Research Square

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Preventive Effects of SGLT2 Inhibitors on Cisplatin-Induced Nephrotoxicity in Patients with Solid Tumors and Diabetes: A Multicenter, Retrospective Cohort Study

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Research Article

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Abstract

Background

Cisplatin (CDDP)-induced nephrotoxicity (CIN) is a major dose-limiting toxicity. Preclinical models suggest that sodium-glucose cotransporter 2 (SGLT2) inhibitors, used in the management of diabetes, activate multidrug and toxin extrusion (MATE) transporters by altering luminal sodium and hydrogen ion gradients via the sodium-hydrogen exchanger 3 (NHE3), thereby promoting cisplatin efflux from proximal tubular cells. This study aimed to investigate the clinical preventive effect of SGLT2 inhibitors on CIN in patients with solid tumors and concurrent type 2 diabetes.

Methods

A multicenter, retrospective cohort study was conducted across 16 institutions in Japan. Eligible patients were aged ≥ 20 years with solid tumors and type 2 diabetes who received high-dose CDDP (≥ 50 mg/m^2)-based chemotherapy. We compared patients receiving SGLT2 inhibitors with those receiving metformin. Patients receiving dipeptidyl peptidase-4 (DPP-4) inhibitors were excluded. To minimize confounding from baseline patient characteristics, inverse probability of treatment weighting (IPTW) using the stabilized average treatment effect (sATE) was applied.

Results

After sATE-IPTW adjustment, the incidence of CIN was significantly lower in the SGLT2 inhibitor group than in the metformin group (17.9% vs. 45.2%, *P* = 0.034). The decline in renal function was significantly mitigated in the SGLT2 inhibitor group, as evidenced by better preservation of serum creatinine, creatinine clearance, and estimated glomerular filtration rate (all *P* < 0.05). A multivariate logistic regression analysis identified the use of SGLT2 inhibitors as an independent protective factor against CIN (odds ratio [OR] 0.247, *P* = 0.001), whereas preexisting cardiac disease was identified as an independent risk factor (OR 3.107, *P* = 0.042).

Conclusions

SGLT2 inhibitors significantly and robustly reduce the risk of CIN in patients with solid tumors and type 2 diabetes. The concomitant use of SGLT2 inhibitors represents a promising renoprotective strategy to safely maintain the dose intensity of CDDP-based chemotherapy in clinical practice.

BACKGROUND

Cisplatin (CDDP), a platinum-based chemotherapeutic agent, serves as a cornerstone in the treatment of various solid tumors [1]. Despite its proven clinical efficacy, nephrotoxicity represents a major dose-limiting factor, frequently necessitating dose reduction or treatment discontinuation. Standard renoprotective measures, such as aggressive hydration, diuretic administration, and magnesium supplementation, are routinely implemented in clinical practice. Despite these preventive interventions, acute kidney injury occurs in approximately 20–40% of patients receiving CDDP-based chemotherapy [2–5]. To address this substantial incidence of CDDP-induced nephrotoxicity (CIN), the development of novel preventive strategies is imperative.

The mechanisms underlying CIN have been investigated extensively using experimental models and cell culture systems. The primary pathophysiological pathway involves CDDP accumulation within proximal tubular epithelial cells [6], which triggers a cascade of deleterious events, including increased oxidative stress mediated by reactive oxygen species [6, 7], promotion of apoptosis [6, 8], and propagation of intrarenal inflammatory responses [9]. Building on these mechanistic insights, numerous therapeutic candidates possessing antioxidant, anti-inflammatory, and anti-apoptotic properties have been evaluated in CIN animal models, with many demonstrating apparent renoprotective effects [6]. However, clinical translation of these strategies has been limited. When tested in human subjects, most candidates exhibit substantially reduced efficacy or complete ineffectiveness, and none have achieved clinical application. These translational failures suggest that therapeutic strategies focused solely on ameliorating cellular damage and downstream inflammatory cascades are insufficient. Accordingly, alternative approaches targeting CDDP accumulation itself merit investigation.

Renal handling of CDDP is mediated by multiple transporters expressed in proximal tubular cells. In particular, CDDP is taken up from the blood across the basolateral membrane primarily via organic cation transporter 2 (OCT2) and is subsequently extruded into the tubular lumen through multidrug and toxin extrusion proteins (MATE1 and MATE2-K) located on the apical membrane [10, 11]. We have previously used a combination of a FAERS (FDA Adverse Event Reporting System)-based pharmacovigilance analysis, hospital electronic medical records, and preclinical studies to demonstrate that altered intrarenal CDDP accumulation is closely linked to nephrotoxicity in both experimental and clinical settings [12]. These observations raise the possibility that enhancing MATE-mediated efflux from proximal tubular cells may mitigate CIN. Because MATE transport is driven by a transmembrane proton gradient, changes in luminal sodium–hydrogen handling could potentially influence its activity.

Sodium–glucose cotransporter 2 (SGLT2) and sodium–hydrogen exchanger 3 (NHE3) are both expressed on the apical membrane of proximal tubular cells and play central roles in glucose and sodium handling [13, 14]. Based on their functional interplay, SGLT2 inhibition may modify the proton gradient that drives MATE-dependent transport. Ongoing translational work by our group has generated complementary preclinical evidence supporting this concept. In mouse models of CIN, SGLT2 inhibitor (SGLT2i) attenuated renal injury in association with reduced proximal tubular CDDP accumulation. In parallel, in vitro studies suggested a functional interaction between MATE1 and NHE3. Given the current indications for SGLT2i, a feasible approach to evaluate their renoprotective effects is to investigate these agents in patients with cancer and diabetes.

We conducted a multicenter, retrospective observational study to evaluate whether SGLT2i use mitigates CIN in patients with solid tumors and concomitant type 2 diabetes mellitus.

METHODS

Patients

This multicenter retrospective study was conducted at 16 hospitals in Japan. Patients were eligible if they were aged 20 years or older with solid cancers and type 2 diabetes and received high-dose CDDP (≥ 50 mg/m^2)-based chemotherapy for the first time. The study included patients who were administered SGLT2i (canagliflozin, dapagliflozin empagliflozin, ipragliflozin, luseogliflozin, and tofogliflozin) or metformin for 1 week before and after CDDP administration. Concomitant use of other antidiabetic medications was permitted; however, patients taking dipeptidyl peptidase-4 (DPP-4) inhibitors were excluded.

Data collection

The following information was retrospectively extracted from medical records at each institution: patient characteristics (age, sex, height, weight, body mass index [BMI], primary cancer, and history of chemotherapy, cardiac disease, and hypertension), laboratory data (alanine aminotransferase [ALT], aspartate aminotransferase [AST], serum creatinine [SCr], estimated glomerular filtration rate [eGFR], hemoglobin A1c [HbA1c], potassium, and albumin), and treatment-related factors (CDDP dose, chemotherapy cycle, chemotherapy regimens, diabetic medications, renal protection measures [diuretics, type of hydration, and magnesium supplementation], prophylactic antiemetics, and concomitant medications that cause nephrotoxicity or MATE-inhibitor). Nephrotoxicity was evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5. Specifically, for increased SCr, Grade 1 was defined as >upper limit of normal (ULN) − 1.5×ULN, Grade 2 as > 1.5–3.0×ULN, Grade 3 as > 3.0–6.0×ULN, and Grade 4 as > 6.0×ULN. The SCr value measured immediately before the first CDDP administration was used as the baseline. The worst creatinine level was defined as the peak creatinine value recorded within the chemotherapy treatment period from the index date. In addition, the percent changes in SCr levels, creatinine clearance (CCr), and eGFR from baseline were assessed.

Statistical analysis

The primary endpoint was the incidence of CIN during the CDDP administration period, which was compared between the metformin and SGLT2i groups. To minimize the impact of confounding factors, we used the stabilized average treatment effect (sATE) of the inverse probability treatment weighting (IPTW) model derived from a logistic regression model to balance observable characteristics (covariates: age, female sex, BMI, eGFR, HbA1c, cardiac disease, hypertension, albumin level, CDDP dose, type of hydration, type of diuretic, Mg supplementation, angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, MATE-inhibitor [irinotecan, diltiazem, diphenhydramine, famotidine, and trimethoprim], non-steroidal anti-inflammatory drugs, proton pump inhibitor, and cycle of chemotherapy). Variables were included in the model based on existing knowledge of risk factors for nephrotoxicity and the literature

[5, 15–18]. Categorical variables were analyzed using the chi-square test, and continuous variables were analyzed using the Student's *t*-test or Wilcoxon rank-sum test.

The rates of change in SCr, CCr, and eGFR were calculated using the following formula: (worst value - baseline value) × 100/baseline value.

A logistic regression analysis was performed to extract risk factors for the development of nephrotoxicity, adjusting for potential confounding by age, sex, cardiac disease, hypertension, Mg supplementation, CDDP dose, and use of SGLT2i. Variables were selected a priori based on the literature and their clinical relevance.

A sensitivity analysis was performed using the weighted average treatment effect on the treated (ATT) and average treatment effect on the controls (ATC). Furthermore, a stratified analysis was conducted within the SGLT2i group according to the presence or absence of concomitant metformin use. All statistical tests were two-sided, and *P*-values of < 0.05 indicated statistical significance. All analyses were performed using JMP 14.3 (SAS Institute, Cary, NC, USA).

RESULTS

Baseline characteristics of patients

A total of 156 patient records were collected. The effective sample sizes, adjusted by sATE weighting, were 94 in the metformin group and 56.7 in the SGLT2i group. After adjustment using sATE weighting, baseline patient characteristics were well balanced between the groups, with the exception of ALT/AST levels and certain antidiabetic medications (Table 1). Supplementary Table S1 summarizes the cancer types and chemotherapy regimens.

Table 1
Patient Characteristics

		Unadjusted					sATE weighting				
		Metformin		SGLT2i		SMD	Metformin		SGLT2i		SMD
		n = 94		n = 62			ESS = 94		ESS = 56.7		
SEX	Female, n (%)	18	(19.2)	12	(19.4)	0.005	19.2		19.4		0.005
Age	Mean (SD)	65.4	(8.8)	65.4	(8.1)	< 0.001	65.4	(8.8)	64.7	(9.9)	0.075
	Median (IQR)	67.5	(61, 71)	67.5	(61, 71)						
BMI	Mean (SD)	23.9	(4.1)	24.7	(3.8)	0.183	23.9	(4.3)	24.1	(3.6)	0.049
	Median (IQR)	23.0	(21.3, 25.6)	24.5	(21.9, 26.1)						
Cardiac disease	Yes, n (%)	12	(12.8)	7	(11.3)	0.045	12.8		12.9		0.006
Hypertension	Yes, n (%)	44	(46.8)	39	(62.9)	0.328	46.8		39.6		0.146
Chemotherapy history	Yes, n (%)	22	(23.4)	6	(9.7)	0.376	23.4		23.3		0.002
eGFR, mL/min	Mean (SD)	78.3	(20.7)	77.5	(20.4)	0.040	78.3	(17.9)	79.8	(19.0)	0.070
	Median (IQR)	74.7	(64.4, 87.3)	76.1	(61.6, 89.9)						
Alb level, g/dL	Mean (SD)	4.0	(0.6)	4.0	(0.5)	0.044	3.9	(0.6)	4.0	(0.5)	0.082
	Median (IQR)	4.0	(3.6, 4.4)	4.0	(3.8, 4.3)						
ALT, U/L	Mean (SD)	25.8	(19.4)	20.7	(17.0)	0.239	25.8	(17.9)	20.8	(16.4)	0.257
	Median (IQR)	21.5	(14.0, 30.0)	16.0	(13.0, 22.0)						
AST, U/L	Mean (SD)	24.9	(17.5)	21.3	(12.4)	0.232	24.9	(14.2)	20.0	(10.3)	0.320
	Median (IQR)	20.0	(16.0, 26.6)	18.0	(15.0, 25.0)						
HbA1c, %	Mean (SD)	7.1	(1.2)	6.8	(0.9)	0.268	7.1	(1.2)	7.0	(1.0)	0.083
	Median (IQR)	6.8	(6.2, 7.8)	6.6	(6.2, 7.2)						
K level, mEq/L	Mean (SD)	4.3	(0.4)	4.2	(0.3)	0.194	4.3	(0.4)	4.3	(0.3)	0.029
	Median (IQR)	4.2	(4.0, 4.5)	4.2	(4.0, 4.3)						
Antidiabetic drugs	αGI, n (%)	11	(11.7)	2	(3.2)	0.327	11.7		1.6		0.414

ACE, angiotensin-converting enzyme; αGI, α-glucosidase inhibitor; ALT, alanine aminotransferase; Alb, albumin; ARB, angiotensin II receptor blocker; AST, aspartate aminotransferase; BMI, body mass index; CDDP, cisplatin; eGFR, estimated glomerular filtration rate; ESS, effective sample size; GLP1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, hemoglobin A1c; IQR, interquartile range; MATE, multidrug and toxin extrusion; PPI, proton pump inhibitor; sATE, stabilized average treatment effect; SD, standard deviation; SGLT2i, sodium/glucose cotransporter 2 inhibitor; SMD, standardized mean difference; SU, Sulfonylurea; NSAIDs, non-steroidal anti-inflammatory drugs

MATE inhibitors in this study population include the following: irinotecan, diltiazem, diphenhydramine, famotidine, and trimethoprim.

		Unadjusted					sATE weighting				
		Metformin		SGLT2i		SMD	Metformin		SGLT2i		SMD
	GLP1 RA, n (%)	6	(6.4)	9	(14.5)	0.268	6.4		16.5		0.321
	Insulin, n (%)	16	(17.0)	9	(14.5)	0.069	17.0		20.8		0.097
	SU or Glinides, n (%)	17	(18.1)	8	(12.9)	0.144	18.1		10.6		0.215
	Thiazolidine, n (%)	4	(4.3)	0	(0.0)	0.298	4.3		0		0.300
CDDP dose, mg/m^2	Mean (SD)	72.2	(10.1)	73.0	(10.5)	0.077	72.2	(10.1)	71.8	(11.5)	0.032
	Median (IQR)	75.0	(64.8, 80.0)	77.5	(62.5, 80.0)						
Chemotherapy cycle	Mean (SD)	2.7	(1.5)	2.7	(1.7)	0.005	2.7	(1.5)	2.9	(1.8)	0.107
	Median (IQR)	2.0	(2.0, 3.8)	2.0	(2.0, 4.0)						
Short hydration	Yes, n (%)	22	(23.4)	17	(27.4)	0.092	23.4		24.1		0.016
Diuretic	Yes, n (%)	82	(87.2)	59	(95.2)	0.285	87.2		89.2		0.062
Mg supplementation	Yes, n (%)	66	(70.2)	46	(74.2)	0.089	70.2		67.4		0.060
Concomitant drugs	ACE inhibitor, n (%)	4	(4.3)	1	(1.6)	0.157	4.3		4.2		0.005
	ARB, n (%)	19	(20.2)	31	(50.0)	0.657	20.2		23.3		0.075
	MATE inhibitor, n (%)	7	(7.5)	4	(6.5)	0.039	7.5		5.4		0.082
	NSAIDs, n (%)	11	(11.7)	12	(19.4)	0.212	11.7		14.1		0.072
	PPI, n (%)	17	(18.1)	23	(37.1)	0.435	18.1		20.8		0.066

ACE, angiotensin-converting enzyme; αGI, α-glucosidase inhibitor; ALT, alanine aminotransferase; Alb, albumin; ARB, angiotensin II receptor blocker; AST, aspartate aminotransferase; BMI, body mass index; CDDP, cisplatin; eGFR, estimated glomerular filtration rate; ESS, effective sample size; GLP1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, hemoglobin A1c; IQR, interquartile range; MATE, multidrug and toxin extrusion; PPI, proton pump inhibitor; sATE, stabilized average treatment effect; SD, standard deviation; SGLT2i, sodium/glucose cotransporter 2 inhibitor; SMD, standardized mean difference; SU, Sulfonylurea; NSAIDs, non-steroidal anti-inflammatory drugs

MATE inhibitors in this study population include the following: irinotecan, diltiazem, diphenhydramine, famotidine, and trimethoprim.

Incidence of nephrotoxicity

The overall incidence of nephrotoxicity was 45.2% in the metformin group and 17.9% in the SGLT2i group ($P < 0.001$). As shown in Table 2, the incidence of CTCAE Grade 1 nephrotoxicity was 42.7% in the metformin group and 11.7% in the SGLT2i group, while those of Grade 2 were 2.5% and 6.2%, respectively. The difference in the incidence of nephrotoxicity between the two groups was significant ($P = 0.034$).

Table 2
Incidence of nephrotoxicity (CTCAE ver.5)

	Metformin		SGLT2i		*P*-value
	n	%	n	%	
WNL	49	54.8	47	82.1	0.034
Grade 1	38	42.7	7	11.7	
Grade 2	2	2.5	3	6.2	

CTCAE, Common Terminology Criteria for Adverse Events; WNL, within normal limits

Rate of change in SCr, CCr, and eGFR

Significant differences were found in the median rates of change in SCr, CCr, and eGFR between the two groups in all subsequent cycles (*P* = 0.002, *P* = 0.002, and *P* = 0.002, respectively) (Fig. 1).

Risk factors for nephrotoxicity

In univariate and multivariate analyses, cardiac disease was identified as a significant independent risk factor for nephrotoxicity (odds ratio [OR] = 3.107, 95% confidence interval [CI] 1.042 to 9.262, *P* = 0.042). Conversely, receiving an SGLT2i was an independent protective factor against the development of nephrotoxicity (OR = 0.247, 95% CI 0.107 to 0.568, *P* = 0.001) (Table 3).

Table 3
Risk factors for nephrotoxicity

	Univariate				**Multivariate**			
	OR	**95%CI**		***P*-value**	**OR**	**95%CI**		***P*-value**
Age	0.964	0.923	1.008	0.098	0.962	0.915	1.011	0.112
Female	1.227	0.485	3.107	0.666	1.347	0.475	3.818	0.575
Hypertension	1.543	0.75	3.173	0.236	1.65	0.765	3.556	0.201
Cardiac disease	2.337	0.829	6.589	0.106	3.107	1.042	9.262	0.042
Mg supplementation	1.015	0.458	2.248	0.97	0.824	0.336	2.021	0.672
CDDP dose	1.01	0.975	1.047	0.579	1.002	0.964	1.042	0.913
SGLT2i group	0.375	0.181	0.781	0.007	0.247	0.107	0.568	0.001

CDDP, cisplatin; CI, confidence interval; OR, odds ratio; SGLT2i, sodium-glucose cotransporter 2 inhibitor

Sensitivity analysis

Supplementary Table S2 shows the patient characteristics for the ATT and ATC weighting analysis. Using ATT and ATC weighting, the incidence of nephrotoxicity (Supplementary Table S3) and rates of change in SCr, CCr, and eGFR (Supplementary Table S4) were all significantly better in the SGLT2i group, consistent with the results of the primary analysis. Furthermore, in both analyses, the use of SGLT2i was associated with a reduced incidence of nephrotoxicity (Supplementary Table S5). In the stratified analysis of the SGLT2i group according to the presence or absence of concomitant metformin use, these parameters did not differ with respect to metformin use (Supplementary Tables S6–8).

DISCUSSION

In this multicenter retrospective cohort study, concomitant use of SGLT2i was associated with a significantly lower incidence of CIN than that for metformin use in patients with solid tumors and type 2 diabetes receiving high-dose CDDP-based chemotherapy. After

adjustment using IPTW (sATE weighting), the incidence of nephrotoxicity was 17.9% in the SGLT2i group, which was significantly lower than that in the metformin group (i.e., 45.2%). Furthermore, the rates of change in SCr, CCr, and eGFR were significantly better preserved in the SGLT2i group. A multivariate analysis further showed that SGLT2i use was independently associated with lower odds of CIN, whereas preexisting cardiac disease was associated with higher odds. Consistent results were obtained in sensitivity analyses using ATT and ATC weighting. Furthermore, the renoprotective effects of SGLT2i were observed regardless of concomitant metformin use. Consequently, the findings from both the primary and sensitivity analyses suggest that the clinical utility of SGLT2i for the prevention of CIN is robust.

An important strength of the present study is that it was not purely exploratory but rather was designed as a translational clinical investigation grounded in our group's parallel preclinical work using CIN mouse models and transporter-based in vitro systems. Our ongoing translational studies have suggested that SGLT2i attenuates renal injury in association with reduced proximal tubular CDDP accumulation and that a functional interaction between MATE1 and NHE3 may underlie this effect. The present clinical findings are consistent with this biological framework and thus extend our bench-side observations into a clinically relevant population. Although the current study does not provide direct mechanistic proof in humans, it offers translational support for the hypothesis that modulation of proximal tubular transporter function represents a novel strategy for CIN prevention.

Both animal experiments and clinical studies have suggested that DPP-4 inhibitors exert renoprotective effects and prevent acute kidney injury through their anti-inflammatory properties [19], attenuation of oxidative stress [20], and inhibition of apoptosis [20]. Accordingly, to evaluate the clinical association of SGLT2i with CIN risk, patients receiving DPP-4 inhibitors were excluded. Instead, we selected metformin, a biguanide, as the control group, reflecting contemporary prescribing patterns and patient characteristics in Japan [21]. Although the renoprotective efficacy of metformin against CIN has not been established, metformin acts as a substrate for MATE1 and MATE2-K, potentially causing competitive inhibition of the transport of other substrates, including creatinine [22, 23]. Furthermore, metformin has been shown to mitigate renal functional decline in diabetic nephropathy via AMPK activation and the promotion of autophagy [24]. These diverse pharmacological mechanisms may introduce confounding bias into the evaluation of renal function. To address this potential source of bias, we conducted a stratified analysis according to concomitant metformin use within the SGLT2i-treated population, and the findings remained consistent with those of the primary analysis. Taken together, these results suggest that the observed association was unlikely to be explained solely by metformin-related confounding. Ishigami et al. [25] reported no significant association between SGLT2i use and the development of CIN. However, their single-center, retrospective study differed from the present investigation in several key methodological aspects. The diagnostic criteria for nephrotoxicity and observation period differed between the cohorts. Additionally, rigorous covariate adjustment techniques, such as IPTW, were not employed in this previous study, and a substantial baseline imbalance in CDDP dosage was observed between the two studies. Furthermore, approximately 60% of participants received concomitant DPP-4 inhibitors, and several baseline characteristics were dissimilar, specifically regarding metformin use, magnesium supplementation, and the prevalence of hypertension. These methodological discrepancies and variations in baseline clinical characteristics likely account for the divergent findings between the two studies.

Recent experimental models and in vitro studies have reported that SGLT2i use mitigates CIN [26–29]. SGLT2i protect renal tissue by decreasing oxidative stress markers (such as MDA) [28], restoring antioxidant enzymes (e.g., SOD and catalase), and suppressing inflammatory cytokines (e.g., TNF-α and IL-1β) [28]. Mechanistically, they reduce the cellular uptake of CDDP in the proximal tubules and inhibit apoptosis [27]. The current study supports for value of modulating proximal tubular transporter function as a novel strategy for CIN prevention. The present results are biologically plausible and broadly consistent with previous experimental studies showing renoprotective effects of SGLT2i in CIN models. CIN is primarily driven by its accumulation within proximal tubular cells, caused by an imbalance between OCT2-mediated uptake and MATE-mediated efflux [6, 27]. Alterations in luminal Na+ dynamics induced by SGLT2 inhibition may influence the activity of NHE3 and MATE transporters, thereby promoting the efflux of CDDP and reducing its intracellular accumulation [10, 11, 30]. Our group's ongoing preclinical work using mouse models and transporter-based in vitro systems supports the biological plausibility of this mechanism. Furthermore, the identification of cardiac disease as an independent risk factor in the multivariate analysis is clinically sound [15, 31, 32]. From the perspective of cardiorenal crosstalk, hemodynamic vulnerability due to impaired cardiac function [31, 32] exacerbates renal ischemia and tubular damage caused by CDDP. On the other hand, the reliance on SCr for renal function assessment in this study necessitates careful interpretation from a pharmacokinetic perspective. The renal elimination of creatinine depends not solely on glomerular filtration but also, to a certain extent (approximately 20% to 30%), on active secretion mediated by the proximal tubules [33]. Specifically, creatinine is taken up into tubular epithelial cells via OCT2 on the basolateral membrane and is subsequently excreted into the tubular lumen through MATE1 and MATE2-K on the apical membrane [6, 10]. If our hypothesis holds true in the clinical setting, it is plausible that the tubular secretion of creatinine—which, like CDDP, serves as

a substrate for MATE transporters—may be concurrently upregulated. Theoretically, we cannot exclude the possibility that the observed attenuation of SCr elevation and mitigation of CCr/eGFR decline partially reflect an artifactual enhancement in creatinine clearance secondary to MATE activation, rather than the prevention of CDDP-induced glomerular injury. Consequently, reliance on SCr alone may be inadequate to rigorously establish whether SGLT2i exerts a true GFR-preserving effect in the context of CIN. Future prospective studies must incorporate evaluations utilizing cystatin C, an alternative biomarker that reflects the true glomerular filtration rate independently of MATE-mediated tubular secretion [33, 34]. This approach will more accurately delineate the genuine renoprotective efficacy of SGLT2i and help elucidate their underlying molecular mechanisms.

This study has some limitations. First, owing to its retrospective observational design, the influence of unmeasured confounders cannot be eliminated. However, the application of the IPTW to the multicenter cohort data allowed us to minimize the influence of confounders—including age, renal function, comorbidities, and concurrent medications—in the inter-group comparisons. This approach improved the internal validity of our findings. Second, the study population was limited to Japanese patients with diabetes, and the effective sample size was limited; therefore, caution should be exercised when generalizing the findings to other racial or ethnic populations and to patients without diabetes. Third, individual quantifiable data for heart disease (e.g., cardiac output and ejection fraction) were not available; therefore, we defined heart disorders based only on the medical history of cardiac diseases, such as angina or myocardial infarction. Fourth, since urine dipstick data for hematuria/proteinuria were not available, these could not be considered in this study. Finally, because this was a clinical data-based study, it does not provide direct molecular evidence of reduced intracellular CDDP accumulation or the functional activation of MATE transporters in the human proximal tubule.

CONCLUSION

Among patients with solid tumors and type 2 diabetes receiving high-dose CDDP-based chemotherapy, concomitant SGLT2i use was associated with a substantially lower risk of CIN and better preservation of renal function than those for metformin use. In patients with type 2 diabetes scheduled for CDDP-based chemotherapy, SGLT2i represents a compelling therapeutic option not only for glycemic control but also as a robust renoprotective strategy to maintain chemotherapy dose intensity. To establish this approach as a novel supportive care strategy in cancer pharmacotherapy, large-scale prospective trials in diverse patient populations, incorporating evaluations based on cystatin C, are highly warranted. Furthermore, translational research elucidating detailed transporter dynamics is warranted.

Abbreviations

ALT
alanine aminotransferase
AST
aspartate aminotransferase
ATC
average treatment effect on the controls
ATT
average treatment effect on the treated
BMI
body mass index
CCr
creatinine clearance
CIN
Cisplatin-induced nephrotoxicity
CDDP
Cisplatin
DPP-4
dipeptidyl peptidase-4
CTCAE
Common Terminology Criteria for Adverse Events
eGFR
estimated glomerular filtration rate

HbA1c
hemoglobin A1c
IPTW
inverse probability of treatment weighting
MATE
multidrug and toxic compound extrusion
NHE3
sodium–hydrogen exchanger 3
sATE
stabilized average treatment effect
SCr
serum creatinine
SGLT2
sodium–glucose cotransporter 2
ULN
upper limit of normal

Declarations

Ethics Approval and Consent to Participate:

The study was approved by the Institutional Review Boards of all participating institutions and by the Ethics Committee of Tokushima University Hospital (approval No. 4609-3). All participants were treated in accordance with the principles outlined in the Declaration of Helsinki. The Ethics Committee of Tokushima University Hospital, the coordinating center, waived the requirement for informed consent owing to the retrospective nature of the study. Data were used after allowing patients to refuse to participate using an opt-out form.

Consent for Publication:

Not applicable.

Competing Interests:

The authors declare that the study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Data Availability

The data that support the findings of this study are available from the study group. However, restrictions apply to the availability of these data, as they were used under a license for the current study and are therefore not publicly available. The data are, nevertheless, available from the corresponding author, Toshinobu Hayashi.

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Figures

Figure 1

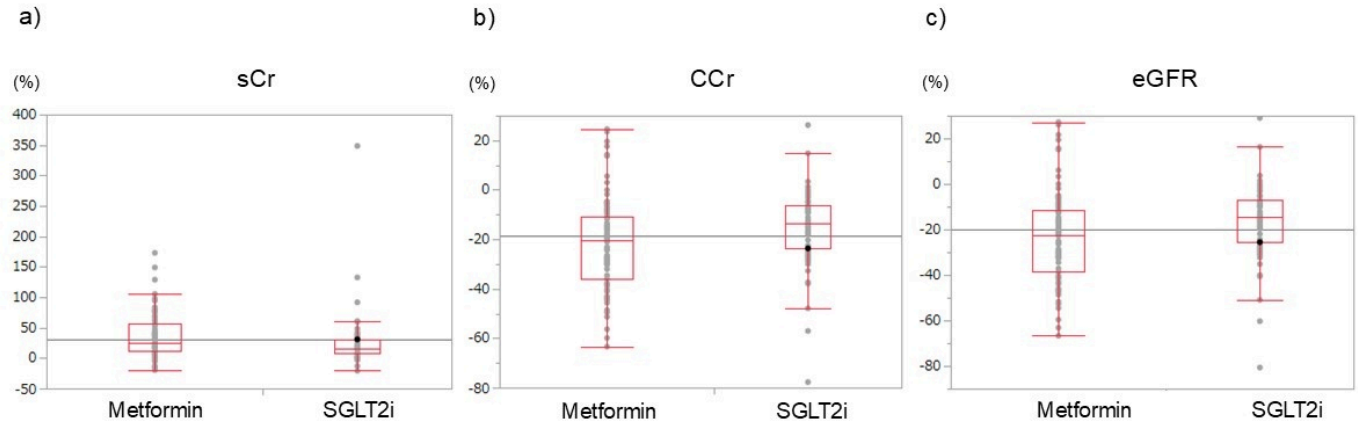


Figure 1

Percentage changes in SCr, CCr, and eGFR

The median (IQR) rates of change in (a) SCr, (b) CCr, and (c) eGFR in the metformin and SGLT2i groups are shown.

CCr, creatinine clearance; eGFR, estimated glomerular filtration rate; IQR, interquartile range; SCr, serum creatinine; SGLT2i, sodium-glucose cotransporter 2 inhibitor

Supplementary Files

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