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ORIGINAL ARTICLE

Influence of *UGT1A1* polymorphism on etoposide plus platinum-induced neutropenia in Japanese patients with small-cell lung cancer

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Abstract

Background The association between *UGT1A1* polymorphism and etoposide-induced toxicities is still not clear. The aim of this study was to assess the association between uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) gene polymorphism and severe hematologic toxicities in Japanese patients receiving etoposide plus platinum chemotherapy for small-cell lung cancer.

Methods This retrospective analysis included patients with small-cell lung cancer who had received their first-line chemotherapy with etoposide plus cisplatin or carboplatin, between October 2008 and April 2018, at the University of Fukui Hospital. The relationship between *UGT1A1* polymorphisms and first-cycle neutropenia as well as thrombocytopenia was evaluated.

Results A total of 55 patients were enrolled. The incidence of grade 4 neutropenia during the first cycle of etoposide-based chemotherapy was higher in patients with homozygous (hmz) polymorphisms for *UGT1A1*28* and **6* (**28/*28*, **6/*6*, and **6/*28*) than in patients with wild-type (wt) (**1/*1*) and heterozygous (htz) (**1/*28* and **1/*6*) polymorphisms (88% vs 43% $P=0.03$). The incidence of febrile neutropenia and grade 4 thrombocytopenia, however, was not significantly different. Multivariate analysis suggested that grade 4 neutropenia associated significantly with an hmz *UGT1A1* genotype [odds ratio (OR) 11.3; $P=0.04$] and administration of granulocyte colony-stimulating factor (G-CSF) before the neutrophil counts dropped to < 500 cells/μL (OR; $P=0.01$).

Conclusions *UGT1A1*28* and *UGT1A1*6* mutations might be regarded as predictors for etoposide-induced grade 4 neutropenia.

Keywords Etoposide · Neutropenia · Polymorphism · Small-cell lung cancer · UGT1A1

Introduction

Etoposide, a semisynthetic derivative of podophyllotoxin with antitumor activity, inhibits topoisomerase II. It is widely used in the treatment of small-cell lung cancer (SCLC), testicular cancer, lymphoma, and leukemia [1]. The dose-limiting toxicity of etoposide in SCLC patients is hematologic toxicity, particularly neutropenia. In patients treated with etoposide in combination with cisplatin (PE) or carboplatin (CE), grade 4 neutropenia was reported in 65% and 53% cases, respectively [2, 3]. Severe neutropenia requires dose reduction, delay in treatment, or even discontinuation of chemotherapy [4, 5]. It also carries the risk of life-threatening infections, compromising patient outcomes [6–8]. Therefore, it is important to determine the risk factors

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for severe neutropenia in patients receiving etoposide plus platinum chemotherapy.

Etoposide is mainly excreted as hydroxyl acid derivatives and glucuronides [9]. The glucuronides account for the disposition of 15–35% of the administered etoposide [10]. Uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) is reported to be the principal enzyme responsible for the formation of etoposide glucuronides in vitro [11, 12].

UGT1A1 polymorphisms are known to result in reduced expression or activity of UGT1A1 and predispose individuals to Gilbert's syndrome, a benign form of episodic jaundice [13, 14]. With several tyrosine kinase inhibitors, such as nilotinib, sorafenib, pazopanib, and sunitinib, it was reported that *UGT1A1* polymorphisms were associated with treatment-related hyperbilirubinemia [15–17]. Furthermore, polymorphism of the *UGT1A1* gene is known to play an important role in irinotecan pharmacokinetics and severe toxicity. Irinotecan, a camptothecin analog with anticancer activity via the inhibition of topoisomerase I, is a prodrug metabolized by carboxylesterase to form an active metabolite SN-38. SN-38 is inactivated through biotransformation into SN-38 glucuronide (SN-38G) by UGT1A1 [18, 19]. Genetic polymorphisms of *UGT1A1* include *UGT1A1*28* and *UGT1A1*6*, leading to decreased formation of SN-38G, and thus delayed metabolism of SN-38 [20]. In Japanese cancer patients, a correlation between *UGT1A1*28* and **6* genotypes and irinotecan-induced toxicities has been reported [21, 22], and optimizing irinotecan dosage based on *UGT1A1* genotypes has helped reduce the toxicities. However, the association between *UGT1A1* polymorphism and etoposide-induced toxicities is still not clear.

In this study, we have retrospectively evaluated the association between severe hematologic toxicities and polymorphisms in *UGT1A1*28* and **6* in Japanese SCLC patients receiving etoposide-based chemotherapy.

Patients and methods

Patients

Patients with SCLC who had received PE or CE as first-line chemotherapy, and had *UGT1A1* genotyping done before or after the etoposide-based chemotherapy, between August 2009 and April 2018, at the University of Fukui Hospital, were analyzed retrospectively by reviewing their medical records. At our institute, *UGT1A1* genotyping was outsourced to SRL, Inc., Tokyo, Japan, and polymorphisms were analyzed using the Invader assay [23].

Classification of *UGT1A1* polymorphisms

We classified the *UGT1A1* polymorphisms into two groups: wild type (wt) (**1/*1*) or heterozygous (htz) (**1/*28* and **1/*6*), and homozygous (hmz) (**28/*28*, **6/*6*, and **6/*28*). The double state (**6/*28*) was classified as hmz based on the results of previous studies [22, 24].

Treatment

The PE regimen included intravenous (i.v) administration of 80 mg/m^2 cisplatin on day 1 and 100 mg/m^2 etoposide on days 1, 2, and 3 every 3 or 4 weeks. Patients getting the CE regimen were administered with carboplatin area under the curve (AUC) of 5 i.v. on day 1 and 80–100 mg/m^2 of etoposide i.v. on days 1, 2, and 3 every 3 or 4 weeks.

Assessments

Nadir neutrophil and platelet counts during the first cycle of PE or CE chemotherapy were recorded as major outcomes. Toxicities were assessed based on the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Grade 4 neutropenia (neutrophil counts of <500 cells/μL) and grade 4 thrombocytopenia (platelet counts of $<25{,}000$ cells/μL) were defined as severe hematologic toxicities. According to the Japanese Society of Medical Oncology Clinical Guidelines, febrile neutropenia was defined as axillary temperature ≥ 37.5 °C or an oral temperature ≥ 38.0 °C in patients and a peripheral neutrophil counts <500 cells/μL or expected to fall below 500 cells/μL [25].

The baseline variables that potentially influenced chemotherapy-induced neutropenia were assessed in each patient. These included age, sex, body surface area, Eastern Cooperative Oncology Group performance status (ECOG PS), stage of the disease, the initial dose of etoposide given, and concurrent use of radiation, use of aprepitant or fosaprepitant. The baseline blood cell (leucocyte, neutrophil, and platelet) counts, administration of granulocyte colony-stimulating factor (G-CSF) before the neutrophil counts dropped to <500 cells/μL, baseline levels of serum albumin, total bilirubin, serum creatinine, and creatinine clearance (Ccr) were also included in the baseline variables. We calculated Ccr was from serum creatinine levels using the Cockcroft–Gault equation [26].

The study protocol was approved by the Research Ethics Committee at the University of Fukui under the condition that all data be processed and analyzed anonymously (approved no. 20170035). The study also conforms to the provisions of the Declaration of Helsinki.

Statistical analysis

Continuous data are summarized as medians (interquartile range). Categorical data presented as frequencies (percentage) were compared using the Fisher's exact test. The Mann–Whitney's *U* test was used to compare the non-normally distributed variables between groups. A univariate analysis was performed to identify the risk factors for grade 4 neutropenia after etoposide-based chemotherapy. Variables with a significance level of < 20% were included in the multivariate logistic regression model. The final model was built by stepwise logistic regression. The results are reported as odds ratios (ORs) with 95% confidence intervals (CIs). All statistical tests were 2-sided, and *P* values of less than 0.05 were considered 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, version 3.2.2) [27]. More precisely, it is a modified version of R commander (version 2.2-3) designed to add statistical functions frequently used in biostatistics.

Results

Patients' characteristics

We evaluated 55 out of 71 patients who had received first-line etoposide-based chemotherapy for SCLC and had completed *UGT1A1* genotyping, between August 2009 and April 2018. Two patients were excluded, since the first cycle could not be completed. Fourteen patients were excluded due to concurrent use of radiation.

Of the 55 patients evaluated, 25 (46%) were wt, 22 (40%) were htz, and 8 (15%) were hmz for *UGT1A1*28* and **6* polymorphisms (Table 1). The baseline characteristics of these patients are comparable between the two groups and have been summarized in Table 2.

Incidence of hematotoxicity and febrile neutropenia

During the first cycle of etoposide-based chemotherapy, the incidence of grade 4 neutropenia, was significantly higher ($P = 0.03$) in the hmz group compared to the wt/htz group (Table 3). The neutrophil nadir time was comparable between the two groups (day 14 vs day 14; $P = 0.89$). There were 1 (13%) and 7 (15%) cases of febrile neutropenia in the hmz and the wt/htz groups, respectively ($P = 1.00$). None of the patients died from febrile neutropenia. Grade 4 thrombocytopenia occurred in 13% ($n = 1$) of the hmz group and in 13% ($n = 6$) of the wt/htz group. This difference was not statistically significant ($P = 1.00$).

Table 1 Frequencies of *UGT1A1* genotype in this study

UGT1A1 genotype	$n = 55$
Wild type or heterozygous group	47 (86%)
Wild type	
**1/*1*	25 (46%)
Heterozygous	
**1/*28*	13 (24%)
**1/*6*	9 (16%)
Homozygous group	8 (15%)
Homozygous	
**28/*28*	2 (4%)
**6/*6*	2 (4%)
Double heterozygous	
**28/*6*	4 (7%)

UGT UDP-glucuronosyltransferase

Risk factors for grade 4 neutropenia

The results of the univariate and multivariate analyses of the association between grade 4 neutropenia during first cycle of etoposide-based chemotherapy and clinical variables are shown in Table 4. Grade 4 neutropenia showed a significant association with homozygous *UGT1A1* genotype, and administration of G-CSF before the neutrophil counts dropped to < 500 cells/μL.

Discussion

In this study, we demonstrate that hmz *UGT1A1 *28* and **6* genotypes are associated with the incidence of grade 4 neutropenia, in SCLC patients receiving etoposide plus platinum chemotherapy (Table 3). Based on the multivariate analysis, patients hmz for *UGT1A1 *28* and **6* are more likely to get grade 4 neutropenia from etoposide (Table 4).

UGT1A1 has been shown to be the major glucuronidating isoform of etoposide, in vitro [11, 12]. Therefore, genetic polymorphisms can lead to decreased UGT1A1 activity, which in turn can cause the severe toxicity induced by long exposures to etoposide. In addition, *UGT1A1*28/*28* is shown to be significantly associated with a lower clearance of etoposide in children with acute lymphoblastic leukemia [28]. Although not significantly associated with incidences of febrile neutropenia, it should be noted that grade 4 neutropenia is a risk factor. Therefore, as with irinotecan, *UGT1A1* polymorphisms may help in predicting the etoposide-induced neutropenia.

Table 2 Baseline demographics and clinical characteristics of the study patients

UGT1A1 genotype	Wild type or heterozygous group ($n=47$)	Homozygous group ($n=8$)	*P* value
Male	39 (83%)	6 (75%)	0.63
Female	8 (17%)	2 (25%)	
Age (years)	69 (65–74)	72 (69–74)	0.26
≥ 70 years	23 (49%)	5 (63%)	0.71
BSA (m^2)	1.62 (1.52–1.70)	1.63 (1.49–1.70)	0.85
≥ 1.6 m^2	26 (55%)	4 (50%)	1.00
ECOG PS (0/1/2/3)	18/16/1/1	2/4/2/0	0.90
Limited disease	9 (9%)	1 (13%)	1.00
Extensive disease	37 (79%)	7 (88%)	
Large cell neuroendocrine carcinoma	1 (2%)	0	
Etoposide plus cisplatin	8 (17%)	2 (25%)	0.63
Etoposide plus carboplatin	39 (83%)	6 (75%)	
Initial dose of etoposide (mg/m^2)	96 (84–98)	96 (91–98)	0.62
90–100 mg/m^2	33 (70%)	6 (75%)	1.00
G-CSF administration before neutrophil dropped to < 500 cells/μL	26 (55%)	4 (50%)	1.00
With aprepitant or fosaprepitant	18 (38%)	4 (50%)	0.70
Neutrophil (cells/μL)	4523 (3062–5616)	3976 (2950–4935)	0.50
< 3000 cells/μL	11 (24%)	2 (25%)	1.00
Total bilirubin (mg/dL)	0.5 (0.4–0.7)	0.9 (0.7–0.9)	0.02
≥ 1.2 mg/dL	5 (14%)	0	1.00
Creatinine clearance (mL/min)	68 (55–90)	78 (62–85)	0.79
< 60 mL/min	15 (32%)	2 (25%)	1.00
Albumin (g/dL)	3.5 (3.0–4.0)	3.1 (2.9–3.5)	0.10
< 3.5 g/dL	21 (45%)	5 (63%)	0.40

Values are presented as number or median (25th percentile–75th percentile)

ECOG PS Eastern Cooperative Oncology Group performance status, *G-CSF* granulocyte colony-stimulating factor, *UGT* UDP-glucuronosyltransferase, *BSA* body surface area

Table 3 Incidence of hematotoxicity and febrile neutropenia during first cycle of chemotherapy

UGT1A1 genotype	Wild type or heterozygous group ($n=47$)	Homozygous group ($n=8$)	*P* value
Neutrophil nadir (cells/μL)	564 (357–1068)	335 (191–473)	0.04
Neutrophil nadir time (day)	14 (12–17)	14 (13–14)	0.89
Grade 4 neutropenia	20 (43%)	7 (88%)	0.03
Febrile neutropenia	7 (15%)	1 (13%)	1.00
Platelet nadir (cells/μL)	83,000 (48,500–148,500)	67,500 (35,200–142,700)	0.54
Grade 4 thrombocytopenia	6 (13%)	1 (13%)	1.00

Values are presented as number or median (25th percentile–75th percentile)

UGT UDP-glucuronosyltransferase

The patients with *UGT1A1*28/*28*, **6/*6*, and **6/*28* genotypes reportedly comprise 8.8% of the Japanese population [29]. In the present study, *UGT1A1* homozygous group was higher (15%) than the Japanese population. Previous studies have shown a higher prevalence of *UGT1A1*28/*28* genotype in lung cancer compared with other malignancies [30].

As reported previously [31, 32], the only baseline patient characteristic that showed a relative association with *UGT1A1* polymorphism was the serum bilirubin level (Table 2), though how it affects the outcome of etoposide-based chemotherapy is not clear. The total clearance of etoposide in patients with obstructive jaundice (bilirubin > 2.0 mg/dL) is comparable to that in patients with normal

Table 4 Univariate and multivariate analyses of association between grade 4 neutropenia during the first cycle of etoposide-containing chemotherapy and clinical variables

	n = 55	OR	95% CI	*P* value	OR	95% CI	*P* value
*UGT1A1*28* and **6* homozygous genotypes	8 (15%)	9.11	1.04–440.24	0.03	11.30	1.17–108.00	0.04
Female	10 (18%)	0.96	0.19–4.80	1.00			
Age (≥ 70 years)	28 (51%)	1.43	0.44–4.76	0.59			
BSA (≥ 1.6 m^2)	30 (55%)	1.94	0.59–6.62	0.28			
ECOG PS (≥ 2)	15 (27%)	0.88	0.22–3.38	1.00			
Etoposide plus cisplatin regimen	10 (18%)	1.04	0.21–5.24	1.00			
Initial dose of etoposide (< 90 mg/m^2)	16 (29%)	0.36	0.08–1.38	0.14			
G-CSF administration before neutrophil dropped to < 500 cells/μL	30 (55%)	0.24	0.06–0.83	0.02	0.21	0.06–0.70	0.01
With aprepitant or fosaprepitant	22 (40%)	0.94	0.28–3.17	1.00			
Neutrophil (< 3000 cells/μL)	13 (24%)	0.55	0.12–2.28	0.53			
Total bilirubin (≥ 1.2 mg/dL)	5 (9%)	0.24	0.01–2.61	0.35			
Creatinine clearance (< 60 mL/min)	17 (30%)	0.89	0.24–3.25	1.00			
Albumin (< 3.5 g/dL)	26 (47%)	1.43	0.44–4.74	0.59			

UGT UDP-glucuronosyltransferase, *BSA* body surface area, *ECOG PS* Eastern Cooperative Oncology Group performance status, *G-CSF* granulocyte colony-stimulating factor

hepatic functions [33]. It, therefore, appears that the baseline serum bilirubin level is not as significant a risk factor for neutropenia, as is the *UGT1A1* genotype.

Age, abnormal renal function, and hypoalbuminemia have all been reported as risk factors for etoposide-induced hematologic toxicity [34, 35]. Reduced plasma etoposide clearance in the older patients was linked to higher incidences of grade 4 neutropenia [34]. Approximately 35% of the intravenously administered etoposide is unmetabolized and excreted in the urine [10]; impaired renal function can, therefore, negatively impact etoposide clearance, and its administration has to be carefully adjusted. In a previous study, low serum albumin levels did not affect the total etoposide clearance; instead, it caused an increase in unbound and free etoposide. These factors have to be considered to show a strong association between *UGT1A*1 polymorphisms and etoposide-induced grade 4 neutropenia. However, they were not associated with grade 4 neutropenia based on our univariate and multivariate analyses.

We acknowledge there have been several limitations in this study. First, it is a single institution, retrospective study with a relatively small population of patients. A multicentre, prospective study would, therefore, be required to confirm our findings. Second, the blood etoposide concentrations were not measured. Previous studies have shown that *UGT1A1 *28/*28* associates with etoposide clearance in children [28], but our study population comprised of adults. Moreover, race and ethnicity also affect the relationship between *UGT1A1* polymorphisms and etoposide clearance. Studies are, therefore, needed to validate the role of *UGT1A1* polymorphisms in etoposide clearance, in adult Japanese patients.

In conclusion, this is the first study to associate etoposide-induced grade 4 neutropenia with *UGT1A1* polymorphisms in SCLC patients. Like irinotecan therapy, etoposide-based chemotherapy may also benefit from *UGT1A1* genotyping. However, further pharmacokinetic studies are needed to validate these results.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent The need for informed consent was waived because of the retrospective nature of the study.

References

1. O'Dwyer PJ, Leyland-Jones B, Alonso MT et al (1985) Etoposide (VP-16-213): current status of an active anticancer drug. N Engl J Med 312:692–700
2. Noda K, Nishiwaki Y, Kawahara M et al (2002) Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. New Engl J Med 346:85–91

3. Okamoto H, Watanabe K, Kunikane H et al (2007) Randomised phase III trial of carboplatin plus etoposide vs split doses of cisplatin plus etoposide in elderly or poor-risk patients with extensive disease small-cell lung cancer: JCOG 9702. Br J Cancer 97:162–169
4. Hryniuk W, Bush H (1984) The importance of dose intensity in chemotherapy of metastatic breast cancer. J Clin Oncol 2:1281–1288
5. Levin L, Hryniuk WM (1987) Dose intensity analysis of chemotherapy regimens in ovarian carcinoma. J Clin Oncol 5:756–767
6. Crawford J, Dale DC, Lyman GH (2004) Chemotherapy-induced neutropenia: risks, consequences, and new directions for its management. Cancer 100:228–237
7. Kuderer NM, Dale DC, Crawford J et al (2006) Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. Cancer 106:2258–2266
8. Lyman GH, Michels SL, Reynolds MW et al (2010) Risk of mortality in patients with cancer who experience febrile neutropenia. Cancer 116:5555–5563
9. Fleming RA, Miller AA, Stewart CF (1989) Etoposide: an update. Clin Pharm 8:274–293
10. D'Incalci M, Rossi C, Zucchetti M et al (1986) Pharmacokinetics of etoposide in patients with abnormal renal and hepatic function. Cancer Res 46:2566–2571
11. Watanabe Y, Nakajima M, Ohashi N et al (2003) Glucuronidation of etoposide in human liver microsomes in specifically catalyzed by UDP-glucuronosyltransferase 1A1. Drug Metab Dispos 31:589–595
12. Wen Z, Tallman MN, Ali SY et al (2007) UDP-glucuronosyltransferase 1A1 is the principal enzyme responsible for etoposide glucuronidation in human liver and intestinal microsomes: structural characterization of phenolic and alcoholic glucuronides of etoposide and estimation of enzyme kinetics. Drug Metab Dispos 35:371–380
13. Bosma PJ, Chowdhury JR, Bakker C et al (1995) The genetic basis of the reduced expression of bilirubin UDP-glucuronosyltransferase 1 in Gilbert's syndrome. N Engl J Med 333:1171–1175
14. Takeuchi K, Kobayashi Y, Tamaki S et al (2004) Genetic polymorphisms of bilirubin uridine diphosphate-glucuronosyl transferase genein Japanese patients with Crigler–Najjar syndrome or Gilbert's syndrome as well as in healthy Japanese subjects. J Gastroenterol Hepatol 19:1023–1028
15. Abumiya M, Takahashi N, Niioka T et al (2014) Influence of UGT1A1 6, 27, and 28 polymorphisms on nilotinib-induced hyperbilirubinemia in Japanese patients with chronic myeloid leukemia. Drug Metab Pharmacokinet 29:449–454
16. Meza-Junco J, Chu QS, Christensen O et al (2009) UGT1A1 polymorphism and hyperbilirubinemia in a patient who received sorafenib. Cancer Chemother Pharmacol 65:1–4
17. Xu CF, Reck BH, Xue Z et al (2010) Pazopanib-induced hyperbilirubinemia is associated with Gilbert's syndrome UGT1A1 polymorphism. Br J Cancer 102:1371–1377
18. Rivory LP, Robert J (1995) Identification and kinetics of a beta-glucuronide metabolite of SN-38 in human plasma after administration of the camptothecin derivative irinotecan. Cancer Chemother Pharmacol 36:176–179
19. Haaz MC, Rivory L, Jantet S et al (1997) Glucuronidation of SN-38, the active metabolite of irinotecan, by human hepatic microsomes. Pharmacol Toxicol 80:91–96
20. Araki K, Fujita K, Ando Y et al (2006) Pharmacogenetic impact of polymorphisms in the coding region of the *UGT1A1* gene on SN-38 glucuronidation in Japanese patients with cancer. Cancer Sci 97:1255–1259
21. Ando Y, Saka H, Ando M et al (2000) Polymorphisms of UDP-glucuronosyltransferase gene and irinotecan toxicity: a pharmacogenetic analysis. Cancer Res 60:6921–6926
22. Minami H, Sai K, Saeki M et al (2007) Irinotecan pharmacokinetics/pharmacodynamics and UGT1A genetic polymorphisms in Japanese: roles of *UGT1A1*6* and **28*. Pharmacogenet Genom 17:497–504
23. Hasegawa Y, Sarashina T, Ando M et al (2004) Rapid detection of UGT1A1 gene polymorphisms by newly developed Invader assay. Clin Chem 50:1479–1480
24. Satoh T, Ura T, Yamada Y et al (2011) Genotype-directed, dose-finding study of irinotecan in cancer patients with *UGT1A1*28* and/or *UGT1A1*6* polymorphisms. Cancer Sci 102:1868–1873
25. Japanese Society of Medical Oncology (2012) Practical guideline of febrile neutropenia (FN). Nankodo Co. Ltd., Tokyo
26. Cockcroft DW, Gault MH (1976) Prediction of creatinine clearance from serum creatinine. Nephron 16:31–41
27. Kanda Y (2013) Investigation of the freely-available easy-to-use software "EZR" (Easy R) for medical statistics. Bone Marrow Transplant 48:452–458
28. Kishi S, Yang W, Boureau B et al (2004) Effects of prednisone and genetic polymorphisms on etoposide disposition in children with acute lymphoblastic leukemia. Blood 103:67–72
29. Fukui T, Mitsufuji H, Kubota M et al (2011) Prevalence of topoisomerase I genetic mutations and *UGT1A1* polymorphisms associated with irinotecan in individuals of Asian descent. Oncol Lett 2:923–928
30. Nishikawa Y, Kanai M, Narahara M et al (2017) Association between *UGT1A1*28*28* genotype and lung cancer in the Japanese population. Int J Clin Oncol 22:269–273
31. Moriya H, Saito K, Helsby N et al (2013) The association between heterozygosity for *UGT1A1*6. UGT1A1*28*, and variation in the serum total-bilirubin level in healthy young Japanese adults. Genet Test Mol Biomark 17:464–469
32. Kringen MK, Piehler AP, Grimholt RM et al (2014) Serum bilirubin concentration in healthy adult North-Europeans is strictly controlled by the *UGT1A1* TA-repeat variants. PLoS One 9:e90248. https://doi.org/10.1371/journal.pone.0090248
33. Hande KR, Wolff SN, Greco FA et al (1990) Etoposide kinetics in patients with obstructive jaundice. J Clin Oncol 8:1101–1107
34. Joel SP, Shah R, Clark PI et al (1996) Predicting etoposide toxicity: relationship to organ function and protein binding. J Clin Oncol 14:257–267
35. Mick R, Ratain MJ (1991) Modeling interpatient pharmacodynamic variability of etoposide. J Natl Cancer Inst 6:1560–1564