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Association of nephrotoxicity during platinum-etoposide doublet therapy with *UGT1A1* polymorphisms in small cell lung cancer patients

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ABSTRACT

Objectives: Etoposide is a key agent in the treatment of small cell lung cancer (SCLC). Uridine diphosphate (UDP)–glucuronosyltransferase 1A1 (UGT1A1) is thought to be largely responsible for the glucuronidation of etoposide as well as that of irinotecan, suggesting that polymorphisms of *UGT1A1* might be predictive of etoposide toxicity. We therefore examined the relation between *UGT1A1* polymorphisms and toxicity profile during platinum-etoposide doublet therapy in SCLC patients.

Materials and Methods: SCLC patients who underwent platinum-etoposide doublet therapy and molecular testing for *UGT1A1* genotype were reviewed for the occurrence of adverse events during treatment.

Results: A total of 41 SCLC patients received platinum-etoposide doublet therapy and were genotyped for *UGT1A1*6* and *UGT1A1*28* alleles. These alleles were detected in 15 (36.6%) patients, with the genotypes of **6/–*, **6/*6*, **28/–*, **28/*28*, or **6/*28* being observed in 9 (22.0%), 2 (4.9%), 2 (4.9%), 1 (2.4%), and 1 (2.4%) patients, respectively. The presence of these alleles was significantly associated with an increase in serum creatinine concentration of grade ≥2 (incidence of 66.7% for patients with the alleles versus 11.5% for those without, $P < 0.001$). Multivariate analysis also showed that these *UGT1A1* alleles were significantly associated with therapy-induced nephrotoxicity (odds ratio of 19.30, 95% confidence interval of 2.50–149.00, $P < 0.005$). Although the differences did not achieve statistical significance, the incidence of other severe toxicities including febrile neutropenia was also slightly higher in patients with the *UGT1A1*6* or *UGT1A1*28* alleles than in those without them.

Conclusion: Our results reveal an association between *UGT1A1* polymorphisms and toxicity of platinum-etoposide doublet therapy in SCLC patients, suggesting that close monitoring for toxicity, especially nephrotoxicity, is warranted for patients with such variant alleles receiving this treatment.

1. Introduction

The antitumor action of etoposide is due to inhibition of DNA topoisomerase II and the consequent introduction of strand breaks into DNA [1]. Combination therapies with etoposide and a platinum agent (cisplatin or carboplatin) are the standard of care for patients with small cell lung cancer (SCLC) [2–6], but some treated individuals experience serious hematologic or nonhematologic toxicities including nephrotoxicity. Predictive factors for adverse events of platinum-etoposide doublet therapy for SCLC have not been identified to date, however.

Uridine diphosphate (UDP)–glucuronosyltransferase 1A1 (UGT1A1) targets bilirubin and endogenous steroids as well as drugs and other xenobiotics for glucuronidation [7]. Polymorphisms of the *UGT1A1* gene affect the expression or activity of the encoded enzyme, with the *UGT1A1*6* (211 G > A, G71R) allele being associated with reduced UGT1A1 activity [8] and the *UGT1A1*28* ($[TA]_7TAA$ instead of $[TA]_6TAA$) allele with reduced gene transcription [9,10]. Such polymorphisms of *UGT1A1* have been associated with severe toxicity of irinotecan, which is a target for glucuronidation by UGT1A1 [11–15]. Etoposide has also been found to be metabolized by UGT1A1 [16–18], and the *UGT1A1*28* allele is associated with reduced clearance of the drug in patients with leukemia [19]. These observations suggest that genetic polymorphisms of *UGT1A1* might determine etoposide

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glucuronidation activity and the toxicity of platinum-etoposide doublet therapy for SCLC. We have now performed a retrospective study to examine the influence of polymorphisms of *UGT1A1* on the toxicity of platinum-etoposide doublet therapy in patients with SCLC.

2. Materials and methods

2.1. Patients and clinical information

We studied SCLC patients who had been genotyped for *UGT1A1*6* and *UGT1A1*28* and received platinum-etoposide doublet therapy at Kyushu University Hospital or Harasanshin Hospital between December 2008 and June 2017. Genotyping of *UGT1A1* has been approved and its cost is reimbursed for prediction of side effects related to treatment with irinotecan in Japan. Given that irinotecan-based chemotherapy is a standard treatment for SCLC in Japan, genotyping of *UGT1A1* is frequently performed in clinical practice. We retrospectively evaluated clinical data including patient characteristics (age, sex, primary disease, previous treatment, evidence of distant metastasis, complications, Eastern Cooperative Oncology Group [ECOG] performance status, smoking history), the dosage and schedule of platinum-etoposide doublet therapy, hydration volume, regular use of nonsteroidal anti-inflammatory drugs (NSAIDs), radiotherapy, and *UGT1A1* genotype. We examined the data for hematologic and nonhematologic toxicities over the entire course of platinum-etoposide doublet therapy. Severe toxicity was defined as hematologic toxicity of grade ≥3 or nonhematologic toxicity of grade ≥2 according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE, version 4.0). Serum creatinine concentration was measured by an enzymatic method [20,21] with blood samples collected in the morning. A change in serum creatinine concentration was defined as the maximum concentration over the entire course of platinum-etoposide doublet therapy minus the baseline value. Nephrotoxicity was defined as an increase in the serum creatinine level of grade ≥2 during platinum-etoposide doublet therapy. Creatinine clearance was calculated with the Cockcroft-Gault formula: creatinine clearance (mL/min) = (140 – age [years]) × weight (kg) × 0.85 (if female)/(72 × serum creatinine [mg/dL]). This study was performed according to the opt-out method based on the hospital website and in accordance with the Declaration of Helsinki, and it was approved by the Institutional Review Board of each institution.

2.2. Genotyping

Genotyping for *UGT1A1*6* and *UGT1A1*28* of *UGT1A1* was performed with the Invader *UGT1A1* Molecular Assay (Third Wave Technologies) [22]. A genotype characterized by the absence of both *UGT1A1*6* and *UGT1A1*28* alleles was designated *UGT1A1–/–*, with *UGT1A1*6/–* and *UGT1A1*28/–* indicating each polymorphism in the heterozygous state, *UGT1A1*6/*6* and *UGT1A1*28/*28* denoting each variant allele in the homozygous state, and *UGT1A1*6/*28* referring to the presence of both polymorphisms in the heterozygous state.

2.3. Statistical analysis

Differences in the change in serum creatinine level or creatinine clearance were analyzed with the unpaired Student's *t* test, and those in the frequency of toxicities with Fisher's exact test. Multivariate analysis of the association between nephrotoxicity and clinicopathologic factors was performed with a logistic regression model. Clinicopathologic factors with a *P* value of < 0.15 in univariate analysis were subjected to the multivariate analysis. All statistical analysis was performed with EZR software [23]. A *P* value of < 0.05 was considered statistically significant.

Table 1
Characteristics of the study patients (n = 41).

Characteristic	*n*	%
Median age (range), years	64 (52–82)	
Sex		
Male	31	75.6
Female	10	24.4
Performance status (ECOG)		
0–1	30	73.2
≥2	11	26.8
Smoking history		
Never-smoker	3	7.3
Smoker	38	92.7
Prior systemic chemotherapy		
No	37	90.2
Yes	4	9.8
Concurrent radiotherapy		
Yes	9	22.0
No	32	78.0
Platinum agent		
Cisplatin	20	48.8
1–2 cycles	7	35.0
3–4 cycles	13	65.0
Carboplatin	21	51.2
1–2 cycles	3	14.3
3–4 cycles	16	76.2
5–6 cycles	2	9.5
UGT1A1 genotype		
–/–	26	63.4
**6/–*	9	22.0
**6/*6*	2	4.9
**28/–*	2	4.9
**28/*28*	1	2.4
**6/*28*	1	2.4

3. Results

3.1. Patient characteristics

A total of 41 patients who had received platinum-etoposide doublet therapy for SCLC and who were genotyped for *UGT1A1* was studied. Etoposide was administered intravenously in all patients. The demographics and clinical characteristics of the study participants are shown in Table 1. The median age of the subjects was 64 years (range, 52–82 years), 31 (75.6%) were male, and 20 (48.8%) received cisplatin combination chemotherapy. The *UGT1A1–/–* genotype was detected in 26 (63.4%) patients and variant alleles of *UGT1A1* in 15 (36.6%) patients, with the genotypes **6/–*, **6/*6*, **28/–*, **28/*28*, or **6/*28* being apparent in 9 (22.0%), 2 (4.9%), 2 (4.9%), 1 (2.4%), and 1 (2.4%) patients, respectively.

3.2. UGT1A1 genotype and toxicity of platinum-etoposide doublet therapy

Hematologic and nonhematologic toxicities over the entire course of platinum-etoposide doublet therapy in the SCLC patients were reviewed according to *UGT1A1* genotype (Table 2 and Supplementary Table S1). A significant association was apparent between *UGT1A1* polymorphisms and an increase in serum creatinine level of grade ≥2 (incidence of 66.7% for patients with *UGT1A1*6* or *UGT1A1*28* versus 11.5% for *UGT1A1–/–*, $P < 0.001$) (Table 2). The change in serum creatinine concentration (mean of 0.58 versus 0.095 mg/dL, $P < 0.001$) and that in creatinine clearance (mean of –30.08 versus –10.60 mL/min, $P < 0.01$) were significantly greater in patients with *UGT1A1*6* or *UGT1A1*28* than in those with the *UGT1A1–/–* genotype (Fig. 1). Given the possibility that the platinum agent, especially cisplatin, might have contributed to nephrotoxicity of the doublet therapy, we examined the changes in serum creatinine level and creatinine clearance in patients who were treated with cisplatin-etoposide doublet therapy (Fig. 2). The differences in the changes in serum creatinine concentration (mean of

Table 2
Number (%) of patients with toxicities during platinum-etoposide doublet therapy according to *UGT1A1* polymorphism status.

Toxicity	Grade	*UGT1A1–/–* (*n* = 26)	*UGT1A1*6* or *UGT1A1*28* (*n* = 15)	*P* value
Increased serum creatinine level	1	14 (53.8)	3 (20.0)	0.050
	≥2	3 (11.5)	10 (66.7)	**< 0.001**
Elevation in T.Bil	1	1 (3.8)	1 (6.7)	1.000
	≥2	1 (3.8)	1 (6.7)	1.000
Elevation in AST	1	7 (26.9)	6 (40.0)	0.492
	≥2	4 (15.4)	2 (13.3)	1.000
Elevation in ALT	1	7 (26.9)	4 (26.7)	1.000
	≥2	3 (11.5)	2 (13.3)	1.000
Elevation in ALP	1	13 (50.0)	6 (40.0)	0.746
	≥2	4 (15.4)	1 (6.7)	0.636
Elevation in γ-GTP	1	5 (19.2)	3 (20.0)	1.000
	≥2	5 (19.2)	5 (33.3)	0.453
Nausea	1	4 (15.4)	2 (13.3)	1.000
	≥2	5 (19.2)	6 (40.0)	0.272
Vomiting	1	2 (7.7)	1 (6.7)	1.000
	≥2	0 (0.0)	0 (0.0)	
Anorexia	1	3 (11.5)	2 (13.3)	1.000
	≥2	6 (23.1)	6 (40.0)	0.300
Febrile neutropenia	≥3	6 (23.1)	6 (40.0)	0.300
Neutropenia	1–2	5 (19.2)	1 (6.7)	0.388
	≥3	20 (76.9)	12 (80.0)	1.000
Anemia	1–2	22 (84.6)	11 (73.3)	0.434
	≥3	3 (11.5)	4 (26.7)	0.390
Thrombocytopenia	1–2	17 (65.4)	7 (46.7)	0.328
	≥3	4 (15.4)	5 (33.3)	0.248

P values for comparisons between the two groups (heterozygotes or homozygotes for *UGT1A1*6* or *UGT1A1*28* alleles versus *UGT1A1–/–* genotype) were determined with Fisher's exact test, and those of < 0.05 are shown in bold. Pneumonitis was also retrospectively reviewed, but no patients developed this toxicity. Abbreviations not defined in text: T. Bil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; γ-GTP, γ-glutamyl transpeptidase.

0.83 versus 0.19 mg/dL, $P < 0.01$) and creatinine clearance (mean of –43.38 versus –19.85 mL/min, $P < 0.05$) during therapy between patients with *UGT1A1*6* or *UGT1A1*28* and those with the *UGT1A1–/–* genotype (respectively) were still significant in the subgroup treated with cisplatin-etoposide.

Although an increase in serum creatinine level of grade ≥2 was more frequent for patients treated with cisplatin-etoposide than for those treated with carboplatin-etoposide (55.0% versus 9.5%, $P = 0.003$), multivariate logistic regression analysis revealed that treatment with cisplatin was not an independent risk factor for nephrotoxicity of platinum-etoposide doublet therapy. The only independent risk factor identified was the presence of a *UGT1A1* variant allele (odds ratio of 19.30, 95% confidence interval of 2.50–149.00, $P < 0.005$) (Table 3). *UGT1A1* variants were more frequent in patients treated with cisplatin-etoposide than in those treated with carboplatin-etoposide (50.0% versus 23.8%, data not shown), which might have contributed to the imbalance in the incidence of nephrotoxicity between the two regimens.

Although the differences did not achieve statistical significance, the frequency of febrile neutropenia was higher (40.0% versus 23.1%, $P = 0.300$) (Table 2) and its duration was longer (mean of 6.3 versus 4.3 days, $P = 0.140$) (Supplementary Fig. S1) in patients with *UGT1A1*6* or *UGT1A1*28* than in those with the *UGT1A1–/–* genotype. The frequency of hepatobiliary toxicities of grade ≥2 such as elevation in γ-glutamyl transpeptidase (33.3% versus 19.2%, $P = 0.453$) and that of gastrointestinal toxicities of grade ≥2 such as nausea (40.0% versus 19.2%, $P = 0.272$) and anorexia (40.0% versus 23.1%, $P = 0.300$) were slightly higher in patients with *UGT1A1* variant alleles than in those with the *UGT1A1–/–* genotype (Table 2). Severe hematologic toxicities of grade ≥3 such as anemia (26.7% versus 11.5%, $P = 0.390$) and thrombocytopenia (33.3% versus 15.4%, $P = 0.248$) were also observed more frequently in patients with *UGT1A1* variant alleles than in those with the *UGT1A1–/–* genotype (Table 2).

4. Discussion

Both *UGT1A1*6* and *UGT1A1*28* alleles are associated with toxicity of irinotecan, in particular with diarrhea, neutropenia, and febrile neutropenia [11–15]. We have now shown that the incidence of nephrotoxicity associated with platinum-etoposide doublet therapy was significantly higher in SCLC patients with these *UGT1A1* alleles than in those wild type for *UGT1A1*. About 35% of administered etoposide is excreted into urine in the unmodified form, with the remainder of the drug being metabolized either by the cytochrome P450 (CYP) pathway or by UGT1A1 [18,24] (Supplementary Fig. S2). In the CYP pathway,

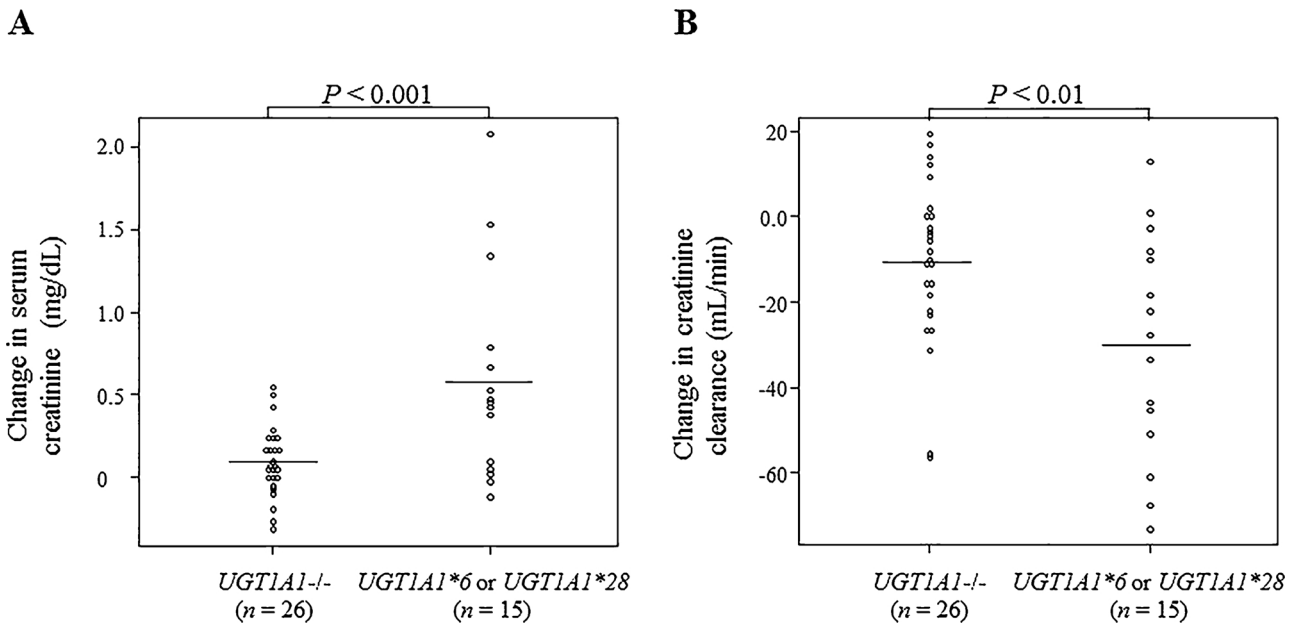

Fig. 1. Changes in serum creatinine concentration (**A**) and in creatinine clearance (**B**) during platinum-etoposide doublet therapy in SCLC patients with the *UGT1A1–/–* genotype or with *UGT1A1* variant alleles. Bars indicate mean values. *P* values were determined with the unpaired Student's *t*-test.

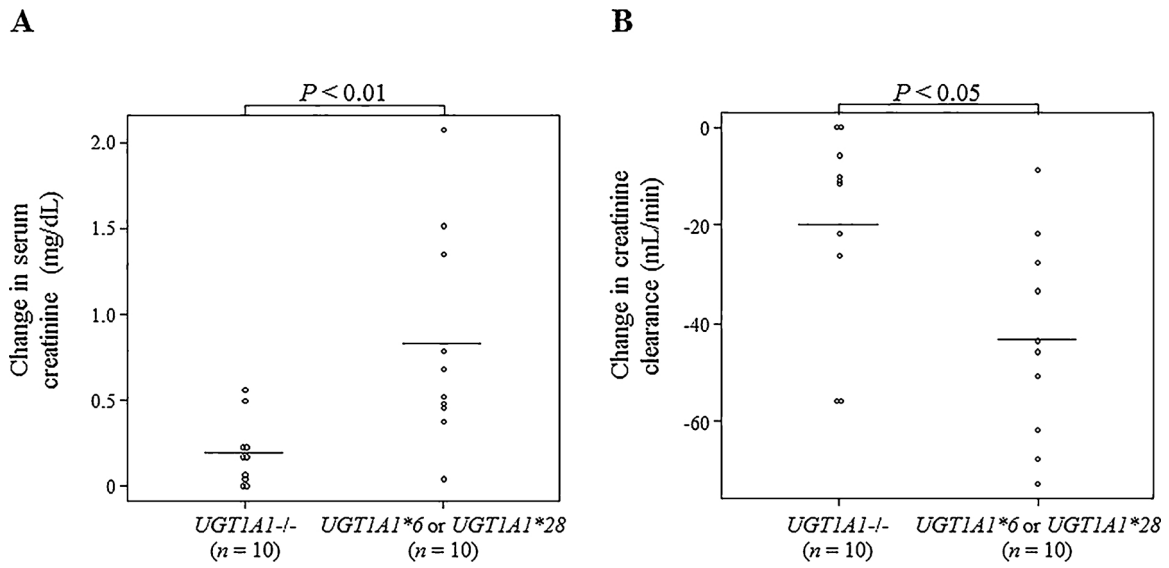

Fig. 2. Changes in serum creatinine concentration (**A**) and in creatinine clearance (**B**) during cisplatin-etoposide doublet therapy for SCLC patients with the *UGT1A1–/–* genotype or with *UGT1A1* variant alleles. Bars indicate mean values. *P* values were determined with the unpaired Student's *t*-test.

Table 3
Univariate and multivariate logistic regression analysis of risk factors for nephrotoxicity during platinum-etoposide doublet therapy.

		Nephrotoxicity		Univariate analysis		Multivariate analysis	
Factor		Yes (n = 13) *n* (%)	No (n = 28) *n* (%)	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Sex	Male	10 (32.3)	21 (67.7)	1.11 (0.20–8.05)	1.000		
	Female	3 (30.0)	7 (70.0)				
Age (years)	≥75	0 (0.0)	4 (100.0)	0.00 (0.00–3.24)	0.288		
	< 75	13 (35.1)	24 (64.9)				
PS (ECOG)	0–1	12 (40.0)	18 (60.0)	0.16 (0.00–1.36)	0.127	0.46 (0.03–7.83)	0.592
	≥2	1 (9.1)	10 (90.9)				
Concurrent RT	Yes	5 (55.6)	4 (44.4)	3.61 (0.61–23.33)	0.113	1.32 (0.12–14.30)	0.818
	No	8 (25.0)	24 (75.0)				
Regular use of NSAIDs	Yes	4 (33.3)	8 (66.7)	1.11 (0.19–5.61)	1.000		
	No	9 (31.0)	20 (69.0)				
Platinum agent	Cisplatin	11 (55.0)	9 (45.0)	10.86 (1.82–121.20)	**0.003**	3.22 (0.19–54.70)	0.419
	Carboplatin	2 (9.5)	19 (90.5)				
Etoposide dosage (mg/m^2)	100	12 (44.4)	15 (55.6)	9.91 (1.17–476.83)	**0.031**	4.88 (0.20–118.00)	0.330
	< 100	1 (7.1)	13 (92.9)				
UGT1A1 genotype	–/–	3 (11.5)	23 (88.5)	13.99 (2.49–110.05)	< **0.001**	19.30 (2.50–149.00)	< **0.005**
	*6/–	6 (66.7)	3 (33.3)				
	*6/*6	2 (100.0)	0 (0.0)				
	*28/–	2 (100.0)	0 (0.0)				
	*28/*28	0 (0.0)	1 (100.0)				
	*6/*28	0 (0.0)	1 (100.0)				

P values of < 0.05 are shown in bold. Multivariate analysis was performed with variables that showed a *P* value of < 0.15 in univariate analysis. For *UGT1A1* genotype, comparisons were performed between heterozygotes or homozygotes for *UGT1A1*6* or *UGT1A1*28* alleles versus the *UGT1A1–/–* genotype with Fisher's exact test. Abbreviations not defined in text: PS, performance status; RT, radiotherapy; OR, odds ratio; CI, confidence interval.

etoposide is O-demethylated by CYP3A4 and CYP3A5 to etoposide catechol, which then undergoes sequential one-electron oxidations to etoposide quinone catalyzed by myeloperoxidase [18,25–27]. Although etoposide catechol and etoposide quinone inhibit topoisomerase II as does etoposide, these metabolites possess an oxidative reactivity and are more cytotoxic than is etoposide [18,26,28,29]. Metabolism of administered etoposide by UGT1A1 yields etoposide glucuronide, which is removed from cells by ATP-binding cassette (ABC) multidrug transporters [16–18]. Such elimination of etoposide by the UGT1A1 pathway has been found to be attenuated in patients with *UGT1A1* variant alleles, resulting in an increased concentration of etoposide and the preferential generation of etoposide catechol via the CYP pathway [19]. Etoposide has been shown to induce cytotoxicity in human kidney proximal tubule cells via the generation of reactive oxygen species and signaling by extracellular signal–regulated kinase (ERK) [30,31], with the incidence of nephrotoxicity in SCLC patients receiving platinum-etoposide doublet therapy having previously been found to be 1.8% to 6.5% [2–6]. On the other hand, platinum agents (cisplatin or carboplatin) predominantly undergo renal elimination and are not metabolized by UGT1A1 [32,33]. Our results now suggest that a decrease in UGT1A1 activity or expression and consequent attenuation of etoposide glucuronidation associated with the presence of *UGT1A1* variant alleles result in increased nephrotoxicity of platinum-etoposide doublet therapy.

Various factors such as cardiac disease, hypertension, hydration volume, and use of NSAIDs have been identified as confounding factors for cisplatin-induced nephrotoxicity [34–36]. In the present study, all 20 patients treated with cisplatin-etoposide received an adequate hydration volume (≥3000 mL, data not shown), and there were no significant factors related to the occurrence of nephrotoxicity other than

UGT1A1 polymorphisms in this subgroup (Supplementary Table S2). The mean dose of cisplatin or etoposide delivered per course of cisplatin-etoposide therapy was similar in patients who experienced nephrotoxicity and those who did not (Supplementary Table S3). Among the 11 patients who received cisplatin-etoposide treatment and experienced nephrotoxicity, 6 (54.5%) discontinued the treatment because of the nephrotoxicity and all of these patients changed treatment regimen to carboplatin-etoposide doublet therapy (data not shown). The proportion of patients who changed treatment regimen from cisplatin to carboplatin as a result of adverse events was higher for those with *UGT1A1* variant alleles than for those wild type for *UGT1A1* (60.0% versus 10.0%, $P = 0.057$) (Supplementary Table S4). These findings suggest that carboplatin-etoposide chemotherapy might be more suitable for patients with such *UGT1A1* alleles.

The frequency and duration of febrile neutropenia were increased in patients with *UGT1A1* variant alleles compared with those with the *UGT1A1–/–* genotype. The frequencies of severe hematologic (grade ≥ 3) or nonhematologic (grade ≥ 2) toxicities were also slightly higher in patients with the variant alleles than in those with the *UGT1A1–/–* genotype. Furthermore, among the 13 patients who experienced nephrotoxicity during platinum-etoposide treatment, individuals with *UGT1A1*6* or *UGT1A1*28* also tended to experience more such severe hematologic and nonhematologic toxicities compared with those wild type for *UGT1A1* (Supplementary Fig. S3). These results suggest that *UGT1A1* polymorphisms may also be associated with hematologic and other nonhematologic toxicities of platinum-etoposide doublet therapy. Although patients 12 and 13 in Supplementary Fig. S3 both had the *UGT1A1*28/–* genotype and were treated with cisplatin-etoposide and carboplatin-etoposide, respectively, patient 13 experienced more severe adverse events than did patient 12. It is possible that patient 13 harbored additional genetic variants related to the pharmacokinetics of etoposide—such as those of *CYP3A* [27], *ABCC1* [37], *ABCC2* [38], *ABCC3* [38,39], or *ABCB1* [38]—in addition to *UGT1A1*28*.

There are several limitations to the present study. First, the pharmacogenetic relation between *UGT1A1* genotype and the metabolic products of etoposide was not investigated. Second, we were not able to assess genotypes for other genes known to contribute to the pharmacokinetics of etoposide such as *CYP3A* [27], *ABCC1* [37], *ABCC2* [38], *ABCC3* [38,39], and *ABCB1* [38] those mentioned above. And third, the relatively small number of patients and the retrospective nature of the study limit the conclusions that can be drawn. Further studies are thus needed to confirm our findings.

In conclusion, our results suggest that a decrease in etoposide glucuronidation activity associated with *UGT1A1* polymorphisms results in increased nephrotoxicity of platinum-etoposide doublet therapy in SCLC patients. Close monitoring of nephrotoxicity is thus recommended during platinum-etoposide doublet therapy in patients positive for such *UGT1A1* variant alleles.

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Conflict of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2018.11.002.

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