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# 傾向スコアマッチング解析を用いた シスプラチン誘発性腎障害に対する20%マンニトール製剤と 15%マンニトール・ソルビトール製剤の効果の比較

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# Comparison of the effect of 20% mannitol or 15% mannitol plus 5% sorbitol on cisplatin-induced nephrotoxicity: a propensity score matching analysis

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**Abstract**

A 20% mannitol formulation（20% Man）is oversaturated and requires careful handling compared with a 15% mannitol plus 5% sorbitol formulation（15% Man-S）. In this study, we compared the incidence of cisplatin-induced nephrotoxicity（CIN）and the occurrence of safety concerns between 20% Man and 15% Man-S using a propensity score matching analysis. This was a single center, retrospective study of cancer patients receiving their first cycle of cisplatin between July 1, 2020 and June 30, 2022. CIN was defined as all grade serum creatinine elevation based on the National Cancer Institute Common Toxicity Criteria for Adverse Events（CTCAE）version 5.0. To minimize the effects of potential confounding variables from selection bias, propensity score matching was done. A total of 211 patients were enrolled in the study, of whom 126 received 20% Man and 85 received 15% Man-S. After propensity score matching, 61 pairs were established. CIN with CTCAE criteria（grade 1 or higher）was observed in 21.3% of the patients in the 20% Man group and 16.4% in the 15% Man-S group. No significant differences were observed between the two groups with respect to CIN incidence as determined by CTCAE criteria（$p = 0.64$）. There were no significant differences in the occurrence of CIN or safety between the 20% Man and 15% Man-S groups. The administration of 15% Man-S has the advantage of being less prone to crystallization at lower temperatures compared with 20% Man.

**Keywords:** Cisplatin-induced neurotoxicity; Mannitol; Crystallization; Sorbitol

## 1. Introduction

Cisplatin（CDDP）is an important chemotherapeutic agent for treating a variety of cancers, including head and neck, esophageal, lung, and genitourinary cancer. Its mechanism of action involves the inhibition of deoxyribonucleic acid（DNA）synthesis through the formation of intra- and inter-strand DNA crosslinks. Although CDDP is a potent chemotherapeutic drug, it may cause severe nausea and vomiting, myelosuppression, and nephrotoxicity. CDDP-induced nephrotoxicity（CIN）is the major dose-limiting toxicity, which occurs in approximately 20%–30% of patients[1-5]. CIN usually occurs within the first 10 days following CDDP administration and may persist for up to 3 weeks[6]. Several mechanisms may explain the pathogenesis of CIN, including

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proximal tubular injury, inflammatory response, oxidative stress, and vascular injury to the kidneys[7]. Hypomagnesemia is also a common event associated with CIN[8,9]. Risk factors for CIN include older age, comorbidity with diabetes mellitus or chronic kidney disease, high peak plasma-free platinum concentration, and cumulative CDDP dose[7].

The main strategies for preventing CIN involves the administration of normal saline hydration, diuretics, magnesium supplementation, and avoiding potential nephrotoxins. In particular, mannitol is commonly used as an osmotic diuretic to prevent CIN and a meta-analysis revealed that mannitol is an effective and safe drug for reducing CIN[10].

In Japan, mannitol is available in two formulations: 20% mannitol（20% Man）and 15% mannitol plus 5% sorbitol（15% Man-S）. When a mannitol solution is exposed to low temperatures, crystallization may occur. This requires that the bag be warmed in hot water and periodically shaken to redissolve the crystals. Otherwise, there is a risk of administering crystallized mannitol. Thus, storage temperatures for mannitol must be carefully controlled and the solution should be carefully monitored prior to administration. In particular, the 20% formulation is oversaturated and should be treated with caution compared with the 15% formulation. However, there is no clear data demonstrating the differences in stability between 20% Man and 15% Man-S under low-temperature conditions.

20% Man is widely used in Japan[11]; however, the differences in efficacy and safety between the two formulations are unknown and the appropriate composition of mannitol for CIN prevention remains unclear. Furthermore, the concentration of mannitol during short hydration is specified as 20% in the guideline[12].

In this study, we compared the incidence of CIN and the occurrence of safety concerns between 20% Man and 15% Man-S. We also examined the stability of 20% Man and 15% Man-S under low-temperature conditions to demonstrate the storage advantages of 15% Man-S.

## 2. Materials and Methods

### 2.1. Study design and patients

This retrospective study evaluated cancer patients（age ≥ 16 years old）who received their first cycle of CDDP treatment at the Iwate Medical University Hospital between July 1, 2020, and June 30, 2022. We switched from 20% Man to 15% Man-S in July 2021 due to concerns about medical safety issues related to the crystallization of 20% Man. The study was approved by the Ethics Committee of the Iwate Medical University（MH2022-117）and was performed in accordance with the Declaration of Helsinki. Patients treated with CDDP doses less than 60 mg/m$^2$, concurrent treatment with zoledronate, and having serum levels above the upper limit for creatinine, alanine aminotransferase（AST）, aspartate aminotransferase（ALT）, or total bilirubin（T-Bil）were excluded.

### 2.2. Target adverse events

The adverse events（AEs）for 20% Man and 15% Man-S were described almost identically in the package inserts and interview forms, and the information on AEs was insufficient. To identify the differences in AEs between 20% Man and 15% Man-S, we used the Japanese Adverse Drug Event Report（JADER）database of the Pharmaceuticals and Medical Devices Agency（PMDA）, which is a large spontaneous reporting system reflecting clinical practice in Japan. Data from April 2004 to April 2022 were collected from the PMDA website. The database consists of four tables: patient demographic information, drug information, adverse reactions, and primary disease. In the drug information tables, the contribution of drug-related AEs is categorized into three codes: “suspected drug,” “concomitant drug,” and “interaction.” We only analyzed cases that were categorized as “suspected drug.” The AEs names are defined using the Medical Dictionary for Regulatory Activities/Japanese version 25.0. Table 1 lists the AEs of 20% Man and 15% Man-S from the JADER database. We targeted the AEs, hyperkalemia, hyponatremia, anaphylactic shock, and liver disorders, which were reported in ≥5 cases. In addition, because injection site reactions（infusion site extravasation, injection site dermatitis, phlebitis, skin necrosis）were reported more frequently in the 15% Man-S group, we included them in this study.

### 2.3. Date collection

Data collected through the electronic patient

**Table 1 The numbers of adverse events cases listed in the JADER database**

| SOC | | PT (*n*) |
|---|---|---|
| Renal and urinary disorders | 20% Man | Acute kidney injury (13), Renal disorder (4), Renal failure (2), Renal impairment (1), Micturition urgency (1), Micturition urgency (1), Pollakiuria (1) |
| | 15% Man-S | Acute kidney injury (2) |
| General disorders and administration site conditions | 20% Man | Infusion site extravasation (1), Drug ineffective (1), Multiple organ dysfunction syndrome (1) |
| | 15% Man-S | Infusion site extravasation (1), Injection site dermatitis (1) |
| Skin and subcutaneous tissue disorders | 20% Man | Stevens-Johnson syndrome (3), Toxic epidermal necrolysis (2) |
| | 15% Man-S | Skin necrosis (1) |
| Investigations | 20% Man | Blood pressure decreased (1), Blood electrolytes abnormal (1) |
| | 15% Man-S | Blood pressure decreased (1), |
| Vascular disorders | 15% Man-S | Phlebitis (1) |
| Metabolism and nutrition disorders | 20% Man | Hyperkalemia (14), Hyponatremia (6), Metabolic acidosis (3), Dehydration (2), Hypokalemia (2), Hypoglycemia (2), Decreased appetite (1) |
| Nervous system disorders | 20% Man | Altered state of consciousness (4), Neuroleptic malignant syndrome (3), Cerebral infarction (2), Brain edema (2), Epilepsy (1), Superior sagittal sinus thrombosis (1), Mental impairment (1), Headache (1), Seizure (1) |
| Cardiac disorders | 20% Man | Acute myocardial infarction (3), Atrioventricular block complete (1), Bundle branch block left (1), Ventricular tachycardia (1), Cardiac failure (1), Atrial fibrillation (1) |
| Hepatobiliary disorders | 20% Man | Liver disorder (5), Hepatic function abnormal (1) |
| Immune system disorders | 20% Man | Anaphylactic shock (4), Anaphylactic reaction (1), Anaphylactoid reaction (1) |
| Others | 20% Man | Angle closure glaucoma (3), Rhabdomyolysis (2), Pulmonary edema (1), Hypercoagulation (1), Thrombocytopenias (1), Tracheo-esophageal fistula (1), Nausea (1), Vomiting (1), Toxicity to various agents (1), Subdural haematoma (1) |

JADER, Japanese Adverse Drug Event Report; SOC, system organ class; PT, preferred term.

record system included patient characteristics [age, gender, body mass index (BMI), creatinine clearance (CCr), AST, ALT, T-Bil, serum potassium, serum sodium, cancer site, history of diabetes mellitus (DM)], administered chemotherapy, mannitol (CDDP dose, chemotherapy regimen, mannitol composition and dose, injection site), and concomitant drugs [non-steroidal anti-inflammatory agents (NSAIDs), loop diuretic, Mg supplementation, hydration volume]. The Cockcroft–Gault equation was used to calculate CCr.[13)]

### 2.4. Outcome measures

Renal function was determined based on serum creatinine (sCr) levels. CIN was defined as an all grade sCr elevation based on the National Cancer Institute Common Toxicity Criteria for AEs (CTCAE) version 5.0. In addition, the criteria outlined in Kidney Disease: Improving Global Outcomes (KDIGO) were used to define acute kidney injury. KDIGO criteria was defined as an increase in sCr by ≥ 0.3 mg/dL within 48 h or an increase in sCr to ≥ 1.5 times the baseline within 7 days. With respect to the safety of mannitol, hyperkalemia, hyponatremia, anaphylactic shock, injection site reactions, and liver disorders ("ALT increased," "AST increased," or "T-Bil increased") were evaluated according to the CTCAE. These were assessed using the maximum or minimum value within 3 weeks of the first cycle of CDDP-based chemotherapy.

### 2.5. Foreign insoluble matter test for 20% Man and 15% Man-S

The foreign insoluble matter test was done for

20% Man and 15% Man-S under low-temperature conditions (5°C for 1 h, 6 h, 24 h, and 168 h) during the winter season. Three lots of each mannitol formulation were tested. The samples were stored under low-temperature conditions without being removed from the outer packaging. After subjecting the samples to low-temperature conditions, they were returned to room temperature and examined at 1 h. The foreign insoluble matter test for both formulations was performed according to method #1 of "The Japanese pharmacopoeia eighteenth edition."

### 2.6. Statistical analysis

Propensity score matching was performed to adjust baseline characteristics between the two groups. The propensity score was calculated using a logistic regression analysis, which included the following 17 factors: age, gender, obesity (BMI ≥ 25 kg/m$^2$), history of a DM, CCr, cancer type, chemotherapy regimen, CDDP dose, NSAIDs use, loop diuretic drug use, mannitol dose ( ≥ 45 mg), injection site (central vein or peripheral vein), hydration volume (>2.5 L/d), supplementation of Mg, AST, ALT, hydration for at least 2 days. One - to - one matching between the groups was done using the caliper matching method (caliper 0.2).

A univariate analysis was performed to compare background factors between patients administered 20% Man or 15% Man-S. Continuous variables are presented as the median (interquartile range) and compared using the Wilcoxon rank sum test. Categorical variables were compared using Fisher's exact test. All statistical analyses were performed using the EZR software program (Saitama Medical Center, Saitama, Japan)[14]. All $p$ values were reported as two-sided and $p < 0.05$ was considered statistically significant.

## 3. Results

### 3.1. Patient enrollment

The flow diagram for the enrolled patients is shown in Fig. 1. Of the 329 cancer patients who received 20% Man or 15% Man-S to prevent CIN, we excluded 118 patients because 52 had liver impairment before treated CDDP, 50 patients were administered CDDP doses less than 60 mg/m$^2$, 12 patients experienced renal impairment before CDDP treatment, 6 patients were missing data on bilirubin, and 1 patient used zoledronate. As a result, a total of 211 patients were enrolled in the study, of which 126 patients received 20% Man and 85 patients received 15% Man-S.

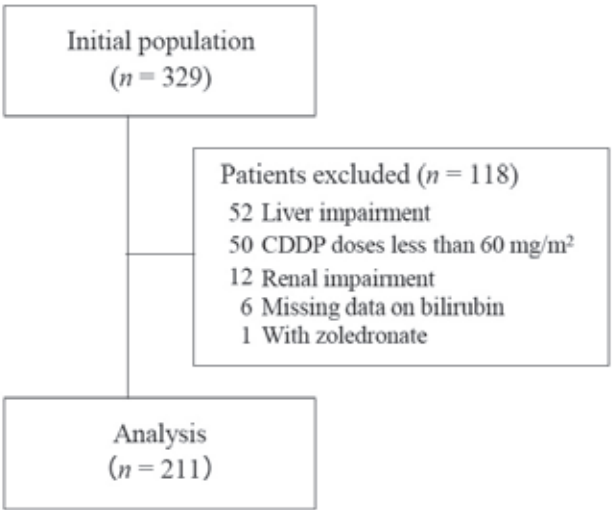


Fig. 1. Flow diagram for participant enrollment

### 3.2. Patient characteristics

The baseline characteristics for the 20% Man and 15% Man-S groups before and after propensity score matching are listed in Table 2. All patients received mannitol prior to CDDP administration. Prior to matching, the 15% Man-S group were significantly more likely to have diabetes mellitus, although there were no significant differences observed between the groups after propensity score matching with respect to any other covariates.

### 3.3. Outcomes

The incidence of CIN with CTCAE criteria and KDIGO criteria, liver disorders, anaphylactic shock, injection site reactions, hyperkalemia, hyponatremia in the 20% Man and 15% Man-S groups is listed in Table 3. CIN with CTCAE criteria (grade 1 or higher) was observed in 21.3% of the patients in the 20% Man group and 16.4% in the 15% Man-S group. CIN with KDIGO criteria was observed in 4.9% of the patients in the 20% Man group and 1.6% in the 15% Man-S group. No significant differences were observed between the two groups with respect to CIN incidence as measured by CTCAE and KDIGO criteria ($p$ = 0.64 and 0.62, respectively). The incidence of increased AST (grade 1 or higher) for the 20% Man and 15% Man-S groups was 14.8%

**Table 2 Baseline patient characteristics**

| Characteristic | Before matching | | | After matching | | |
|---|---|---|---|---|---|---|
| | 20% Man | 15% Man-S | *p* | 20% Man | 15% Man-S | *p* |
| Patients | 126 | 85 | | 61 | 61 | |
| Age, median [IQR] | 67 [62, 71] | 66 [59, 71] | 0.51 | 67 [59, 70] | 67 [59, 71] | 0.74 |
| Gender, male (%) | 94 (74.6) | 70 (82.4) | 0.24 | 48 (78.7) | 46 (75.4) | 0.83 |
| BMI, ≥ 25 kg/m$^2$ (%) | 31 (24.6) | 14 (16.5) | 0.17 | 9 (14.8) | 11 (18.0) | 0.81 |
| CCr, mL/min, median [IQR] | 80 [68, 94] | 77 [66, 94] | 0.34 | 76 [66, 88] | 78 [65, 96] | 0.50 |
| Cancer site (%) | | | | | | |
| Head and neck | 65 (51.6) | 41 (48.2) | 0.082 | 33 (54.1) | 30 (49.2) | 0.82 |
| Lung | 37 (29.4) | 17 (20) | | 14 (23.0) | 17 (27.9) | |
| Urothelium | 15 (11.9) | 12(14.1) | | 8 (13.1) | 10 (16.4) | |
| Stomach | 7 (5.6) | 8 (9.4) | | 6 (9.8) | 4 (6.6) | |
| Others | 2 (1.6) | 7 (8.3) | | - | - | |
| Chemotherapy regimen | | | | | | |
| CDDP | 43 (34.1) | 25 (29.4) | 0.90 | 19 (31.1) | 18 (29.5) | 0.98 |
| CDDP + GEM | 16 (12.7) | 14 (16.5) | | 10 (16.4) | 10 (16.4) | |
| CDDP + PEM | 6 (4.8) | 2 (2.4) | | - | 2 (3.3) | |
| CDDP + PEM + BEV | 3 (2.4) | 2 (2.4) | | 2 (3.3) | 2 (3.3) | |
| CDDP + TS-1 | 7 (5.6) | 6 (7.1) | | 6 (9.8) | 4 (6.6) | |
| CDDP + VNR | 13 (10.3) | 6 (7.1) | | 5 (8.2) | 6 (9.8) | |
| CDDP + VP-16 | 5 (4) | 4 (4.7) | | 2 (3.3) | 3 (4.9) | |
| CDDP + DTX + 5-FU | 21 (16.7) | 19 (22.4) | | 14 (23.0) | 12 (19.7) | |
| CDDP + PEM + Pembrolizumab | 6 (4.8) | 2 (2.4) | | 1 (1.6) | 2 (3.3) | |
| CDDP + other | 6 (4.8) | 5 (5.9) | | 2 (3.3) | 2 (3.3) | |
| CDDP dose, mg/m$^2$, median [IQR] | 75 [69, 80] | 73 [67, 80] | 0.48 | 75 [60, 80] | 75 [68, 80] | 0.48 |
| History of a DM, yes (%) | 21 (16.7) | 25 (29.4) | 0.041 | 14 (23.0) | 15 (24.6) | 1 |
| Concomitant drug | | | | | | |
| NSAIDs | 10 (7.9) | 8 (9.4) | 0.80 | 5 (8.2) | 6 (9.8) | 1 |
| Loop diuretic | 65 (51.6) | 41 (48.2) | 0.68 | 32 (52.5) | 27 (44.3) | 0.47 |
| Mannitol dose, ≥ 45 g (%) | 82 (65.1) | 57 (67.1) | 0.88 | 41 (67.2) | 40 (65.6) | 1 |
| Hydration volume, > 2.5 L/d (%) | 84 (66.7) | 65 (76.5) | 0.17 | 46 (75.4) | 43 (70.5) | 0.68 |
| Hydration for at least 2 days, yes (%) | 76 (60.3) | 56 (65.9) | 0.47 | 38 (62.3) | 37 (60.7) | 1 |
| Supplementation of Mg, yes (%) | 112 (88.9) | 72 (84.7) | 0.41 | 53 (86.9) | 51 (83.6) | 0.80 |
| Injection site | | | | | | |
| central vein | 24 (19) | 22 (25.9) | 0.31 | 15 (24.6) | 13 (21.3) | 0.83 |
| peripheral vein | 102 (81) | 63 (74.1) | | 46 (75.4) | 48 (78.7) | |
| AST, IU/L, median [IQR] | 18 [15, 21] | 18 [15, 21] | 0.89 | 18 [16, 21] | 18 [15, 21] | 0.72 |
| ALT, IU/L, median [IQR] | 15 [12, 19] | 15 [11, 22] | 0.85 | 15 [11, 19] | 16 [11, 22] | 0.52 |

IQR, interquartile range; BMI, body mass index; CDDP, cisplatin; GEM, gemcitabine; PEM, pemetrexed; BEV, bevacizumab; TS-1, tegafur + gimeracil + oteracil potassium; VNR, vinorelbine; VP-16, etoposide; DTX, docetaxel; 5-FU, 5-fluorouracil; NSAIDs non-steroidal anti-inflammatory agents; DM, diabetes mellitus.

and 26.2%, respectively. Similarly, the incidence of increased ALT (grade 1 or higher) for the 20% Man and 15% Man-S groups was 27.9% and 37.7%, respectively. No significant differences were observed with respect to increased AST and ALT ($p$ = 0.18 and 0.34, respectively). There were no significant differences with respect to injection site reactions, hyperkalemia, and hyponatremia. There were no cases of anaphylactic shock.

### 3.4. Foreign insoluble matter test

The results of the foreign insoluble matter test for the 20% Man and 15% Man-S groups are shown in Table 4. For the 20% Man group, a few crystals were observed after 1 hour storage at 5℃ and the amount increased over time, whereas only a few crystals were observed in the 15% Man-S group after 168 hours of storage. Furthermore, an increase in crystals over time was observed in

**Table 3　Outcomes in the 20% Man and 15% Man-S groups**

| Outcomes | All grade | $p^a$ | Grade | | | |
|---|---|---|---|---|---|---|
| | | | 1 | 2 | 3 | 4 |
| CIN, yes, *n* (%) | | | | | | |
| CTCAE | | | | | | |
| 20% Man | 13 (21.3) | 0.64 | 12 | 1 | - | - |
| 15% Man-S | 10 (16.4) | | 9 | 1 | - | - |
| KDIGO | | | | | | |
| 20% Man | 3 (4.9) | 0.62 | - | - | - | - |
| 15% Man-S | 1 (1.6) | | - | - | - | - |
| Liver disorders, yes, *n* (%) | | | | | | |
| AST increased | | | | | | |
| 20% Man | 9 (14.8) | 0.18 | 9 | - | - | - |
| 15% Man-S | 16 (26.2) | | 15 | 1 | - | - |
| ALT increased | | | | | | |
| 20% Man | 17 (27.9) | 0.34 | 16 | 1 | - | - |
| 15% Man-S | 23 (37.7) | | 20 | 3 | - | - |
| T-Bil increased | | | | | | |
| 20% Man | 3 (4.9) | 1 | 3 | - | - | - |
| 15% Man-S | 2 (3.3) | | 2 | - | - | - |
| Anaphylactic shock, yes, *n* (%) | | | | | | |
| 20% Man | - | N/A | - | - | - | - |
| 15% Man-S | - | | - | - | - | - |
| Injection site reactions, yes, *n* (%) | | | | | | |
| 20% Man | 5 (8.2) | 0.44 | - | 5 | - | - |
| 15% Man-S | 2 (3.3) | | 1 | 1 | - | - |
| Hyperkalemia, yes, *n* (%) | | | | | | |
| 20% Man | 16 (26.2) | 1 | 15 | 1 | - | - |
| 15% Man-S | 16 (26.2) | | 15 | - | 1 | - |
| Hyponatremia, yes, *n* (%) | | | | | | |
| 20% Man | 50 (82) | 0.14 | 46 | 2 | - | 2 |
| 15% Man-S | 42 (68.9) | | 37 | 4 | 1 | - |

[a] 20% Man vs 15% Man-S

**Table 4　Foreign insoluble matter test for 20% Man and 15% Man-S**

| | Lot No | Foreign insoluble matter test | | | |
|---|---|---|---|---|---|
| | | 5°C, 1 h | 5°C, 6 h | 5°C, 24 h | 5°C, 168 h |
| 20% Man | 2H030 | Detection[a] | Detection[a] | Detection[b] | Detection[b] |
| | 2K031 | Detection[a] | Detection[a] | Detection[a] | Detection[c] |
| | 2N032 | Detection[a] | Detection[a] | Detection[a] | Detection[b] |
| 15% Man-S | 2H026 | Non-detection | Non-detection | Non-detection | Detection[a] |
| | 2K027 | Non-detection | Non-detection | Non-detection | Detection[a] |
| | 3A028 | Non-detection | Non-detection | Non-detection | Detection[a] |

[a] A few small crystals
[b] A dozen or so small crystals
[c] A dozen or so small crystals and large needle crystals >1 cm

the 20% Man group after storage in low to room temperature, but not for 15% Man-S.

## 4. Discussion

There have been reports stating that there was no significant difference in the increase in urinary volume between the two groups after administering 20% Man and 15% Man-S to rats（Package insert. “MANNITOL-S INJECTION.”), however the impact on humans is unclear. This is the first report to

compare different compositions of mannitol for the incidence of CIN and the occurrence of safety concerns. The incidence of CIN was not significantly different between the 20% Man and 15% Man-S groups. To evaluate renal function, we used sCr parameters as recommended by the CTCAE criteria for chemotherapy. In addition, KDIGO criteria were used as an indicator to evaluate the acute phase of CIN. CIN with CTCAE criteria（grade 1 or higher）was observed in 21.3% of the patients in the 20% Man group and 16.4% in the 15% Man-S group. In contrast, CIN with KDIGO criteria was observed in 4.9% of the patients in the 20% Man group and 1.6% in the 15% Man-S group. The incidence of CIN based on CTCAE and KDIGO criteria was largely consistent with previous studies[15-18]. In addition, we analyzed the differences in AEs between the 20% Man and 15% Man-S groups using the JADER database, because the differences in AEs for these drugs were unclear. After evaluating the incidence of those AEs, there were no significant differences in liver disorders, anaphylactic shock, injection site reactions, hyperkalemia, or hyponatremia between the two groups.

The solubility of mannitol at 20°C is approximately 16 w/v%（20% Mannitol Injection interview form, 5th Edition, 2021）. It is important to exercise caution when storing mannitol during the winter season as its solubility is affected by temperature. Specifically, the 20% formulation is oversaturated and requires careful handling compared with the 15% formulation. Our study focused on the presence of foreign insoluble matter in both the 20% Man and 15% Man-S under low-temperature conditions. We demonstrated that the likelihood of crystallization is lower in the 15% Man-S formulation compared with the 20% Man formulation. Thus, 15% Man-S may be a more viable option in regions experiencing colder temperatures.

Various protocols have been used in clinical practice to prevent nephrotoxicity following CDDP treatment. Mannitol is widely used as a diuretic for the prevention of CIN. We prioritized maintaining the same volume of liquid rather than the amount of mannitol when switching from the 20% Man to the 15% Man-S. This is because both the 20% Man and the 15% Man-S have a volume of 300 mL per bag. For example, if 300 mL of the 20% Man was administered, switching to the 15% Man and adjusting for the amount of mannitol would require one bag plus an additional 100 mL. This would complicate the administration process. As a result of switching methods in this way, we found no difference in the incidence of CIN between the 20% Man and the 15% Man-S. A previous systematic review and meta-analysis indicated the effect of mannitol on CIN and mannitol doses ≥ 25 g may exert a better effect[10]. In this study, all patients received 30 g or more of mannitol; however, a previous randomized trial and cohort study indicated that mannitol is ineffective at preventing CIN[19,20]. Thus, the use of mannitol as a preventive measure for CIN is controversial. Other strategies have been reported to prevent CIN. Hydration is the most reasonable strategy to decrease the incidence of CIN[21]. Systematic review and meta-analysis showed that the administration of Mg seems to be the best strategy for the prevention of CIN[22]. In addition, several studies have reported the feasibility and efficacy of short hydration, including 1.6 to 2.5 L of fluid with Mg supplementation and forced diuresis with mannitol and furosemide[16,23]. In the present study, many patients received hydration and Mg supplementation along with mannitol as a preventive protocol for CIN.

Miyoshi et al. reported that high-dose CDDP, comorbidities of cardiac disease, and hypertension, are independent risk factors for CIN[24]. In contrast, Komaki et al. reported that lower blood pressure prior to CDDP administration and the use of renin-angiotensin system inhibitors is associated with the incidence of CIN[25]. Okamoto et al. reported that the co-administration of NSAIDs is a risk factor for CIN[26]. In addition, age >65 years, DM, and hypoalbuminemia are also risk factors for CIN[27-29]. Thus, risk factors for CIN may differ depending on the study, which could be attributed to differences in the CDDP-based chemotherapy regimen, definition of nephrotoxicity, preventive protocol for CIN, and patient characteristics. In the present study, propensity score matching analysis was done to control for confounding factors. The results indicated that no significant differences were evident in the incidence of CIN between the 20% Man and 15% Man-S groups.

Sorbitol is a sugar alcohol which has been used as an excipient in formulations of various drugs and as a parenteral nutritional agent. The 15%

Man-S formulation prevents crystal precipitation by adding sorbitol to 15% Man. Hereditary fructose intolerance (HFI) is a genetic disorder that results from the deficiency of the liver enzyme aldolase B[30]. The intravenous injection of sorbitol in HFI patients results in hypoglycemia, lactic acidosis, or hepatic and renal impairment because the glycolytic and gluconeogenic pathway are impaired. Therefore, intravenous injection products containing sorbitol are contraindicated for use in patients with HFI. However, HFI is a very rare disease and there have only been a few reports in Japan[31]. We demonstrated that there was no difference in the incidence of nephrotoxicity between 20% Man and 15% Man-S in patients receiving CDDP. However, 15% Man-S should not be used in patients with HFI.

In the present study, the incidence of liver disorders (increased AST and ALT levels) was slightly higher in the 15% Man-S group compared with the 20% Man group, although not significantly. Nevertheless, most cases of liver dysfunction were classified as Grade 1 and the majority of patients had improved before the second cycle of CDDP-based chemotherapy. Therefore, we conclude that there is no clinical distinction in the occurrence of liver dysfunction between the 20% Man and 15% Man-S groups.

This study had several limitations. First, it was a retrospective study conducted in a single center. A randomized, multicenter study will be necessary to validate these findings. Secondly, we could not assess several risk factors, such as the co-administration of renin-angiotensin system inhibitors, hypoalbuminemia, hypomagnesemia, comorbid cardiac diseases, and blood pressure. Mannitol was switched in all chemotherapy regimens in July 2021, therefore selection bias may be relatively small. In fact, the patient backgrounds of both groups before propensity score matching did not show significant differences except for a history of DM. However, the inability to consider all risk factors for CIN is considered the most significant limitation of this study. Third, we could not evaluate the AEs of CDDP, such as nausea and vomiting, myelosuppression, and hearing disorder, with the exception of CIN. Furthermore, we focused only on specific AEs caused by 20% Man and 15% Man-S extracted from the JADER database, and we could not consider the severity of these AEs during the extraction. Finally, we could not evaluate the level of oral hydration, such as oral rehydration solutions with water supplementing ability equivalent to intravenous electrolyte maintenance infusion.

## 5. Conclusion

After controlling for covariates, there were no significant differences in the incidence of CIN or safety between the 20% Man and 15% Man-S groups. Both 20% Man and 15% Man-S are available for CIN prevention; however, 15% Man-S is contraindicated for patients with HFI. In addition, 15% Man-S has the advantage of being less prone to crystallization at lower temperatures compared with 20% Man.

## 6. Competing interests

The authors declare no conflict of interest.

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