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ORIGINAL ARTICLE

The role of ABCB1 polymorphism as a prognostic marker for primary central nervous system lymphoma

Ting Wu[1] · Hui Kang[1] · Dongxiao Zhuang[2] · Yan Ma[1] · Zhiguang Lin[1] · Dina Suolitiken[1] · Bobin Chen[1] · Xiaoping Xu[1]

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Abstract

To investigate the possible role of functional single nucleotide polymorphism (SNP) in circadian genes as prognostic markers of primary central nervous system lymphoma (PCNSL). We conducted a prospective study using data from Huashan Hospital 2006–2015 and followed up 91 PCNSL patients until June 30, 2016. The survival of patients with different prognostic factors was compared by log-rank test. Univariate and multivariate analyses were performed by Cox regression. During a long-term follow-up (6–110 months), overall survival (OS) was 32 months (95% CI, 13.3–91.1) and progression-free survival (PFS) was 23 months (95% CI, 9.0–41.0) for the entire cohort. Age ($P = 0.046$, $P = 0.001$) and performance status (PS) score ($P = 0.013$, $P = 0.003$) showed differences in OS and PFS. ABCB1 rs1045642 variant showed significant difference in PFS between patients with CC genotype and those with CT/TT genotypes ($P = 0.020$). In multivariate analysis, age (HR = 2.3; 95% CI, 1.2–4.2, $P = 0.008$), PS (HR = 2.4; 95% CI, 1.3–4.4, $P = 0.007$), and ABCB1 rs1045642 (HR = 1.9; 95% CI, 1.0–3.3, $P = 0.036$) were the independent risk factors for PFS. In our results, the most important prognostic factors associated with higher risk of progression were ABCB1 rs1045642 CC genotype, PS > 2, and older age.

Keywords ABCB1 gene · Primary central nervous system lymphoma · Single nucleotide polymorphism · Prognostic factors

Introduction

Primary central nervous system lymphoma (PCNSL) is a rare, extranodal form of non-Hodgkin lymphoma (NHL) that occurs in the brain, eyes, leptomeninges, or spinal cord in the absence of systemic lymphoma. PCNSL is estimated to account for up to 1% of all lymphomas, 4–6% of all extranodal lymphomas, and about 3% of all CNS tumors [1]. The vast majority of PCNSL (> 95%) are diffuse large B cell lymphomas (DLBCL) [2], expressing B cell markers and corresponding to the non-germinal center B cell–like (non-GCB) DLBCL subtype with a $CD10^-$, $BCL6^+$, and $IRF4/MUM1^+$ pattern [3]. Despite substantial improvements in the treatment of PCNSL, the overall prognosis remains poor, with a median progression-free survival (PFS) of 12 months and a median overall survival (OS) of about 3 years in most studies [4]. Further investigation is needed to define more efficient therapeutic strategy by revealing biomarkers that can be used to stratify different subgroups of patients before making therapeutic decision, and to predict the course and the outcome of the disease. Among clinical characteristics, only age and performance status (PS) have been consistently identified as independent prognostic factors for PCNSL outcomes [5, 6]. Although a number of PCNSL outcome-associated biomarkers were identified and found to be associated with PCNSL prognosis, very few are applied in routine clinical practice [7–9].

Evaluating genetic variability of patients offers another promising approach to predict prognosis of non-Hodgkin lymphoma. Recently, several studies reported that host genetic

Ting Wu, Hui Kang and Dongxiao Zhuang contributed equally to this work.

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✉ Bobin Chen
bbchen@fudan.edu.cn

✉ Xiaoping Xu
xpxu1111@163.com

[1] Department of Hematology, Huashan Hospital, Shanghai Medical College, Fudan University, 12 Urumqi Middle Road, Shanghai 200040, China

[2] Department of Neurologic Surgery, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai, China

variations in DNA repair and one-carbon metabolism gene polymorphisms could stratify risk for OS in DLBCL and follicular lymphoma (FL) after accounting for demographic and clinical factors [10, 11]. Metabolic pathway enzymes are involved in activation and detoxification of environmental carcinogens as well as drug metabolism. Their genetic polymorphisms, such as cytochrome P450 (CYP), glutathione S-transferase (GST), and N-acetyltransferases (NAT) were proven to be useful factors in the prediction of NHL prognosis and survival [12–14]. However, to date, no single nucleotide polymorphism (SNP) has been identified as a prognostic indicator for PCNSL.

Based on the strength of evidence of previously published studies, the following candidate genetic variants were chosen for our analysis (Supplementary Table S1): DNA repair genes [11](BRCA1 rs16942, XRCC4 rs1056502, ERCC2 rs13181), one-carbon metabolism gene [10] (BHMT rs585800, SHMT rs1979276, TCN1 rs526934, GGH rs719235, MTHFR rs1801131), and metabolism genes [15] (ABCB1 rs1045642, NAT1 rs15561). Here, we analyzed candidate SNP genotypes and clinical characteristics in 91 cases with PCNSL and evaluated the possible association.

Methods

Patients and study design

A total of 91 PCNSL patients who were pathologically diagnosed at our institution between June 2006 and December 2015 were reviewed. These cases were partly included in previous study [16]. Diagnoses were established according to the WHO classification. All patients were seronegative for HIV. Clinical information was obtained from the patients' medical records. Standard contrast-enhanced magnetic resonance imaging (MRI) scans of the brain were performed at diagnosis. CT scans of chest, abdomen, and pelvis and bone marrow biopsies were performed at the time of diagnosis to exclude systemic involvement. ^{18}F-2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) scans were performed in some of these patients. Cerebrospinal fluid (CSF) analysis was performed when leptomeningeal disease was suspected. This study was approved by the Huashan Hospital of Fudan University ethical committee on human experimentation. All participants provided written informed consent.

Treatment and follow-up

Among all the 91 patients, the backbone of treatment is high-dose methotrexate (HD-MTX, 3–5 g/m^2) alone or in a regimen. Forty-four percent (40 patients) were treated with chemotherapy only, and 56.0% (51 patients) received chemotherapy with consolidation whole-brain radiotherapy (WBRT). The median dose of WBRT was 36 Gy. Systemic MTX-based chemotherapy regimens included HD-MTX, rituximab (R), idarubicin (IDA), and teniposide (Vm26). Of all the patients with PCNSL, high-dose MTX monotherapy was given to 20 patients, while 18 patients (19.8%) received HD-MTX combined with rituximab (375 mg/m^2) chemotherapy. Thirty patients were treated with HD-MTX along with idarubicin (10 mg/m^2) and others received the combination of HD-MTX and teniposide (100 mg/m^2). The treatments were repeated every 3 weeks and continued for 6 or 8 cycles.

Assessment of response was performed with MRI scans of the brain or FDG-PET scans prior to the fourth cycle of chemotherapy. Subsequently, patients continued to be followed up with brain MRI after every other cycle. After completion of the treatments, the patients underwent brain MRI every 3–6 months or if clinically necessary. Response to treatment in PCNSL was classified as progressive disease if increase of tumor volume was more than 25% or new lesions occurred on brain MRI. As the endpoint of the study, OS was calculated from the date of diagnosis to June 30, 2016 or death from any cause. PFS was determined from the date of diagnosis until progression or the last follow-up evaluation, namely June 30, 2016.

SNP genotyping and genetic analysis

Analysis of 10 SNP genotypes in DNA repair, one-carbon metabolism, and metabolism genes was performed for patients by sequencing. Gene names, chromosomal location, and the SNP database IDs used for genotyping are listed in Table S1 (Supplementary Material). Genomic DNA was extracted from the collected peripheral blood samples using a TIANGEN TIANamp Genomic DNA Kit (TIANGEN, China) according to the manufacturer's protocol. The quality of DNA was examined consistently by measuring the 260/280 and 260/230 absorbance ratios. Only samples with high quality of DNA (ratios > 1.8) were used. Polymerase chain reaction was performed using a TIANGEN Golden Easy PCR System (PR05830, TIANGEN, China) on a thermocycler (ABI, Grand Island, NY, USA) according to the manufacturer's instructions. The amplified products were separated by gel electrophoresis on 2% agarose gel. All fragments of the amplification were purified with the AxyPrep DNA Gel Extraction kit according to the manufacturer's instructions (Axygen Sci, Inc.). Direct sequencing was performed with those purified products. All primer sequences are listed in the supplementary material.

Statistical analysis

Clinical data were summarized in terms of means, medians, and percentages. The Kaplan–Meier method was

used to estimate OS and PFS. Alleles and genotype frequencies were analyzed by using the online software SHEsis. The Hardy–Weinberg equilibrium of genetic polymorphisms was assessed by Pearson's chi-squared test. Univariate analysis was performed using log-rank test, and multivariate analyses was done by Cox regression. All reported *P* values were two-sided, and a *P* value < 0.05 was considered statistically significant. Statistical analyses were performed with Stata SE 12 software (StataCorp LP, College Station, TX, USA).

Results

Clinical characteristics of patients

The general features of the patients in this study are summarized in Table 1, including 35 females and 56 males. The median age at diagnosis was 55 years (range, 24–74 years). Clinical presentation was characterized by the following symptoms: intracranial hypertention (51, 56.0%), motor deficit (19, 20.9%), lalopathy (12, 13.2%), vision disorder (7, 7.7%), and cognitive disturbances (2, 2.2%). Twenty-two patients had a performance status (PS) of 0–2, and 69 patients had a PS of 3–4. In the pretreatment CSF examination, the protein, glucose, and chlorides were examined in 52 patients. An increased CSF protein concentration was found in 20 patients (37.0%). As shown in the brain MRI at diagnosis, 51.6% of patients had deep parenchymal lesions, defined as present within basal ganglia, corpus callosum, brainstem, and cerebellum. Thirty-eight patients had a single tumor lesion, and 53 patients (58.2%) had multiple tumor lesions. Forty-three patients had a biopsy to ascertain the definite diagnosis, others received surgery. The histopathological diagnosis was diffuse large B cell type lymphoma in all 91 PCNSL patients.

Table 1 Clinical characteristics of the PCNSL cohort

Characteristic	Data
Sex	
Female	35 (38.5%)
Male	56 (61.5%)
Age	
Median	55 (24~74)
≥ 55 years	45 (49.5%)
Initial symptoms	
Intracranial hypertention (headache, nausea, emesis)	51 (56.0%)
Motor deficit	19 (20.9%)
Lalopathy	12 (13.2%)
Vision disorder	7 (7.7%)
Cognitive deficit	2 (2.2%)
Performance status, > 2	22 (24.2%)
Serum LDH, elevated	37 (40.7%)
Serum β2-MG, elevated	29 (31.9%)
Urinary β2-MG, elevated	19 (20.9%)
CSF analysis	
Protein, abnormal	20 (37.0%)
Glucose, abnormal	15 (27.8%)
Chlorides, abnormal	17 (31.5%)
MRI features	
Deep-seated brain lesions involved	47 (51.6%)
Numbers of lesions, ≥ 2	53 (58.2%)
Definite diagnostic procedure	
Stereotactic or navigation-guided needle biopsy	43 (47.3%)
Surgical resection	48 (52.7%)
Histology	A 11 diffuse large B cell lymphoma

Prognostic factors

Number of factors in the survival analysis are summarized in Table 2. The patients were followed up for a median duration of 58 months (range 6–110 months). At the end of the follow-up period, 42 patients survived and 49 deceased. The median OS was 32 months (95% CI, 13.3–91.1) and PFS for PCNSL patients was 23 months (95% CI, 9.0–41.0). Patients younger than 55 years had longer OS (53 months vs. 27 months; $P = 0.046$; Fig. 1c) and PFS (35 months vs. 13 months; $P = 0.001$; Fig. 1a) than the older patients. Patients with a grade of ECOG performance status (PS) > 2 at initial diagnosis had shorter OS (25 months vs. 41 months; $P = 0.013$; Fig. 1d) and PFS (13 months vs. 27 months; $P = 0.003$; Fig. 1b) than those with PS ≤ 2. Other candidate factors, such as sex, serum lactate dehydrogenase, cerebrospinal fluid protein/glucose/chlorides elevation, serum/urine β2-MG elevation, involvement of deep brain structures, tumor resection or not, and tumor numbers were not prognostic in our population. Additionally, the treatment modality and chemotherapy regimens had no prognostic significance for PFS or OS.

Allele and genotype frequencies

All studied SNPs, except BHMT rs585800, SHMT rs1979276, and TCN1 rs526934, were in Hardy–Weinberg equilibrium. The three SNPs were not included into this study to evaluate the relationship between SNPs and survival among the patients. Of the 91 PCNSL patients, the allele frequency was 70.3% for BRCA1 rs16942A, 69.8% for XRCC4 rs1056503G, 94.5% for ERCC2 rs13181T, 72.5% for GGH rs719235G, 83.0% for MTHFR rs1801131A, 63.2% for ABCB1

Table 2 Univariate analysis of clinical factors for PFS and OS of 91 patients with PCNSL

Variables	N	PFS		OS	
		Month	*P* value	Month	*P* value
Age			0.001		0.046
≥55 years	45	13		27	
<55 years	46	35		53	
Sex			0.369		0.387
Male	56	23		28	
Female	35	25		33	
Performance status			0.003		0.013
>2 score	22	13		25	
≤2 scores	69	17		41	
Serum LDH			0.479		0.732
Elevated	37	26		32	
Normal	54	23		40	
Serum β2-MG			0.334		0.281
Elevated	29	16		27	
Normal	62	27		53	
Urinary β2-MG			0.607		0.243
Elevated	19	27		57	
Normal	72	21		31	
CFS protein			0.941		0.512
Elevated	20	24		28	
Normal	32	21		53	
CFS glucose			0.555		0.556
Elevated	15	17		27	
Normal	37	32		56	
CFS chlorides			0.181		0.100
Elevated	17	16		27	
Normal	35	26		57	
Deep-seated brain lesions involved			0.223		0.193
Yes	47	35		53	
No	44	17		28	
Number of lesion			0.529		0.747
Single	38	23		28	
≥2	53	27		40	
Surgical resection			0.468		0.412
Yes	48	23		40	
No	43	27		28	
Treatment modality			0.301		0.249
Chemotherapy alone	40	27		28	
Chemotherapy + radiation	51	23		40	
Chemotherapy regimen		0.571		0.202	
HD-MTX	20	17		25	
HD-MTX + R	18	23		28	
HD-MTX + IDA	30	25	58		
HD-MTX + Vm26	23	23	40		

rs1045642C, and 68.7% for NAT1 rs15561C, respectively. The frequencies of the variants' genotype were in accordance with the expected frequencies (Supplementary Table S2).

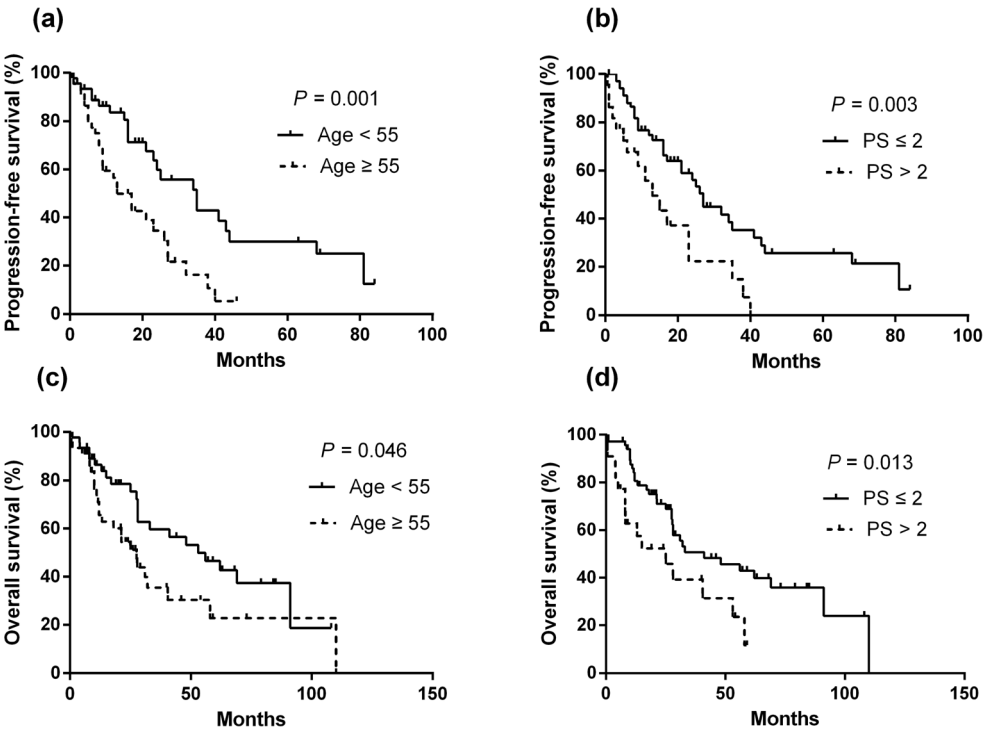

Fig. 1 Comparison of survival according to Age and PS in PCNSL patients. Kaplan–Meier curves for PFS and OS according to Age (**a** and **c**). The cases older than 55 years had significantly worse PFS and OS ($P = 0.001$ and 0.046, respectively. log-rank test). Kaplan–Meier curves for PFS and OS according to PS (**b** and **d**). The cases with PS > 2 had significantly worse PFS and OS ($P = 0.003$ and 0.013, respectively, log-rank test)

Association of SNP genotypes with survival

Among the host genetic variability markers, GGH rs719235 and ABCB1 rs1045642 were identified as the SNP predicting PFS. A significant association was found between GGH rs719235 and PFS. Patients with GG genotype had a prolonged PFS with the comparison to patients carrying T allele (38 months for GG vs. 16 months for TT/TG; $P = 0.028$; Fig. 2b). The T allele at ABCB1 rs1045642 was associated with longer PFS (27 months for TT/CT vs. 16 months for CC; $P = 0.020$; Fig. 2a). However, there was no significant correlation between OS of PCNSL and any of the polymorphisms (Table 3). In order to further determine the relationship between the gene polymorphism and PFS, the Cox proportional hazard regression model was performed to establish the independent prognostic factors. The significant factors in univariate analyses were included in multivariate analysis. In multivariate Cox regression analysis, significantly increased death risk was still observed in patients with old age (HR, 2.282; 95% CI, 1.244–4.186; $P = 0.008$), in patients with high PS (HR, 2.369; 95% CI, 1.273–4.411; $P = 0.007$), and in patients with CC genotype of ABCB1 rs1045642 (HR, 1.851; 95% CI, 1.042–3.290, $P = 0.036$) (Table 4). In both uni- and multivariate analyses, ABCB1 polymorphisms significantly influenced the PFS. The results confirmed that ABCB1 polymorphism was an independent prognostic factor and suggested that the ABCB1 homozygous CC was a high-risk factor for survival.

Discussion

In our study, patients homozygous for the C allele in ABCB1 rs1045642 had a significantly shorter PFS, compared to those

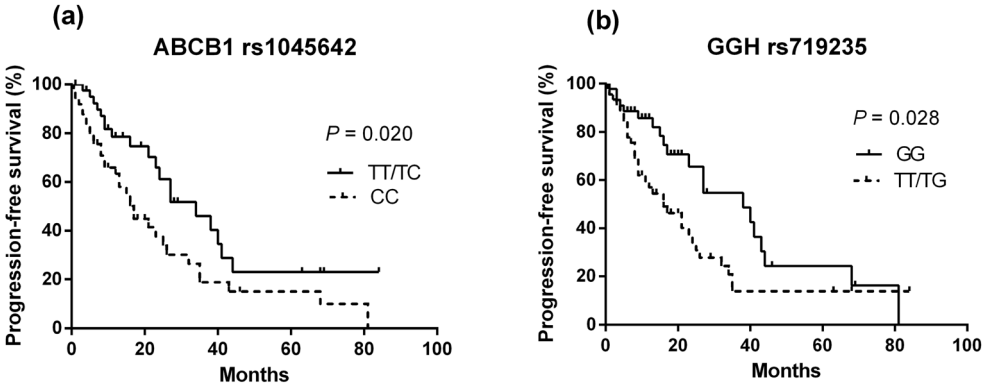

Fig. 2 Kaplan–Meier analyses for PFS of 91 PCNSL patients according to ABCB1 rs1045642 and GGH rs719235. **a** With T versus without T according to ABCB1 genotype at rs1045642. **b** Comparison between GG and TT/TG according to GGH rs719235

Table 3 Main effect of SNP on PFS and OS in the PCNSL patients

Genotype	*N* (%)	PFS		OS		Genotype	*N* (%)	PFS		OS	
		Month	*P* value	Month	*P* value			Month	*P* value	Month	*P* value
BRCA1 rs16942						MTHFR rs1801131					
AA	43 (47.3)	26	0.809	28	0.289	AA	60 (65.9)	24	0.399	33	0.613
AG	42 (46.1)	23		33		CA	31 (34.1)	16		31	
GG	6 (6.6)	13		32		ABCB1 rs1045642					
AG/GG	48 (52.7)	23	0.980	33	0.443	CC	37 (40.6)	16	0.046	280	.565
XRCC4 rs1056503						TT	13 (14.3)	17		91	
GG	46 (50.6)	23	0.931	28	0.934	CT	41 (45.1)	34		56	
TG	35 (38.4)	25		41		TT/CT	54 (59.4)	27	0.020	58	0.292
TT	10 (11.0)	24		12		NAT1 rs15561					
TG/TT	45 (49.4)	24	0.991	41	0.814	CC	46 (50.6)	21	0.132	40	0.297
ERCC2 rs13181						AC	33 (36.2)	35		28	
TT	81 (89.0)	26	0.310	33	0.669	AA	12 (13.2)	17		12	
GT	10 (11.0)	16	28	AC/AA	45 (49.4)	35	0.256	28	0.132		
GGH rs719235											
GG	46 (50.6)	38	0.089	58	0.1887						
TT	5 (5.5)	25		110							
TG	40 (43.9)	16		31							
TT/TG	45 (49.4)	16	0.028	32	0.980						

with at least one T allele. After adjusting for age and PS, we observed a significantly increased risk of disease progression among PCNSL cases with homozygous C allele of ABCB1 rs1045642.

ATP-binding cassette subfamily B member 1 (ABCB1), also called P-glycoprotein 1 (P-gp) or multidrug resistance protein 1 (MDR1), is a key protein that transports a variety of molecules across extracellular and intracellular membranes, with broad substrate specificity [17]. More than 50 genetic mutations have been identified in the human ABCB1 gene [18], and rs1045642 is the most frequent of ABCB1 genetic polymorphism [19]. Earlier studies have suggested that ABCB1 genetic polymorphisms may affect immune responses and apoptosis, which play important roles in various cancers, including breast cancer, gastric cancer, lung cancer, as well as leukemia [20–23]. Ying et al. [24] reported that complete remission/complete remission unconfirmed (CR/CRu) rate in C allele group of ABCB1 rs1045642 was significantly higher than T allele group ($P = 0.009$) in DLBCL patients. The PFS curves of with T (genotype CT and TT) and without T (genotype CC) were significantly different (2-year PFS 46.4% in with T group vs. 73.7% in without T group, respectively; HR = 1.9, $P = 0.045$). They found that genotype CC at locus ABCB1 rs1045642 might contribute to a relatively superior prognosis of DLBCL in a Chinese Jiangsu Han population. The controversial results may be explained as such DLBCL patients received R-CHOP or R-CHOP-like regimens without MTX as initial induction chemotherapy. Gregers et al. [25] have found that ABCB1 rs1045642 polymorphism was significantly associated with risk of relapse ($P = 0.020$) in childhood acute lymphoblastic leukemia (ALL). Compared with 96 patients with the rs1045642 CC variant, 421 patients with the TT or CT variants had reduced risks of relapse in multivariate analysis adjusted for risk, immunophenotype, protocol, and gender ($P = 0.006$).

Table 4 Multivariate analysis of clinical features for PFS of 91 patients with PCNSL

Factors	HR	*P* value	(95% conf. interval)
Age	2.282	0.008	1.244–4.186
PS	2.369	0.007	1.273–4.411
ABCB1	1.851	0.036	1.042–3.290
GGH	1.614	0.162	0.825–3.158

The inferior outcome for PCNSL patients with the ABCB1 rs1045642 CC genotype found in our study was also in agreement with several previous publications in ALL patients [26–28]. PCNSL patients in our study and ALL patients mentioned above all received HD-MTX chemotherapy. MTX is pumped out of the cell by a variety of ATP-binding cassette (ABC) efflux transporters [29]. ABCB1 (MDR1) is one important ABC family gene. The CC genotype of ABCB1 rs1045642 may be eliminating the antitumor drug (MTX) more effectively leading to low intracellular drug concentration and poor prognosis. Suthandriam et al. [30] reported that

patients with ABCB1 rs1045642 polymorphisms appear to have significantly higher MTX plasma concentrations in ALL or NHL patients. Therefore, we need to identify the association of CC genotype with the intracellular and plasma concentration of MTX in the subsequent study.

GGH gene encoded important enzymes of the MTX metabolic pathway. There were a few studies regarding the effect of this GGH polymorphism on side effects and efficacy of MTX in patients with rheumatoid arthritis [31] (RA) and cancer [32]. In our study, GGH rs719235 T carriers had shorter PFS compared to GG genotype group ($P = 0.028$, Fig. 2b). However, this association was not retained in multivariate analysis suggesting minor independent role of this polymorphism. This was consistent with the report suggesting GGH rs719235 was not associated with disease outcome in childhood ALL [33].

In summary, we found that genetic variations in the ABCB1 gene might be potentially associated with survival in patients with PCNSL. The limitation of statistical consideration should be acknowledged for interpretation of our results. We tested 10 SNPs and did not apply correction tests. Despite the limitation, our results were still significant. To our knowledge, this is the first study to evaluate the prognostic value of ABCB1 polymorphisms for PCNSL. As there are no confirming series, this article is still an exploratory study. Further studies are required to confirm our observations and elucidate the functional effects of ABCB1 rs1045642 in a large cohort of primary central nervous system lymphoma.

Authors' contributions Bobin Chen, Hui Kang, and Xiaoping Xu designed the research. Hui Kang, Dongxiao Zhuang, and Dina Suolitiken collected the clinical data. Ting Wu, Hui Kang, Yan Ma, and Zhiguang Lin performed the research. Ting Wu analyzed the data and wrote the manuscript. All authors read and approved the final manuscript.

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Compliance with ethical standards

Ethics approval and consent to participate This study was approved by the Ethics Committee of Huashan Hospital. Written informed consent was obtained from the patients.

Consent for publication Not applicable.

Competing interests The authors declare that they have no competing interests.

Abbreviations PCNSL, primary central nervous system lymphoma; NHL, non-Hodgkin lymphoma; DLBCL, diffuse large B cell lymphomas; SNP, single nucleotide polymorphism; OS, overall survival; PFS, progression-free survival; PS, performance status; CSF, cerebrospinal fluid; HD-MTX, high-dose methotrexate; WBRT, whole-brain radiotherapy; R, rituximab; IDA, idarubicin; Vm26, teniposide; FDG-PET, ^{18}F-2-fluoro-2-deoxy-D-glucose positron emission tomography; MRI, magnetic resonance imaging; LDH, lactate dehydrogenase; β2-MG, β2-microglobulin; ALL, acute lymphoblastic leukemia

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