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Original article

Genetic polymorphisms and vincristine-induced peripheral neuropathy in patients treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone therapy

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ABSTRACT

Vincristine (VCR)-induced peripheral neuropathy (VIPN) is a common and life-long toxicity in lymphoma patients receiving current standard chemotherapy. The association between VIPN and genetic polymorphisms is largely unknown in adult lymphoma patients. To examine the possible relationship between known genetic polymorphisms in patients with pediatric acute lymphoblastic leukemia and incidence of VIPN in adult patients with B-cell lymphoma, we examined *CEP72* rs924607, *ETAA1* rs17032980, *MTNR1B* rs12786200, *CYP3A5* rs776746, rs7963521, and rs1045644 genetic polymorphisms in samples from 56 adult patients with B-cell lymphoma who received rituximab, cyclophosphamide, doxorubicin, VCR, and prednisone (R-CHOP) chemotherapy. Mutation analysis was performed by direct sequencing. The median age was 65 years (range, 30–79). The median cumulative dose of VCR was 12 mg (range, 2–16). VIPN was documented in 42 patients (75%), and 9 (16%) had grade 2–4 VIPN. Age, impaired glucose tolerance, number of cycles of R-CHOP, and VCR cumulative dose were not associated with incidence of VIPN. There was no association between the incidence of grade 2–4 or any grade VIPN and these six genetic polymorphisms. These results indicate that *CEP72*, *MTNR1B*, *ETAA1*, *CYP3A5*, rs7963521, and rs1045644 genetic polymorphisms are not associated with VIPN in patients with B-cell lymphoma who received R-CHOP.

Keywords: lymphoma, vincristine, neuropathy, *CEP72*, R-CHOP

INTRODUCTION

Chemotherapy-induced peripheral neuropathy (PN), which includes sensory, motor, and autonomic symptoms, remains a major comorbidity in cancer patients [1, 2]. In the treatment of lymphoma, vincristine (VCR) is one of the key components of rituximab, cyclophosphamide, doxorubicin, VCR, and prednisone (R-CHOP), which is the standard first-line therapy for diffuse large B-cell lymphoma (DLBCL)[3]. R-CHOP has also been used in the treatment of advanced follicular lymphoma (FL), mantle cell lymphoma, and marginal zone lymphoma (MZL) [4, 5, 6]. More than 60% of patients with DLBCL who received R-CHOP survive 5 years [7, 8]; however, more than 20% of patients experience VCR-induced peripheral neuropathy (VIPN) during the standard CHOP regimen with or without rituximab [9, 10, 11]. A retrospective study in Korea reported that VIPN was observed in 84% of patients with DLBCL or FL who received R-CHOP or R-cyclophosphamide, VCR, and prednisone and was associated with reduced quality of life [12]. The incidence of VIPN is associated with a cumulative dose of VCR and ethnicity [13, 14]. The association of VIPN and ethnicity suggests a possible association of genetic polymorphisms and VIPN.

In the last decade, several single-nucleotide polymorphisms (SNPs) associated with VIPN have been reported, mainly in pediatric patients with acute lymphoblastic leukemia (ALL) [15, 16, 17, 18]. Centrosomal protein of 72 kDa (CEP72) is located in the centrosome and is essential for maintaining microtubule-organizing activity and structural integrity of the centrosome [19], and a SNP in the promoter region of the *CEP72* gene (rs924607) has been the most actively investigated [15, 16, 17, 18, 20]. *Ewing's tumor-*

associated antigen 1 (*ETAA1)* rs17032980 and *melatonin receptor 1B (MTNR1B)* rs12786200 were also associated with VIPN in a North American cohort of a genome-wide study [15, 17]. Moreover, *CYP3A5* rs776746 was detected in an adult ALL patient with the wild type of *CEP72* rs924607 who experienced severe PN [20]. In a recent genome-wide study, rs7963521 and rs1045644, but not *CEP72* rs924607, were associated with the incidence of VIPN [21].

In contrast to pediatric patients with ALL, the association between VIPN and SNPs is largely unknown in adult patients with lymphoma. A recent study including 33 adult patients with lymphoma analyzed chemotherapy-induced PN and *brain derived neurotropic factor (BDNF)* and reported that only the serum BDNF level was associated with VIPN and that *BDNF* SNP (Val66Met) was not associated with VIPN [22]. To evaluate a possible association of genetic polymorphisms in VIPN, we analyzed the incidence of VIPN and *CEP72* rs924607, *ETAA1* rs17032980, *MTNR1B* rs12786200, *CYP3A5* rs776746, rs7963521, and rs1045644 in adult patients with mature B-cell lymphoma who received R-CHOP.

PATIENTS AND METHODS

Patients

This study included 56 patients who were diagnosed with mature B-cell lymphoma between 2003 and 2017 at Mie University Hospital and received R-CHOP chemotherapy as a first-line therapy. The diagnosis in all patients was confirmed according to the 2017 WHO

classification [23].

Clinical information was obtained from the Mie University Hospital records. All patients were treated according to similar protocols at Mie University Hospital. VIPN was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 from 2003 to 2011 and version 4.0 from 2012 to 2017. To evaluate a possible association of comorbidity with VIPN, we collected information on impaired glucose tolerance of the patients, including patients diagnosed with diabetes mellitus before or soon after R-CHOP and those whose hemoglobin A1c level is > 6.2% before or soon after R-CHOP. The study was approved by the institutional review board of Mie University and conducted in accordance with the Declaration of Helsinki.

Genomic DNA extraction and PCR

The specimens used in this analysis were obtained from the oral mucosa or lymphoma tissue of the patients. Genomic DNA was extracted using a spin-column-based DNA isolation kit (Macherey-Nagel, Germany; Cat# 740952.50) according to the manufacturer's protocol. *CEP72* rs924607, *ETAA1* rs17032980, *MTNR1B* rs12786220, *CYP3A5* rs776746, rs7963521, and rs1045644 were amplified by PCR using TaKaRa LA Taq with GC Buffer (TaKaRa). The PCR amplification protocol was as follows: denaturation at 94°C for 3 min; followed by 30 cycles of 30 s at 94°C, 30 s at 60°C, and 90 s at 72°C. These primers were designed to include specific polymorphisms. The PCR primer sequence and PCR product sizes are described in Supplementary Table 1.

Direct sequencing

The PCR products were purified using ExoSAP-IT (Affymetrix/USB) and the QIAquick PCR Purification Kit (QIAGEN) and directly sequenced in both directions using the Applied Biosystems 3130xl Genetic Analyzer (Thermo Fisher Scientific, Inc).

Statistical analysis

Relationships between the two groups were examined using Fisher's exact test. All tests were two-sided, and $P < 0.05$ indicated a significant difference. All analyses were performed using IBM SPSS Statistics 24 (IBM Japan).

RESULTS

Clinical characteristics

Clinical characteristics at diagnosis of all 56 patients with B-cell lymphoma are shown in Table 1. All patients were Japanese. The median age at diagnosis was 65 years (range, 30 to 79 years). Patients were diagnosed with DLBCL (n = 34), FL (n = 20) or MZL (n = 2). All patients were treated with R-CHOP. The cycle of R-CHOP was 6 in 24 patients, 7 in one patient, and 8 in 31 patients. The median VCR cumulative dose was 12 mg (range, 2 to 16 mg).

VIPN

Forty-two (75%) patients developed any grade VIPN during R-CHOP. Nine (16%) patients

experienced grade 2 to 4 VIPN (Table 1). Age, sex, the total number of cycles of R-CHOP, and the presence of impaired glucose tolerance were not related to grade 2 to 4 VIPN (Table 1) or any grade VIPN (data not shown).

Twenty-three (41%) patients required dose reduction or omission of VCR (Table 1). Among the 47 patients who developed grade 0 to 1 VIPN, VCR was stopped or dose-reduced in 17 (36%) patients, mainly because of grade 2 to 3 constipation (n = 9). In contrast, VCR was stopped or dose-reduced in six out of nine (67%) patients who experienced grade 2 to 4 VIPN.

Gene polymorphisms

The associations of six genetic polymorphisms and VIPN are shown in Table 2. The *CEP72* rs924607 TT genotype was detected in 12 patients (21%). None of these 12 patients with the *CEP72* rs924607 TT genotype and 9 (20%) of 44 patients with the *CEP72* rs924607 CC/CT genotype experienced grade 2 to 4 VIPN ($P = 0.18$). No significant association was observed between the incidence of grade 2 to 4 or any grade VIPN and the six SNPs analyzed in this study. Moreover, there was no association between the presence of grade 2 to 3 constipation and the six SNPs examined in this study (data not shown).

Four patients had diabetes mellitus with medication, five patients were HbA1c > 6.2 without medication before R-CHOP, and one patient developed diabetes mellitus after the end of R-CHOP. These 10 patients with diabetes or glucose intolerance did not complain of PN before chemotherapy. The *CEP72* rs924607 TT genotype was more frequently observed in patients with impaired glucose intolerance than in the others (6/10

and 6/46, $P = 0.0038$). There was no significant association between impaired glucose intolerance and the other five SNPs (data not shown).

DISCUSSION

To our knowledge, this is the largest study analyzing genetic polymorphisms and VIPN in adult patients with lymphoma. No significant association was found between VIPN and the six candidate genetic polymorphisms analyzed in this study.

There are several plausible reasons for these results. First, SNPs analyzed in this study were reported in studies of children with ALL, not in lymphoma in adults. The median cumulative VCR dose in our study (12 mg) was much lower than that in a study of children with ALL (47 mg/m^2) [15]. The incidence of grade 2 or above VIPN was 16% in our study and 22-29% in the same children's ALL study [15]. These differences in VCR doses and dose intensity between R-CHOP and pediatric ALL regimens might be a plausible reason for no association between VIPN and those genetic polymorphisms.

Second, differences in patient population may cause different results among studies analyzing risks of VIPN. For example, a *CEP72* TT genotype was associated with VIPN in children and adults with ALL in studies of the North American population [15, 17], but it was not associated with VIPN in studies of a Spanish and an Arab patient cohort [16, 18]. Therefore, there is a possibility that no genetic association was found because our present study included only Japanese patients. Differences in the evaluation of VIPN may also produce different results. We used CTCAE version 3 and 4 for the evaluation, while a

previous study used modified CTCAE version 1 and 2 [15]. Evaluating VIPN using existing toxicity criteria can be difficult, and a more objective and universal method or consensus in evaluating VIPN is needed.

In the present study, patients with impaired glucose tolerance frequently exhibited the *CEP72* TT genotype ($P = 0.0038$). To our knowledge, there is no previous report suggesting a relationship between diabetes and the *CEP72* TT genotype. As *CEP72* encodes a centrosomal protein involved in microtubule formation [19] and the SNP is located at the promoter region [15], further studies to clarify a possible role of the *CEP72* rs924607 TT genotype in developing diabetes are warranted.

A limitation of our present study was a lack of data other than glucose intolerance that interfere with VCR metabolism due to the retrospective nature of the study. Further studies including the analysis of the presence of hepatic disorders, alcohol preference, and the concomitant use of drugs that interfere with VCR metabolism are effective to confirm our results. Another limitation was that we did not analyze the six SNPs in samples from Japanese patients with ALL. Further analysis that includes Japanese ALL patients may better elucidate the race-related biological factors that explain the lack of an association between VIPN and the SNPs in patients with B-cell lymphoma.

In conclusion, our results suggest that the *CEP72*, *MTNR1B*, *ETAA1*, *CYP3A5*, *rs7963521*, and *rs1045644* genetic polymorphisms analyzed in this study are not associated with the incidence of VIPN in adult patients with mature B-cell lymphoma who received R-CHOP. To reduce VIPN, therapeutic strategies that reduce a VCR dose or replace VCR with other agents may be more effective than targeting genetic polymorphisms analyzed in

this study. Specific genetic polymorphisms associated with VIPN needed to be identified in adult patients with lymphoma.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interest AS, KM, MY, and IT report grants from Astellas Pharma, Kyowa Kirin, Ono Pharmaceutical, and Takeda Pharmaceutical, outside the submitted work. NK reports honoraria from Chugai Pharmaceutical and Celgene, and grants from

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Table 1. Patient clinical characteristics and treatment

	All patients	VIPN		
	N = 56	Grade 0 - 1 n = 47	Grade 2 - 4 n = 9	
Characteristics and treatment	No. (%)	No. (%)	No. (%)	*P*
Age at diagnosis, years				
Median (range)	65 (30 - 79)	65 (30 - 79)	63 (50 - 76)	
≤ 60	22 (39)	18 (38)	4 (44)	0.73
> 60	34 (61)	29 (62)	5 (56)	
Sex				
Male	33 (59)	30 (64)	3 (33)	0.14
Female	23 (41)	17 (36)	6 (67)	
Diagnosis				
DLBCL	34 (61)	27 (57)	7 (78)	
FL	20 (36)	19 (40)	1 (11)	
MZL	2 (4)	1 (0)	1 (11)	
Total number of cycles of R-CHOP				
6	24 (43)	22 (47)	2 (22)	0.27
7 or 8*	32 (57)	25 (53)	7 (78)	
VCR cumulative dose, mg				
Median (range)	12 (2 - 16)	12 (2 - 16)	12 (4 - 16)	
VCR administration				
No dose modification or omission	33 (59)	30 (64)	3 (33)	0.14
Dose-modified or omitted	23 (41)	17 (36)	6 (67)	
Comorbidity				
Impaired glucose tolerance	10 (18)	8 (17)	2 (22)	0.65

*, Only one patient received 7 cycles of R-CHOP. This patient experienced grade 1 VIPN.

Table 2. Genotype and grade of vincristine neuropathy

	All patients	VIPN					
	N = 56	Grade 0 - 1 n = 47	Grade 2 - 4 n = 9		Grade 0 n = 14	Grade 1 - 4 n = 42	
Genotype	No. (%)	No. (%)	No. (%)	*P*	No. (%)	No. (%)	*P*
CEP72 rs924607							
C/C+C/T	44 (79)	35 (74)	9 (100)	0.18	10 (71)	34 (81)	0.47
T/T	12 (21)	12 (26)	0 (0)		4 (29)	8 (19)	
C/C	20 (36)	15 (32)	5 (56)	0.25	4 (29)	16 (38)	0.75
C/T+T/T	36 (64)	32 (68)	4 (44)		10 (71)	26 (62)	
ETAA1 rs17032980							
A/A+A/G	53 (95)	44 (94)	9 (100)	1.00	12 (86)	41 (98)	0.15
G/G	3 (5)	3 (6)	0 (0)		2 (14)	1 (2)	
A/A	34 (61)	30 (64)	4 (44)	0.29	8 (57)	26 (62)	0.76
A/G+G/G	22 (39)	17 (36)	5 (56)		6 (43)	16 (38)	
MTNR1B rs12786200							
C/C+C/T	46 (82)	39 (83)	7 (78)	0.65	12 (86)	34 (81)	1.00
T/T	10 (18)	8 (17)	2 (22)		2 (14)	8 (19)	
C/C	15 (27)	12 (26)	3 (33)	0.69	4 (29)	11 (26)	1.00
C/T+T/T	41 (73)	35 (74)	6 (67)		10 (71)	31 (74)	
CYP3A5 rs776746							
A/A+A/G	28 (50)	24 (51)	4 (44)	1.00	5 (36)	23 (55)	0.36
G/G	28 (50)	23 (49)	5 (56)		9 (64)	19 (45)	
A/A	5 (9)	5 (11)	0 (0)	0.58	0 (0)	5 (12)	0.32
A/G+G/G	51 (91)	42 (89)	9 (100)		14 (100)	37 (88)	
rs7963521							
T/T+C/T	51 (91)	42 (89)	9 (100)	0.58	13 (93)	38 (90)	1.00
C/C	5 (9)	5 (11)	0 (0)		1 (7)	4 (10)	
T/T	34 (61)	29 (62)	5 (56)	0.73	8 (57)	26 (62)	0.76
C/T+C/C	22 (39)	18 (38)	4 (44)		6 (43)	16 (38)	
rs1045644							
C/C+C/G	56 (100)	47 (100)	9 (100)	1.00	14 (100)	42 (100)	1.00
G/G	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	
C/C	27 (48)	22 (47)	5 (56)	0.72	8 (57)	19 (45)	0.54
C/G+G/G	29 (52)	25 (53)	4 (44)		6 (43)	23 (55)	

Supplementary Table 1