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Variants of *SLC22A16* Predict the Efficacy of Platinum Combination Chemotherapy in Advanced Non-small-cell Lung Cancer

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Abstract. *Background: Organic cation transporter 6 (OCT6) encoded by solute carrier family 22 member 16 (SLC22A16) is involved in regulating cellular sensitivity and resistance to platinum derivatives. SLC22A16 has functional genetic variants but the association between these variants and the effectiveness of antitumor drugs remains unexplored. Patients and Methods: This study retrospectively analyzed data from 160 patients with advanced non-small cell lung cancer treated with platinum-based combination chemotherapy for first-line chemotherapy between October 2010 and May 2018. We investigated the association between the genetic variant of SLC22A16 and clinical outcomes. Results: Patients with the rs714368 GG genotype had a shorter progression-free survival than those with AA or AG. Gene polymorphism was not associated with adverse effects. The predictive effect of rs714368 was confirmed in multivariate analysis using a Cox proportional hazards model. Conclusion: A genetic variant of SLC22A16 is a potential predictive biomarker for response to platinum-based chemotherapy for non-small cell lung cancer.*

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Treatment of non-small-cell lung cancer (NSCLC) has changed dramatically because of the evolution of kinase inhibitors and the development of immune checkpoint inhibitors. Although selected patients benefit tremendously from the efficacy of these precision medicines, cytotoxic chemotherapy is still important for use in combination with immunotherapy (1-3) or in patients for whom molecular or immunotherapy fails. Platinum derivatives (cisplatin and carboplatin) and third-generation anticancer drugs are key agents for treating NSCLC. Pemetrexed is more effective than other drugs for non-squamous NSCLC (4). Therefore, the combination of platinum derivatives and pemetrexed is standard in such cases. The efficacy of cytotoxic chemotherapy is limited, however, and the mechanisms underlying resistance to it remain unclear. Multiple factors have been found to be associated with cisplatin resistance (5). One of the important mechanisms is the reduction of the intracellular platinum concentration caused by reduction of influx or promotion of efflux.

We previously reported that organic cation transporter 6 (OCT6) is a mediator of platinum influx into cancer cells, and down-regulation of OCT6 is one mechanism of acquired platinum resistance in lung cancer (6), as it is with other platinum derivatives (7). Single nucleotide polymorphisms (SNPs) are the most common type of genetic variation. Polymorphisms of solute carrier family 22 member 16 (*SLC22A16)* are reported to influence doxorubicin pharmacokinetics (8) and are associated with neutropenia in doxorubicin-based chemotherapy (9). However, it is unknown whether *SLC22A16* polymorphisms affect the efficacy of platinum-based cytotoxic chemotherapy. The aim in this study was to clarify the association between SNPs of

Table I. *Patient characteristics (n=160).*

Factor	Value
Age at treatment, years	
Median (range)	67 (40-82)
Gender, n (%)	
Male	117 (73.1%)
Female	43 (26.9%)
Smoking history, n (%)	
Current or former	116 (72.5%)
Never	29 (18.1%)
Unknown	15 (9.4%)
Stage, n (%)	
IIIA	7 (4.4%)
IIIB	19 (11.9%)
IV	134 (83.8%)
Pathology, n (%)	
Squamous cell carcinoma	31 (19.4%)
Adenocarcinoma	109 (68.1%)
Large cell carcinoma	3 (1.9%)
Non-small cell carcinoma	17 (10.6%)
Driver mutation, n (%)	
Sensitive*	36 (22.5%)
Negative	124 (77.5%)
PD-L1 expression, n (%)	
Positive (≥1%)	15 (9.4%)
Negative (<1%) or unknown	145 (90.6%)
Treatment lines	
Median (range)	1 (1-4)
Treatment, n (%)	
Cisplatin + pemetrexed	27 (16.9%)
Carboplatin + pemetrexed	50 (31.2%)
Carboplatin + pemetrexed + bevacizumab	30 (18.8%)
Carboplatin + paclitaxel	15 (9.4%)
Carboplatin + nab-paclitaxel	21 (13.1%)
Cisplatin + gemcitabine	5 (3.1%)
Carboplatin + gemcitabine	5 (3.1%)
Cisplatin + docetaxel	7 (4.4%)

PD-L1: Programmed cell death ligand 1. *Sensitive driver mutation included 31 with epidermal growth factor receptor mutation (15 with exon 19 deletion, 14 with L858R, and two with L861Q, respectively) and five with anaplastic lymphoma kinase fusion gene.

Table II. *The genotypic and allelic frequencies of solute carrier family 22-member 16 single nucleotide polymorphisms (SNPs) determined in this study.*

SNP	Genotype	Frequency (%)	Allelic frequency		
				This study	JPT*
rs714368	AA	64 (40.0%)	A	0.625	0.5903
	AG	72 (45.0%)			
	GG	24 (15.0%)	G	0.375	0.4097
rs12210538	TT	160 (100%)		1.00	1.00

*The 1000 Genomes Project (Phase 3) release V3+ (Accession: PRJEB6930 ID: 257713).

Table III. *Association between solute carrier family 22 member 16 rs714368 single nucleotide polymorphism and response to chemotherapy.*

	Genotype	RR	*p*-Value	DCR	*p*-Value
rs714368					
Dominant model	AA+AG	44.8%	0.827	83.6%	>0.99
	GG	41.7%		83.3%	
Recessive model	AA	37.1%	0.189	83.9%	>0.99
	AG+GG	49.0%		83.3%	

RR: Response rate; DCR: disease control rate.

SLC22A16 and clinical outcomes of patients with NSCLC treated with platinum-based cytotoxic chemotherapy.

Patients and Methods

Patients and chemotherapies. We retrospectively reviewed data from patients with advanced NSCLC who received platinum-based first-line chemotherapy at Nagoya City University Hospital with any of the following regimens: Cisplatin (75 mg/m^2) or carboplatin [area under the curve of 6 mg/ml/min (AUC 6)] plus pemetrexed (500 mg/m^2), with or without bevacizumab (15 mg/kg); carboplatin (AUC 6) plus paclitaxel (200 mg/m^2) or nab-paclitaxel (100 mg/m^2); cisplatin (80 mg/m^2) or carboplatin (AUC 5) plus gemcitabine (1000 mg/m^2); or cisplatin (80 mg/m^2) plus docetaxel (60 mg/m^2). Patients who underwent surgery or curative chemoradiotherapy were excluded. We obtained peripheral blood samples from the patients before treatment in order to analyze SNPs. We recorded patient characteristics, clinical outcomes according to Response Evaluation Criteria in Solid Tumors version 1.1 and adverse effects (myelosuppression, liver function and creatinine) according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 using data supplied by the attending physicians from medical records. All procedures involving human participants were in accordance with the ethical standards of the institutional research committee of Nagoya city university (no. 70-00-0095) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. We obtained written informed consent from all patients, and all medical data were anonymized.

Genomic DNA extraction and detection of drug transporter polymorphisms. Genomic DNA was extracted from the blood samples of 160 patients with NSCLC using QIAamp DNA Mini Kit (Qiagen; Hilden, Germany) according to the manufacturer's instructions. *SLC22A16* SNPs were detected using the StepOnePlus Real-Time PCR System (Applied Biosystems; Foster City, CA, USA) and TaqMan SNP Genotyping Assays (*rs714368*, NM_033125.4:c.146A>G, C___2256675_10; and *rs12210538*, NM_033125.4:c.1226T>C, C__22271871_10). We chose these SNPs based on a previous report (10). All assays were purchased from Applied Biosystems and used in accordance with the manufacturer's instructions.

Statistical analysis. The response rate (RR) was defined as the sum of the complete response (CR) and partial response (PR) rates, and

Table IV. *Association between solute carrier family 22 member 16 rs714368 single nucleotide polymorphism and survival.*

			PFS, days			OS, days		
Model	Genotype	n	Median	95% CI	*p*-Value	Median	95% CI	*p*-Value
Dominant	AA+AG	136	140	113-168	**0.022**	530	433-667	0.85
	GG	24	93	67-126		533	225-1365	
Recessive	AA	64	114	101-163	0.51	551	433-667	0.37
	AG+GG	96	131	113-163		525	408-783	

PFS: Progression-free survival; OS: overall survival; CI: confidence interval. Bold value indicates statistical significance.

the disease control rate (DCR) was defined as the sum of CR, PR and stable disease (SD) rates. RR and DCR were compared using Fisher's exact test, with $p<0.05$ considered statistically significant.

Progression-free survival (PFS) was defined from the date chemotherapy was first begun to the date of disease progression, death, or last follow-up. Overall survival (OS) was defined from the date chemotherapy was first begun to the date of death or last follow-up. These outcomes were analyzed according to SNP genotype using the Kaplan–Meier method and log-rank test, with $p<0.05$ considered statistically significant. Correlations of the frequency of adverse effects (myelosuppression, liver function or renal function) with gene polymorphisms were compared using Fisher's exact test. Finally, we performed multivariate analysis using a Cox proportional hazards model to examine the relationship of clinical outcomes and adverse effects with SNP genotype and clinical characteristics. In this model, we used $p=0.10$ in the log-rank test as the threshold for inclusion of a covariate in the model, with $p<0.05$ subsequently considered statistically significant. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria), which is a modified version of R commander designed to add statistical functions frequently used in biostatistics (11).

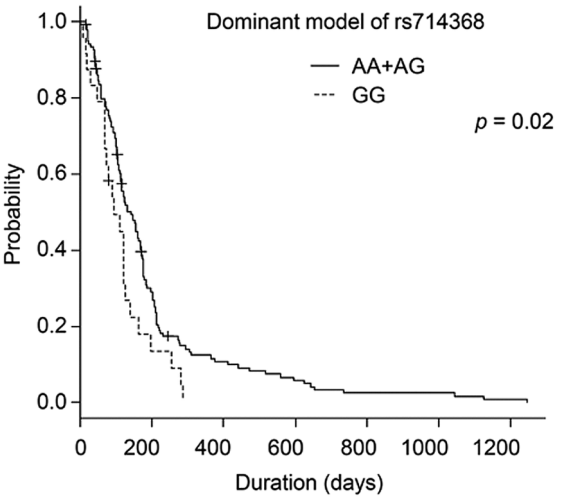

Figure 1. *Progression-free survival according to the dominant model of the solute carrier family 22 member 16 rs714368 single nucleotide polymorphism. These data were analyzed by Kaplan–Meier methods and compared using the log-rank test.*

Results

Data from a total of 160 patients were assessed in this study (Table I). The median age was 67 years, 117 were men, and 116 were current or former smokers. Most patients had disease stage IV (83.8%). The histological diagnosis was lung adenocarcinoma in the majority of patients (68.1%). Thirty-six patients had driver mutations: epidermal growth factor receptor (*EGFR*) mutation in 31 patients (15 with exon 19 deletion, 14 with L858R mutation and two with L861Q mutation) and anaplastic lymphoma kinase fusion gene in five patients. Programmed cell death ligand 1 expression was positive in 15 patients but not evaluated in most (87.5%).

The RR was 43.8%, the DCR was 82.6%, the median PFS was 124 days, and the median OS was 533 days. Two patients were excluded from assessment of treatment response as the treatment efficacy was not evaluated.

The genotypic and allelic frequencies targeted SNPs are shown in Table II. We excluded *rs12210538* as a covariate as all patients in the study had the major homoallele, a finding that concurred with the results of the 1000 Genomes Project data in the East Asian population. Outcomes according to SNPs are shown in Tables III and IV. Carriers of the *rs714368* A allele had a significantly longer median PFS than those with the GG genotype (140 *vs*. 93 days, $p=0.022$) (Figure 1). RR, DCR and OS did not significantly differ by SNP genotype (RR=44.8% *vs*. 41.7%, $p>0.99$; DCR, 83.6% *vs*. 83.3%, $p>0.99$; median OS, 530 *vs*. 533 days, $p=0.85$).

We performed univariate analysis based on patient background to determine factors associated with clinical outcomes (Table V). In addition to carriers of the *rs714368* A allele, patients with stage III disease had a longer PFS than those with stage IV (median=172.5 *vs*. 121 days, $p=0.042$), and those with history of smoking tended to have a longer PFS than never smokers (median=126 *vs*. 108 days, $p=0.076$). Multivariate analysis was conducted to assess predictive factors significantly associated with PFS. Stage, smoking history, and *rs714368*

Table V. *Univariate analysis of survival according to clinical characteristics.*

		PFS			OS		
Characteristic	n	Median, days	95% CI	*p*-Value	Median, days	95% CI	*p*-Value
Age							
<75 Years	135	124	108-161	0.763	551	423-783	0.351
≥75 Years	25	122	100-177		533	390-644	
Gender							
Male	117	121	111-155	0.808	511	418-647	**0.0217**
Female	43	138	72-176		699	422-1484	
Smoking history							
Current/former or unknown	131	126	113-163	0.0761	525	418-647	**0.0401**
Never	29	108	56-147		1036	423-1679	
NSCLC pathology							
Squamous	30	121	99-175	0.881	462	261-663	0.183
Non-squamous	130	125	108-161		551	433-699	
Stage							
III	26	172.5	99-281	**0.042**	663	511-1233	0.209
IV	134	121	108-154		510	408-647	
Gene mutation							
Sensitive*	36	140	56-176	0.607	1066	518-1892	**<0.001**
Negative	124	121	108-155		462	403-641	

NSCLC: Non-small-cell lung cancer; PFS: progression-free survival; CI: confidence interval; OS: overall survival. *Sensitive driver mutation included 31 with epidermal growth factor receptor mutation (15 with exon 19 deletion, 14 with L858R, and two with L861Q, respectively) and five with anaplastic lymphoma kinase fusion gene. Bold values indicate statistical significance.

genotypes were used as covariates in this model. Factors predictive of a poor PFS were stage IV *versus* III disease [hazard ratio (HR)=1.76, 95% confidence interval (CI)=1.117-2.771; *p*=0.015] and *rs714368* GG genotype *versus* AA or AG (HR=1.945, 95% CI=1.212-3.122; *p*=0.006) (Table VI).

There were no associations between gene polymorphisms and adverse effects (myelosuppression, liver function or renal function) (Table VII).

Discussion

Cytotoxic chemotherapy for NSCLC yields paradoxical tumor responses from patient to patient, even among those with similar tumor pathology. For this reason, it is important to find biomarkers predictive of treatment response so as to give more patients greater treatment benefits. In this study, we investigated the association between treatment outcomes in advanced NSCLC treated with platinum-based cytotoxic chemotherapy and SNPs of *SLC22A16*. A novel finding was that A carriers of the *SLC22A16 rs714368* had a longer PFS compared with those with GG genotype.

Platinum derivatives are key drugs for treating lung cancer, particularly when used in combination with immune checkpoint inhibitors (1-3). Additional cytotoxic chemotherapy yields tumor volume reduction, which helps prevent early treatment failure of immune-cytotoxic combination therapy. Platinum-based chemotherapy combined with EGFR tyrosine kinase inhibitors may provide better efficacy than sequential monotherapy (12). Given the importance of cytotoxic chemotherapy in combination with newer agents to treat NSCLC, predictive biomarkers of response or resistance are needed.

Understanding the mechanisms of resistance to cytotoxic chemotherapy is a key issue. Tumor cells become resistant to cisplatin by multiple pathways, including reduction of intake, inactivation by glutathione (13), increased DNA repair (14, 15), and overexpression of drug-efflux pumps (16-18). One of the major factors determining the chemotherapeutic activity of platinum is drug influx (19), as that directly affects the intracellular drug concentration and cell damage the drug causes. The OCT family is associated with the transport of platinum drugs (20). OCT2, expressed at the basolateral membrane of renal tubular epithelial cell, transports cisplatin and is associated with nephrotoxicity (21). Certain OCT2 SNPs have been shown to be associated with this adverse effect of platinum-based chemotherapy for NSCLC (22). Down-regulation of OCT3 in hepatocellular carcinoma leads to diminished cisplatin sensitivity (23). We previously reported that OCT6 contributes to platinum influx into tumor cells. Cisplatin-resistant cell lines have reduced OCT6 expression and lower intracellular platinum accumulation compared with their respective parental cell lines. Up-regulation of OCT6 results in intracellular platinum accumulation and tumor sensitivity to cisplatin (6). OCT6 affects transport into tumor cells not only of cisplatin but also of other platinum derivatives

Table VI. *Multivariate analysis of progression-free survival.*

		HR	95% CI	*p*-Value
Smoking history	Never (*vs.* current/former or unknown)	1.337	0.8663-2.062	0.19
Stage	IV (*vs.* III)	1.76	1.117-2.771	**0.015**
SLC22A16 rs714368	GG (*vs.* AA+AG)	1.945	1.212-3.122	**0.006**

SLC22A16: Solute carrier family 22 member 16; CI: confidence interval; HR: hazard ratio. Bold values indicate statistical significance.

Table VII. *The frequency of adverse event about myelosuppression, liver function and renal function.*

Factor	Grade	Overall (N=160), n (%)	Dominant, n (%)			Recessive, n (%)		
			AA+AG (N=136)	GG (N=24)	*p*-Value	AA (N=64)	AG+GG (N=96)	*p*-Value
White blood cell decreased	3 or 4	50 (31.2)	45 (33.1)	5 (20.8)	0.339	20 (31.2)	30 (31.2)	>0.99
Neutrophil count decreased	3 or 4	70 (43.8)	61 (44.9)	9 (37.5)	0.656	29 (45.3)	41 (42.7)	0.748
Anemia	3 or 4	8 (5.0)	8 (5.9)	0 (0.0)	0.607	3 (4.7)	5 (5.2)	>0.99
Platelet count decreased	3 or 4	36 (22.5)	32 (23.5)	4 (16.7)	0.6	15 (23.4)	21 (21.9)	0.848
Blood bilirubin increased	3 or 4	0 (0.0)	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-
Aspartate aminotransferase increased	3 or 4	3 (1.9)	3 (2.2)	0 (0.0)	>0.99	1 (1.6)	2 (2.1)	>0.99
Alanine aminotransferase increased	3 or 4	5 (3.1)	4 (2.9)	1 (4.2)	0.561	1 (1.6)	4 (4.2)	0.649
Creatinine increased	3 or 4	0 (0.0)	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-

There were no cases of grade 5 adverse events.

(7). In addition, cisplatin-resistant cell lines were also less sensitive to carboplatin or other platinum derivatives than parental cell lines (24). In summary, OCT6 appears to affect cancer cell sensitivity to platinum derivatives, and its down-regulation is associated with tumor platinum resistance.

The *SLC22A* family of transporters have a similar membrane topology: 12 α-helical transmembrane domains, a large extracellular loop between domains 1 and 2, and a large intracellular loop between domains 6 and 7 (25). Among *SLC22A16* polymorphisms, *rs714368* is located at the large extracellular loop and *rs12210538* at domain 8. Most reports of *SLC22A16* SNPs have assessed adverse effect of doxorubicin rather than treatment outcome. Some indicated that the *rs714368* G allele increased exposure to doxorubicin (8) and gastrointestinal events (26). Other studies showed that the *rs714368* A allele increased the incidence of having to delay doses of doxorubicin because of myelosuppression (27), apparently resulting from overexposure to doxorubicin in patients with A-bearing genotypes. These findings suggest *rs714368* may have an important role in modulating doxorubicin pharmacokinetics. In addition, *SLC22A16* may have an especially large adverse influence on hematopoiesis by accumulation of doxorubicin, as the gene's expression is restricted to hematopoietic cells (28) and testis (29) in normal adult tissues. The large difference in the expression of each organ may be the cause of seemingly contradictory associations between SNPs and adverse effects. While the G allele increases drug concentration in the blood, the A allele may increase doxorubicin influx into target tissues such as tumor cells and hematopoietic cells. On the other hand, our study showed no association between rs714368 polymorphisms and adverse effects (Table VII). Although doxorubicin is mainly metabolized in the liver, platinum derivatives are excreted from the kidneys. The differences of drug excretion route may affect the findings regarding adverse effects. As previously mentioned, OCT2 is mainly expressed in renal cells and is associated with nephrotoxicity, and *SLC22A16* polymorphisms may have no influence on adverse effects. the functional implications of differences in SLC22A16 SNPs are still unclear. However, it is reported that other transporters introducing different SNPs affected drug sensitivity of tumor cell lines without changing the transporter expression level (30). Without a change in expression level, *SLC22A16 rs714368* may influence not only pharmacokinetics but also transporter function and influx of drugs, resulting in varied clinical outcomes because of differences in intracellular platinum concentrations.

Platinum derivatives are usually used with third-generation cytotoxic drugs including pemetrexed, which is a key drug in non-squamous NSCLC treatment strategy. Using multiple biomarkers associated with each cytotoxic drug to predict combination chemotherapy outcomes would be a reasonable idea. It is known that treatment outcomes in

pemetrexed containing chemotherapy are influenced by gene polymorphisms of folylpoly-γ-glutamate synthase, an enzyme that metabolizes pemetrexed (31). Tumor markers are also potential predictors of response to chemotherapy or kinase inhibitors (32, 33). Combining several biomarkers may therefore be more informative for predicting treatment response rather than using just one.

This study may have selection bias, as it was a retrospective, single-institution study. However, investigations of how *SLC22A16* gene polymorphisms affect OCT6 function are important in furthering our understanding of tumor response and resistance.

In conclusion, we demonstrated that a *SLC22A16* SNP is a potential biomarker predictive of the effect of platinum-based chemotherapy for advanced NSCLC. A paradigm shift in NSCLC treatment strategies is occurring with the use of cytotoxic chemotherapy combined with immune checkpoint inhibitors or tyrosine kinase inhibitors. Identification of acquired treatment-resistance mechanisms for each particular regimen is important in individualizing treatment for this cancer.

Conflicts of Interest

TO received honorarium by Chugai Pharmaceutical and research funding by Boehringer Ingelheim.

Authors' Contributions

AT and TO designed the study and wrote the initial draft of the article. AT, SF, KS, and YK analyzed gene polymorphisms. AT, TO, SF, KS, TU, OT and KM contributed to the analysis and interpretation of data and assisted in the preparation of the article. TO, SF, KM, KF, YK, TT, HO, MT, YI and AN contributed to data collection and interpretation. All authors reviewed the article and approved the definitive version of the article and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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