow-up data using this study cohort, as well as possibly in a subsequent phase-3 study. In addition, data collected in this study using various biomarkers, such as serum cystatin-C, B2M, L-FABP, NGAL, and urinary NAG, may provide information helpful in designing the phase-3 study using novel and more precise markers than serum creatinine.

Currently, approximately 80% of pediatric cancers can be cured. Minimizing toxicity and maximizing efficacy are therefore important therapeutic goals in the treatment of pediatric patients with cancer. Neutralizing the serious, dose-limiting toxicity of cisplatin, one of the best chemotherapeutic drugs currently available, will contribute not only to minimizing “late adverse effects”, but also to improving the intensity and efficacy of the currently used cisplatin-containing chemotherapy regimen.

Funding

The study is supported by the Clinical Research Fund of the Tokyo Metropolitan Government, Japan.

Conflicts of interest

The authors do not have any competing interests to declare.

Ethical approval

The study has been approved by the institutional review board of the Tokyo Metropolitan Children’s Medical Center, Nihon University School of Medicine, and Saitama Children’s Medical Center. The study is registered with the UMIN-CTR (http://www.umin.ac.jp/icdr/index.html) under identifier UMIN000029215 and will be carried out under the supervision of the three institutional review boards and the study data monitoring committee.

Acknowledgement

The authors express their gratitude to Mr. James Robert Valera for his assistance with editing this manuscript.

References

[1] P.C. Adamson, S.M. Blaney, R. Bagatell, J.M. Skolnik, F.M. Balis, General principles of chemotherapy, in: P.A. Pizzo, D.G. Poplack (Eds.), Principles and Practice of Pediatric Oncology, seventh ed., Wolters Kluwer, Philadelphia, 2016, pp. pp248–315.
[2] W. Lander, S.H. Armenian, A.T. Meadows, S. Bhatia, Late effects of childhood cancer and its treatment, in: P.A. Pizzo, D.G. Poplack (Eds.), Principles and Practice of Pediatric Oncology, seventh ed., Wolters Kluwer, Philadelphia, 2016, pp. pp315–319.
[3] Y.I. Chirino, J. Pedraza-Chaverri, Role of oxidative and nitrosative stress in cisplatin-induced nephrotoxicity, Exp. Toxicol. Pathol. 61 (2009) 223–242 https://doi.org/10.1016/j.etp.2008.09.003.
[4] P.D. Sanchez-Gonzalez, F.J. Lopez-Hernandez, J.M. Lopez-Novoa, A.I. Morales, An integrative view of the pathophysiological events leading to cisplatin nephrotoxicity, Crit. Rev. Toxicol. 41 (2011) 803–821 https://doi.org/10.3109/10408444.2011.602662.
[5] M. Finkel, A. Goldstein, Y. Steinberg, L. Granowetter, H. Trachtman, Cisplatinum nephrotoxicity in oncology therapeutics: retrospective review of patients treated between 2005 and 2012, Pediatr. Nephrol. 29 (2014) 2421–2424 https://doi.org/10.1007/s00467-014-2857-3.
[6] V. Launay-Vacher, J.B. Rey, G. Iannardi-Bagnis, G. Deray, M. Daouphars, Prevention of cisplatin nephrotoxicity: state of the art and recommendation from the European society of clinical pharmacy special interest group on cancer care, Cancer Chemother. Pharmacol. 61 (2008) 903–909 https://doi.org/10.1007/s00280-008-0711-6.
[7] M.H. Solanki, P.K. Chatterjee, M. Gupta, X. Xue, A. Plagov, M.H. Metz, R. Mintz, P.C. Singhal, C.N. Metz, Magnesium protects against cisplatin-induced acute kidney injury by regulating platinum accumulation, Am. J. Physiol. Renal. Physiol. 307 (2014) F369–F384 https://doi.org/10.1152/ajprenal.00096.2015.
[8] L. Bodnar, G. Wcislo, A. Gasowska-Bodnar, A. Synowiec, K. Szaezle-Wcislo, C. Szyszylak, 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 44 (2008) 2608–2614 https://doi.org/10.1016/j.ejca.2008.08.005.
[9] S. Hirai, S. Kaida, T. Ito, S. Hasebe, M. Ueno, H. Udagawa, M. Hayashni, Magnesium premedication prevents Cisplatin-induced nephrotoxicity in patients with esophageal and hypopharyngeal cancer (Japanese), Gan To Kagaku Ryoho 40 (2013) 743–747.
[10] K. Muraki, R. Koyama, Y. Honma, S. Yagishita, T. Shukuya, R. Ohashi, F. Takahashi, K. Kido, S. Iwakami, S. Sasaki, A. Iwase, K. Takahashi, Hydration with magnesium and mannitol without furosemide prevents the nephropathy induced by cisplatin and pemetrexed in patients with advanced non-small cell lung cancer, J. Thorac. Dis. 4 (2012) 562–568 https://doi.org/10.3978/j.issn.2072-1439.2012.10.16.
[11] J.C. Wilkes, E.J. McClIver, G. Sangster, S.B. Kaye, Effects of magnesium supplementation in testicular cancer patients receiving cis-platin: a randomised trial, Br. J. Canc. 54 (1986) 19–23.
[12] T. Yoshiida, S. Nishi, M. Toda, K. Goto, K. Yoh, S. Usunuma, S. Matsumoto, H. Ohmatsu, Y. Ohe, Protective effect of magnesium preloading on cisplatin-induced nephrotoxicity: a retrospective study, Jpn. J. Clin. Oncol. 44 (2014) 346–354 https://doi.org/10.1111/jco.12404.
[13] M. Matsui, Y. Saito, S. Yamaoka, Y. Yokokawa, Y. Morikawa, A. Makimoto, Y. Yuza, Kidney-protective effect of magnesium supplementation in cisplatin-containing chemotherapy for pediatric cancer: a retrospective study, J. Pediatr. Hematol. Oncol. 40 (2018) 379–381 https://doi.org/10.1097/MPH.0000000000001159.
[14] National Cancer Institute, Common terminology criteria for adverse events v4.0, https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40, Accessed date: 22 August 2018.
[15] Iekuni Ichikawa, Pediatric Textbook of Fluids and Electrolytes, Williams and Wilkins, Baltimore, 1990.
[16] W. Stohr, M. Paulides, S. Bielack, H. Jürgens, E. Koscielniak, R. Rossi, T. Langer, J.D. Beck, Nephrotoxicity of cisplatin and carboplatin in sarcoma patients: a report from the late effects surveillance system, Pediatr. Blood Cancer 48 (2007) 140–147.
[17] R.B. Womer, J. Pritchard, T.M. Barratt, Renal toxicity of cisplatin in children, J. Pediatr. 106 (1985) 659–663.