

## Influence of Renal ABC and SLC Transporter Polymorphisms on Cisplatin-induced Nephrotoxicity in Patients with Esophageal Cancer

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### Abstract

**Background:** The individual and collective contributions of genetic polymorphisms in drug transporter genes in human renal proximal tubules to cisplatin-induced nephrotoxicity are still unclear.

**Methods:** In this study, we investigated the effects of polymorphisms in *SLC22A2* (808G>T), *SLC31A1* (rs10981694A>C, rs12686377G>T, rs7851395A>G), *SLC47A1* (rs2289669G>A), *ABCB1* (1236C>A, 2677G>T/A, 3435C>T), *ABCC2* (-24C>T), and *ABCG2* (421C>A) on cisplatin-induced nephrotoxicity in 131 patients with esophageal cancer receiving 5-fluorouracil and cisplatin (FP) chemotherapy. The change rate of the estimated glomerular filtration rate (eGFR) was calculated according to the following formula: eGFR before FP chemotherapy-lowest eGFR during first cycle after FP chemotherapy/eGFR before FP chemotherapy.

**Results:** In univariate analysis, there was a significant correlation between patient age and the change rate of the eGFR by cisplatin ( $P = 0.021$ ). However, there were no significant differences in the change rate of the eGFR by cisplatin between *SLC22A2*, *SLC47A1*, *SLC31A1*, *ABCB1*, *ABCC2*, and *ABCG2* polymorphisms. Multivariate analysis revealed that only age was an independent variable predicting a higher risk of cisplatin-induced acute renal dysfunction.

**Conclusion:** In FP chemotherapy for esophageal cancer patients, cisplatin-induced nephrotoxicity was not affected by polymorphisms in the uptake transporters OCT2 and Ctr1 or efflux transporters MATE1, P-glycoprotein, MRP2, and BCRP. Since degradation of renal function due to aging reduces cisplatin clearance, the cisplatin dosage should be carefully chosen in elderly patients.

**Keywords:** Cisplatin; Nephrotoxicity; CTR1; OCT2; MATE1

### Introduction

Cisplatin (*cis*-diamminedichloroplatinum), a potent platinum-based alkylating anticancer drug, is widely used as therapy for many types of cancer such as lung, breast, bladder, esophageal, head and neck cancers [1-4]. However, the use of cisplatin is limited by severe side effects such as nephrotoxicity, cardiotoxicity, gonadotoxicity, hepatotoxicity, and central and peripheral neurotoxicity [5-7]. Cisplatin is an extremely hydrophilic compound that has difficulty crossing plasma membranes [8]. Cisplatin is excreted primarily by the kidneys, i.e., it is filtered in the glomerulus and is secreted by the human kidney [9]. Consequently, movement of cisplatin through plasma membranes is mediated by transport proteins.

Renal tubular epithelial cells contain brush-border (apical) membranes and basolateral membranes. Cisplatin is a substrate of uptake transporters, organic cation transporter (OCT) 2 (encoded by the *SLC22A2* gene) and copper transporter (Ctr) 1 (encoded by the *SLC31A1* gene), expressed in the basolateral membrane of renal proximal tubules [10-16]. On the other hand, cisplatin is transported by the H<sup>+</sup>/organic cation antiporter multidrug and toxin extrusion transporter (MATE) 1 (encoded by the *SLC47A1* gene) expressed in the renal apical membrane [15-17]. In addition, although cisplatin is not a substrate of ATP-binding cassette (ABC) transporters, such as multidrug resistance-associated protein (MRP) 2 (encoded by the *ABCC2* gene), breast cancer resistance protein (BCRP) (encoded by the *ABCG2* gene) and P-glycoprotein (encoded by the *ABCB1* gene), its metabolites, including cisplatin-thiol and unidentified substances induced by cisplatin, may cause cisplatin-induced nephrotoxicity [18-23]. The activities of these drug transporters in human renal proximal tubules are considered a determinant of cisplatin-induced nephrotoxicity.

In our previous study, we found that cisplatin-induced nephrotoxicity in 95 esophageal cancer patients receiving a 5-fluorouracil (5-FU) and cisplatin (FP) regimen was unaffected by the *SLC22A2* 808G>T polymorphism [24]. This result is different from those of previous studies [25,26]. However, the *ABCC2*-24T variant shows 18.7% reduced activity compared with the -24C/C genotype [27], and clinical evidence has shown that common *ABCC2* polymorphisms may affect the disposition or efficacy of drugs that are known *ABCC2* substrates [28]. In addition, cisplatin induces BCRP and P-glycoprotein in the kidneys [22,29]. Hoffmeyer et al. reported that the expression levels of P-glycoprotein induced by rifampin are lowest in subjects with the *ABCB1* 3435T/T genotype [30]. Therefore, patients with the *ABCB1* 3435T/T genotype may exhibit higher nephrotoxicity. However, the individual and collective contributions of genetic polymorphisms in the above transporters to cisplatin-induced nephrotoxicity are still unclear.

In the present study, we re-examined the influence of the *SLC22A2* 808G>T polymorphism using an increased sample size of 131 patients with esophageal cancer receiving FP chemotherapy. In addition, we investigated the effects of polymorphisms in *SLC31A1* (rs10981694A>C,

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rs12686377G>T, rs7851395A>G), *SLC47A1* (rs2289669G>A), *ABCB1* (1236C>A, 2677G>T/A, 3435C>T), *ABCC2* (-24C>T), and *ABCG2* (421C>A) on cisplatin-induced nephrotoxicity.

## Materials and Methods

### Protocol

This study was approved by the Ethics Committee of Akita University Graduate School of Medicine. Each participant provided informed consent in compliance with the code of ethics of the World Medical Association (Declaration of Helsinki) before this study and signed a human subject institutional review board consent form. Eighty-four esophageal cancer patients receiving FP chemotherapy in this study had participated in our previous studies [24].

The disease was classified according to the UICC International Union against Cancer tumor-node-metastasis (TNM) Classification of Malignant Tumors (sixth edition). Between 2004 and 2014, 131 patients with normal renal function before FP chemotherapy who agreed to genetic analysis of polymorphisms were included in the study. Patients with renal dysfunction who required reduced doses of cisplatin lower than those indicated in the protocol during the first cycle were not included in this study ( $n = 12$ ). We treated patients with stage II - IV disease with esophagectomy with extended lymphadenectomy followed by adjuvant chemotherapy consisting of protracted infusion of 5-FU (800 mg/m<sup>2</sup>/day) on days one to five and cisplatin (80 mg/m<sup>2</sup>/day) on day one. This protocol was repeated every four weeks. After 2009, we treated the stage II and III patients with neoadjuvant chemotherapy or neoadjuvant chemoradiotherapy (40 Gy) consisting of the same protocol followed by surgery. Stage IV patients received definitive chemoradiotherapy or chemotherapy alone. In these patients, chemotherapy consisted of protracted infusion of 5-FU (400 mg/m<sup>2</sup>/day) on days one to five, eight to 12, and cisplatin (40 mg/m<sup>2</sup>/day) on days one and eight. This protocol was repeated every four weeks. After 2009, cisplatin was administered in 500 mL of normal saline solution over 2 h in combination with 5-FU and 2500-3000 mL of hydration. In addition, after 2013, all patients received 8 mEq of magnesium sulfate to prevent nephrotoxicity. However, we were unable to confirm information regarding hydration and the use of magnesium sulfate for treatments given during 2012 owing to incomplete medical records. The toxicity grade was determined by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 criteria.

### Genotyping

Single nucleotide polymorphisms that influence transporter activity were chosen for analysis. DNA was extracted from peripheral blood samples using a QIAamp Blood Kit (Qiagen, Hilden, Germany) and was stored at -80°C until analyzed. Genotyping procedures identifying the G and T alleles of *SLC22A2* (808G>T, rs316019) were performed using a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method described by Wang *et al.* [31]. Genotyping procedures identifying the C and T alleles in exon 12 (1236 C>T, rs1128503), the G and T/A alleles in exon 21 (2677 G>T/A, rs2032582), and the C and T alleles in exon 26 (3435 C>T, rs1045642) of the *ABCB1* gene were performed using PCR-RFLP methods described by Wu *et al.* [32], Tanaka *et al.* [33] and Cascorbi *et al.* [34], respectively. The *ABCG2* 421C>A (rs2231142) and *ABCC2* -24C>T (rs717620) polymorphisms were genotyped by the PCR-RFLP methods of Kobayashi *et al.* [35] and Rau *et al.* [36], respectively. The *SLC47A1* rs2289669G>A and *SLC31A1* rs7851395A>G polymorphisms were genotyped using a fully automated single nucleotide polymorphism (SNP) detection system (prototype i-densy, ARKRAY Inc., Kyoto,

Japan) and by the PCR-RFLP method of He *et al.* [37]. The *SLC31A1* rs10981694A>C and *SLC31A1* rs12686377G>T polymorphisms were genotyped by the PCR-RFLP method of Wu *et al.* [38]. All frequencies for the different loci analyzed were at Hardy-Weinberg equilibrium.

### Statistical analyses

The Shapiro-Wilk test was used to assess distribution. The characteristics of esophageal cancer patients were expressed as the mean  $\pm$  standard deviation (range). The estimated glomerular filtration rate (eGFR) was calculated for each esophageal cancer patient according to the following formula:  $eGFR = 194 \times \text{serum creatinine (Scr) (mg/dL)}^{-1.094} \times \text{age}^{-0.287} \times \text{body surface area (m}^2\text{)} / 1.73$  ( $\times 0.739$  for female). The change rates in laboratory test values were calculated for each patient with esophageal cancer according to the following formula:  $\text{Change rate} = (\text{value before FP chemotherapy} - \text{lowest value during first cycle after FP chemotherapy}) / \text{value before FP chemotherapy}$ . The change rate of the eGFR between genotype groups for each transporter was expressed as the median (quartile 1-quartile 3). The Kruskal-Wallis test or Mann-Whitney U test was used to determine the difference in continuous values between groups. The Spearman's rank correlation coefficient test was used to assess correlations in continuous values between groups, and all results were expressed as a correlation coefficient ( $r$ ). Stepwise multiple linear regression analysis was performed to determine the effect of all factors in a univariate analysis. For each patient, the transporter genotypes were replaced with dummy variables (in 2 groups, 1 and 0; in 3 groups, 1 and 0, 0 and 0, and 0 and 1, respectively). For post-hoc power analysis, the power ( $1 - \beta$ ) was calculated about the results of comparisons of the change rates of eGFR between genotypes for each drug transporter. A 2-sided  $P$ -value less than 0.05 was considered statistically significant. Statistical analysis was performed with SPSS 20.0 for Windows (SPSS IBM Japan Inc., Tokyo, Japan). Power was calculated using G\*Power version 3.1 software.

### Results

The baseline patient characteristics are listed in Table 1. The mean ( $\pm$  SD) age of patients was  $64.5 \pm 7.2$  years, and the mean body weight ( $\pm$  SD) was  $53.1 \pm 9.9$  kg. There were no patients with serious renal or hepatic dysfunction before FP chemotherapy. In univariate analysis, there was a significant correlation between patient age and the change rate of the eGFR by cisplatin ( $P = 0.021$ , Table 2). However, there were no significant differences between substrata of patients by gender, dose of cisplatin in cycle, disease stage, or the change rate of the eGFR by cisplatin (Table 2). In addition, there were no significant differences in the change rate of the eGFR by cisplatin between *SLC22A2*, *SLC47A1*, *SLC31A1*, *ABCB1*, *ABCC2*, and *ABCG2* polymorphisms (Table 2). However, all power levels were less than 50% in comparisons with change rates of eGFR between genotype groups for each drug transporter (*SLC47A1*, *SLC31A1* and *ABCC2*). Multivariate analysis showed that only age was an independent variable predicting a higher risk of cisplatin-induced acute renal dysfunction. The correlation between the change rate in the eGFR and age is shown in Figure 1.

### Discussion

In the present study, in FP chemotherapy for esophageal cancer patients, there were no significant differences in the change rate of the eGFR by cisplatin administration between *SLC22A2* 808G>T or *SLC31A1* (rs10981694A>C, rs12686377G>T and rs7851395A>G) genotypes. The contribution ratio of cisplatin taken up by the transporters OCT2 and Ctr1 is not clear. In patients with reduced OCT2 activity, cisplatin may primarily be transported by Ctr1. Therefore, definitive renal transporter polymorphisms promoting

Gender (male: female)	114:17	
Age (year)	64.5 ± 7.2	(47-89)
Body weight (kg)	53.1 ± 9.9	(32-88)
Body surface area (m <sup>2</sup> )	1.6 ± 0.2	(1.2-2.1)
Laboratory test values		
Estimated Glomerular Filtration Rate (mL/min/1.73 m <sup>2</sup> )	82.1 ± 16.5	(53-136.1)
Serum creatinine (mg/dL)	0.66 ± 0.13	(0.38-0.92)
Blood urea nitrogen (mg/dL)	13.4 ± 4.4	(4.1-28.3)
Aspartate transaminase (IU/L)	20.9 ± 7.4	(8-46)
Alanine transaminase (IU/L)	20.6 ± 13.1	(6-73)
Total bilirubin (mg/dL)	0.5 ± 0.3	(0.1-1.4)
White blood cell (×10 <sup>3</sup> /μL)	6.4 ± 2.2	(2.4-12.8)
Red blood cell (×10 <sup>4</sup> /μL)	395.5 ± 49.8	(240-544)
Platelet (×10 <sup>4</sup> /μL)	256 ± 84	(91-548)
Na (mEq/L)	139 ± 3.1	(132-145)
K (mEq/L)	4.3 ± 0.4	(3-5.5)
CL (mEq/L)	102.4 ± 3	(95-109)
Chemotherapeutic regimen		
Dose of cisplatin/1 cycle (mg)	124.3 ± 12.4	(90:170)
80 mg/m <sup>2</sup> (Day 1): 40 mg/m <sup>2</sup> (Day 1 and Day 8)	76:55	-
Radiation (with: without)	74:57	-
Stage (I : II : III : IVa : IVb)	4 : 24 : 50 : 46 : 7	
SLC22A2 808G>T	G/G : G/T : T/T = 101 : 29 : 1	
SLC47A1 rs2289669G>A	G/G : G/A : A/A = 33 : 71 : 27	
SLC31A1 rs10981694A>C	A/A : A/C : C/C = 100 : 29 : 2	
SLC31A1 rs12686377G>T	G/G : G/T : T/T = 43 : 68 : 20	
SLC31A1 rs7851395A>G	A/A : A/G : G/G = 28 : 58 : 45	
ABCB1 1236C>T	C/C : C/T : T/T = 14 : 53 : 64	
ABCB1 2677G>T/A	G/G : G/T+G/A : T/T+T/T+A/A = 27 : 59 : 45	
ABCB1 3435C>T	C/C : C/T : T/T = 35 : 63 : 33	
ABCC2 -24C>T	C/C : C/T : T/T = 68 : 54 : 9	
ABCG2 421C>A	C/C : C/A : A/A = 66 : 52 : 13	

Data presented as number or mean ± standard deviation (range)

**Table 1:** Clinical characteristics of 131 patients with esophageal cancer before chemotherapy.

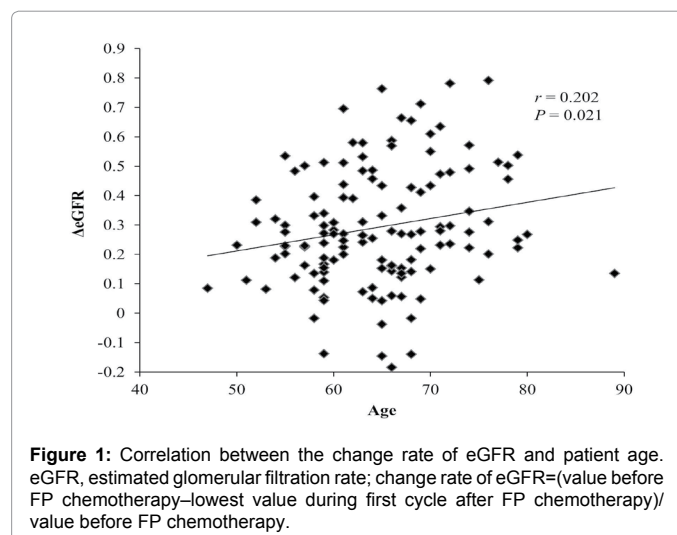
cisplatin-induced nephrotoxicity may not be found. On the other hand, there were no significant differences in the change rate of the eGFR between patients with different MATE1 genotypes. Iwata *et al.* reported that the SLC47A1 rs2289669G>A polymorphism is not associated with cisplatin-induced nephrotoxicity [25]. Although the SLC47A1 rs2289669G>A polymorphism has been reported to be associated with the glucose-lowering effect of metformin [37,39], similar to the result obtained by Iwata *et al.*, our present study also showed that cisplatin-induced nephrotoxicity was not affected by the SLC47A1 rs2289669G>A polymorphism.

In single and multiple regression analyses, cisplatin-induced nephrotoxicity was affected by patient age. Since degradation of

renal function due to aging reduces cisplatin clearance, the cisplatin dosage should be carefully chosen in elderly patients. However, the effects of age on cisplatin-induced nephrotoxicity were limited in our study. Although only two patients who were 80 years of age or older were enrolled in this study, their change rates of eGFR were not high (Figure 1). However, since elderly patients tend to have impaired physiology functions, cisplatin should be administered with caution in these patients.

In this study, cisplatin-induced nephrotoxicity was unaffected by ABCC2 polymorphisms. Sprowl *et al.* have also reported that cisplatin-induced nephrotoxicity is not affected by the ABCC2 -24C>T polymorphism [40]. These data are consistent with our present study. Additionally, Wen *et al.* suggested that cisplatin is conjugated with tripeptide glutathione (GSH) by glutathione S-transferases in renal tubular epithelial cells, and cisplatin-GSH but not cisplatin, is subsequently effluxed by MRP2 to the tubule lumen [19]. Cisplatin-GSH is then metabolized by γ-glutamyltranspeptidase and aminodipeptidase to cisplatin-cysteine (CYS) on the cell surface [41,42], and the cisplatin-CYS conjugate is then reabsorbed. Cisplatin-CYS is metabolized by cysteine-S-conjugate β-lyase to form cisplatin-thiol, which leads to nephrotoxicity [19,43]. According to the discussion of Wen *et al.*, the concentration of cisplatin-GSH in renal tubular epithelial cells would be elevated by the ABCC2 -24T mutation [19]. The formation of cisplatin-GSH reduces the amount of platinum bound to DNA and protects dividing cells from cisplatin nephrotoxicity [44]. Therefore, the formation of cisplatin-GSH and its transport out of the cell seem to be the first steps in detoxification to prevent nephrotoxicity. That is, the elevation of cisplatin-GSH in cells resulting from the ABCC2 mutation does not seem to influence cisplatin-induced nephrotoxicity.

There were some limitations to this study. First, this study was carried out with a small sample size of 131 patients with esophageal cancer receiving FP chemotherapy. Therefore, further studies using a larger sample size are necessary. Second, although hydration and the administration of magnesium sulfate are useful for prevention of cisplatin-induced nephrotoxicity [45], it was not possible to compare these parameters from our study with those in previous studies due to lack of sufficient information. The influence of renal drug transporter polymorphisms on cisplatin-induced nephrotoxicity may differ according to hydration and/or the administration of magnesium



**Figure 1:** Correlation between the change rate of eGFR and patient age. eGFR, estimated glomerular filtration rate; change rate of eGFR=(value before FP chemotherapy–lowest value during first cycle after FP chemotherapy)/value before FP chemotherapy.

	Correlation coefficient (r)	P-value	
Age	0.202	0.021	
Body weight	-0.086	0.331	
Body surface area	-0.057	0.519	
Dose of cisplatin/1 cycle (mg)	-0.060	0.497	
	Median	(25 <sup>th</sup> -75 <sup>th</sup> percentile)	P-value
Gender	-	-	0.789
Male	0.268	(0.155-0.434)	-
Female	0.308	(0.121-0.386)	-
Radiation	-	-	0.293
With	0.255	(0.136-0.457)	-
Without	0.278	(0.202-0.396)	-
Chemotherapeutic regimen/1 cycle	-	-	0.530
80 mg/m <sup>2</sup> (Day 1)	0.274	(0.154-0.471)	-
40 mg/m <sup>2</sup> (Day 1,8)	0.248	(0.157-0.404)	-
<b>Stage</b>			
I	0.239	(0.188-0.380)	0.460
II	0.268	(0.109-0.393)	-
III	0.279	(0.163-0.501)	-
IVa	0.267	(0.139-0.396)	-
IVb	0.230	(0.205-0.256)	-
<b>SNPs</b>			
<b>SLC22A2 808G&gt;T</b>	-	-	0.833
G/G	0.268	(0.154-0.438)	-
G/T+T/T	0.273	(0.162-0.386)	-
<b>SLC47A1 rs2289669G&gt;A</b>	-	-	0.626
G/G	0.279	(0.202-0.433)	-
G/A	0.268	(0.158-0.411)	-
A/A	0.239	(0.138-0.465)	-
<b>SLC31A1 rs10981694A&gt;C</b>	-	-	0.082
A/A	0.276	(0.165-0.465)	-
A/C+C/C	0.202	(0.128-0.309)	-
<b>SLC31A1 rs12686377G&gt;T</b>	-	-	0.701
G/G	0.268	(0.141-0.442)	-
G/T	0.273	(0.185-0.420)	-
T/T	0.252	(0.117-0.474)	-
<b>SLC31A1 rs7851395A&gt;G</b>	-	-	0.117
A/A	0.201	(0.118-0.328)	-
A/G	0.271	(0.188-0.438)	-
G/G	0.282	(0.181-0.480)	-
<b>ABCB1 1236C&gt;T</b>	-	-	0.223
C/C	0.269	(0.142-0.433)	-
C/T	0.283	(0.201-0.485)	-
T/T	0.234	(0.147-0.395)	-
<b>ABCB1 2677G&gt;T/A</b>	-	-	0.244
G/G	0.27	(0.229-0.513)	-
G/T+G/A	0.248	(0.139-0.374)	-
T/T+T/A+A/A	0.255	(0.154-0.433)	-
<b>ABCB1 3435C&gt;T</b>	-	-	0.654
C/C	0.270	(0.165-0.487)	-
C/T	0.276	(0.181-0.410)	-
T/T	0.239	(0.136-0.412)	-
<b>ABCC2 -24C&gt;T</b>	-	-	0.144
C/C	0.244	(0.151-0.370)	-
C/T+T/T	0.298	(0.165-0.484)	-
<b>ABCG2 421C&gt;A</b>	-	-	0.613
C/C	0.271	(0.183-0.438)	-
C/A+A/A	0.264	(0.150-0.428)	-

eGFR: Estimated Glomerular Filtration Rate

**Table 2:** Correlation and comparison of change rate of eGFR between patient backgrounds.

sulfate. Third, we have not investigated the expression of inflammatory markers in this study. The majority of studies under review have reported that these markers are associated with the pathogenesis of cisplatin-induced nephrotoxicity [46]. In addition, Shinke *et al.* have recently reported that urinary kidney injury molecule-1 and/or monocyte chemotactic protein-1 may represent biomarkers of cisplatin-induced nephrotoxicity in lung cancer patients [47]. Hence, these results should be interpreted within the context of the study limitations. However, in FP chemotherapy for patients with esophageal cancer, it became clear that a polymorphism in each drug transporter did not directly affect cisplatin-induced nephrotoxicity alone. A combination of multiple drug transporters, including MATE1, P-glycoprotein, BCRP, and MRP2, reacts with the efflux of cisplatin and its metabolites, resulting in complex transport mechanisms. In addition, other single nucleotide polymorphisms, in addition to the transporter polymorphisms observed in the present study, may influence cisplatin-induced nephrotoxicity. Therefore, further studies are necessary to unravel the pathophysiological mechanisms of cisplatin-induced nephrotoxicity.

In FP chemotherapy for esophageal cancer patients, there were no significant differences in the change rate of the eGFR by cisplatin between uptake transporters *SLC22A2* 808G>T or *SLC31A1* (rs10981694A>C, rs12686377G>T and rs7851395A>G) genotypes, and between efflux transporter *SLC47A1* rs2289669G>A genotypes. In the present study, cisplatin-induced nephrotoxicity was affected by patient age. Cisplatin dosage should be chosen carefully in elderly patients.

#### Conflict of Interest

All of the authors state they have no conflicts of interest.

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