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ORIGINAL ARTICLE

Clinical Effect of CD25 on the Prognosis of Diffuse Large B Cell Lymphoma with Secondary Central Nervous System Relapse

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Abstract

In the present study, we investigated the effects of immunophenotyping on prognosis of diffuse large B cell lymphoma (DLBCL) with central nervous system (CNS) relapse treated with rituximab-CHOP (R-CHOP). CNS relapse occurred in 9.5% of DLBCL patients. At the diagnosis of DLBCL, CD25 was detected in 14.3% of cases. CD25 positivity correlated with an advanced stage, higher R-IPI, higher CNS-IPI, the presence of B symptoms, the presence of extranodal involvement >1, and bone involvement. Moreover CNS relapse was more frequently observed in patients with CD25+ than in those with CD25-. The univariate analysis showed that an advanced stage, high-risk R-IPI, high-risk CNS-IPI, bone involvement, and CD25+ were associated with shorter overall survival (OS). The multivariate analysis confirmed that CD25+ and high-risk CNS-IPI were independent adverse prognostic factors for shorter OS. A Kaplan-Meier analysis revealed the potential of CD25+ as a prognostic factor in patients with CNS relapse and that it correlated with shorter survival. The present results showed that the expression of CD25 in DLBCL patients with CNS relapse was associated with the patient prognosis independent other prognostic factors. The establishment of a treatment strategy for CNS relapse patients with CD25+ DLBCL cells is needed to improve poor outcomes.

Keywords Diffuse large B cell lymphoma · Central nervous system relapse · CD25 · Rituximab

Introduction

Secondary central nervous system (CNS) involvement is a fatal complication in patients with diffuse large B cell lymphoma (DLBCL). The incidence of secondary CNS relapse in DLBCL ranges between 1 and more than 10% [1–3]. Multiple studies have been performed to identify factors that predict the risk of CNS relapse, which include higher clinical risks, an advanced stage, higher serum LDH levels, extranodal involvement with specific organs, such as testis, breast, sinuses, kidney, bone marrow involvement, and the presence of bulky disease [2, 4, 5]. However, none of these risk factors have been confirmed. The German High-Grade Non-Hodgkin's Lymphoma Study Group recently proposed a simplified model, the so-called CNS international prognostic index (CNS-IPI), which stratifies DLBCL patients into three groups based on the presence of an advanced stage, older age, impaired performance status, extranodal involvement at more than one site, elevated serum LDH levels, and kidney/adrenal gland involvement [6]; however, this model is not entirely accurate and has a low positive value [7].

The lymphoma cell immunophenotypes and treatment outcomes of DLBCL patients with CNS involvement currently remain unclear. Flow cytometry is widely used in the diagnosis and monitoring of hematological disorders, such as acute leukemias or lymphomas, in order to detect and characterize abnormal compartments and enumerate rare events. Hu et al. identified CD56+ as a risk factor for acute lymphocytic leukemia (ALL) with CNS relapse [8]. The expression of CD5 was previously reported to be associated with a poor prognosis in DLBCL patients [9]; however, its relationship with CNS relapse remains unknown. CD25 forms one component of the high-affinity heterotrimeric interleukin 2 (IL2) receptor on activated T cells. Its affinity for IL2 and cellular function are tightly regulated and vary in different cell types [10]. CD25 is reported to be expressed in ALL, acute myeloid leukemia (AML), and non-Hodgkin's lymphoma, including DLBCL and follicular lymphoma [11–16]. In ALL and AML, research

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on the role of CD25 has focused on understanding its significance in oncogenic receptor tyrosine kinase signaling and leukemia stem cells [17]. Previous studies suggested that CD25 plays a role in the evolution of refractory ALL or AML [17, 18]. In non-Hodgkin's lymphoma, the expression of CD25 in lymphoma cells was associated with aggressive clinical features and a poor prognosis [19, 20]. However, the relationship between CD25 expression and CNS involvement has not yet been elucidated in detail. We herein investigated the relationship between immunophenotyping and the prognosis of DLBCL patients with secondary CNS relapse treated with R-CHOP.

Patients and Methods

Patients

We conducted a retrospective review of de novo DLBCL patient data between January 2007 and December 2018 at the Japanese Red Cross Society Wakayama Medical Center. Patients with distinct forms of DLBCL, such as intravascular lymphoma, primary effusion lymphoma, and primary mediastinal large B cell lymphoma were excluded from the present study. Primary CNS lymphoma and intraocular lymphoma were also excluded. Primary therapy consisted of R-CHOP (50 mg/m^2 adriamycin on day 1, 750 mg/m^2 cyclophosphamide on day 1, 1.4 mg/m^2 vincristine (maximum 2.0 mg/body) on day 1, 100 mg/body of prednisolone on days 1–5, and 375 mg/m^2 rituximab per cycle). Chemoimmunotherapy was performed every 3 weeks. Patient characteristics were retrospectively evaluated, including age, sex, stage, serum lactate dehydrogenase (LDH), performance status, bulky mass, B symptoms, the revised-international prognostic index (R-IPI), CNS-IPI, the number of extranodal involvement sites, number of R-CHOP courses, number of patients who received dose reduction therapy, and number of patients who underwent local irradiation (Table 1). Informed consent was obtained from all patients. The present study was conducted in accordance with the principles of the Declaration of Helsinki.

Central Nervous System Relapse

CNS disease was diagnosed based on the presence of malignant cells in centrifuged cerebrospinal fluid (leptomeningeal type) and/or the presence of an intracranial or spinal mass by radiological imaging, such as computed tomography or magnetic resonance imaging (parenchymal type) (Table 2). Patients with symptoms suggesting CNS disease without cytological or radiological findings were not regarded as having CNS disease. CNS disease that occurred during systemic complete remission (CR) and systemic active lymphoma was regarded as CNS relapse.

Table 1 Clinical characteristics of 336 DLBCL patients with treated with R-CHOP

	Number of patients (%) 336
Sex	
male	185 (55.1)
female	151 (44.9)
Age	
≤60	92 (27.4)
>60	244 (72.6)
Stage	
I/II	138 (41.1)
III/IV	198 (58.9)
R-IPI	
0–2	193 (57.5)
3–5	143 (42.5)
CNS-IPI	
0–3	192 (57.1)
4–6	144(42.9)
Extranodal sites involved	
≤1	160 (47.6)
>1	176 (52.4)
ECOG	
≤1	114 (33.9)
>1	222 (66.1)
B symptoms	
+	124 (36.9)
–	212 (63.1)
Bulky mass	
+	72 (21.4)
–	264 (78.6)
Double/triple hit (FISH analysis)	
+	3 (0.1)
–	333 (99.9)
Number of R-CHOP courses	
≤4	146 (43.5)
≥5	190 (56.5)
Dose reductions	
+	114 (33.9)
–	222 (66.1)
Local irradiation	
+	51 (15.2)
–	285 (84.8)
Intrathecal prophylaxis	
+	78 (23.2)
–	258 (76.8)
CNS relapse	
+	32 (9.5)
–	304 (90.5)

R-IPI revised-international prognostic index, *CNS-IPI* central nervous system-international prognostic index

Table 2 Details of CNS relapse in 32 patients

	Number of patients (%)
R-CHOP treatment	32 (100)
Type of CNS event	
Parnchymal	20 (62.5)
Leptomenengial	8 (25)
Both	10 (12.5)
Systemic status	
1st CR	18 (56.2)
2nd or more CR	6 (18)
non-CR	8 (25.8)
Outcome	
Death from lymphoma	16 (50)
Death from other causes	6 (18.8)
Alive	10 (31.2)

Histological Examination, Phenotypes, and Fluorescence In Situ Hybridization Analysis

All lymph nodes or related tissue biopsy samples from patients were obtained during the initial presentation. Collected samples were divided into two or more fractions: one for a histological examination, one for a flow cytometric analysis, and one for a cytogenetic analysis. In the histological examination, cells were fixed in formalin and stained with a solution containing hematoxylin-eosin and Wright-Giemsa. Immunostaining was performed using a panel of monoclonal antibodies, including CD20 (L26, Dako), CD10 (Dako), CD56 (Dako), and CD3 (Dako). A histological diagnosis was defined according to the 2008 World Health Organization classification.

Three-color flow cytometry was performed to evaluate the phenotypes of tumor cells at the initial diagnosis. Mononuclear cells were stained with fluorescein isothiocyanate (FITC)- or phycoerythrin (PE)-conjugated mononuclear antibodies as follows: CD1 (Dako, Carpinteria, CA, USA), CD2 (Dako), CD3 (Becton Dickinson Biosciences, San Jose, CA, USA), CD4 (Dako), CD5 (Becton), CD7 (Becton), CD8 (Dako), CD10 (Dako), CD19 (Immunotech), CD20 (Beckman Coulter, Fullerton, CA, USA), CD23 (Dako), CD11c (Beckman), CD25 (Becton), CD34 (Becton), CD56 (Becton), kappa light chain (Dako), and lambda light chain (Dako). A gate was set for identifying lymphocytes characterized by bright CD45 expression and low side scatter properties; it was considered to be positive when positivity was ≥20% of the population, excluding CD4+/CD25+ cells [21]. The phenotypes of lymphoma cells were analyzed using a flow cytometer (FACSCalibur; Becton).

Patients included in the present study had fluorescence in situ hybridization (FISH) information available on their MYC, BCL2, and BCL6 statuses. Lymphomas harboring an MYC translocation, as identified by FISH, were designated as MYC-positive. They were considered to be MYC-positive double-hit/triple-hit lymphomas if they had additional "hits" with translocations involving BCL2 and/or BCL6.

Statistical Analysis

Fisher's exact and Mann-Whitney U tests were used to assess the significance of differences. Overall survival (OS) was calculated from the date of initiation of therapy to the date of the last follow-up or death from any cause. OS was assessed by the Kaplan-Meier method and Log-rank test. Univariate and multivariate Cox's proportional hazard regression models were used to identify factors predictive of CNS relapse. A p value less than 0.05 was considered to be significant. Statistical analyses were performed with the SPSS 11.5 system.

Results

A total of 336 patients with DLBCL were examined, and included 185 males (55.1%) and 151 females (44.9%) with a median age of 69 years (range 23–91 years). Patient characteristics were retrospectively evaluated in Table 1. According to R-IPI and CNS-IPI, 143 (42.5%) and 144 (42.9%) patients, respectively, were included in the high-risk group. A total of 190 patients (56.5%) were treated with ≥5 courses of R-CHOP therapy. Dose reductions were noted in 114 patients (33.9%). Local irradiation was added for 51 patients (15.2%) and intrathecal prophylaxis was administered to 78 patients (23.2%). Thirty-two CNS events (9.5%) were recorded. As shown in Table 2, a total of 62.5% of CNS events were of the parenchymal type, followed by the leptomeningeal type (25%) and both (12.5%). CNS relapse occurred during first CR in more than 50% of patients (56.2%) and in second or later CR in 6 patients (18%).

Receiver operating characteristics (ROC) analysis was performed to determine the optimal cutoff for percent of CD25 expression in lymphoma cells that predicted for worse 5-year OS outcomes. Using a ROC analysis, the optimum cutoff for percent of lymphoma cells expressing CD25 that predicted for worse OS outcomes was 20%: AUC of 0.67 with a sensitivity of 61% and specificity of 84%. Thus patients divided into two groups: patients with more than 20% (CD25+) and patients with less than 20% (CD25-). The main clinical characteristic of patients with CD25 + and CD25- are shown in Table 3. CD25 positivity correlated with an advanced stage, higher R-IPI, higher CNS-IPI, and the presence of B symptoms. The rates of CR after R-CHOP therapy were higher in patients with CD25- than in those with CD25+. The presence of extranodal involvement >1 was more frequently observed in patients with CD25+ than in those with CD25-. Moreover, bone involvement was more frequently observed in patients

Table 3 Comparison of clinical data in groups positive and negative for CD25

	CD25+		CD25-		*p* value
	Median (range)	No. (%)	Median (range)	No. (%)	
Overall		48 (100)		288 (100)	
Sex					0.081
male		32		153	
female		16		135	
Age	69 (36–83)		69 (23–91)		0.147
≤60		9		83	
>60		39		205	
WBC count (×109/L)	63.6 (16–210)		51.0 (18–230)		0.591
≤5000		20		132	
>5000		28		156	
Hb (g/dL)	11.2 (7.6–13.3)		11.4 (6.8–13.1)		0.685
≤10		19		123	
>10		29		165	
Plt count (×109/L)	175 (63–340)		186 (53–412)		0.234
≤15		10		84	
>15		38		204	
Alb (g/dL)	3.2 (2.6–3.8)		3.4 (2.0–3.7)		0.846
≤3.5		14		88	
>3.5		34		200	
LDH (U/L)	540 (412–3760)		460 (340–4200)		0.293
β2MG (mg/dL)	3.2 (1.9–6.2)		3.6 (2.1–6.7)		0.123
sIL2R (U/L)	1303 (460–11,600)		1450 (280–13,200)		0.507
Stage					0.003
I/II		10		128	
III/IV		38		160	
R-IPI					$p < 0.001$
0–2		11		182	
3–5		37		106	
CNS-IPI					$p < 0.001$
0–3		14		178	
4–6		34		110	
ECOG					0.082
≤1		11		103	
>1		37		185	
B symptoms					**$p < 0.001$**
+		30		94	
–		18		194	
Bulky mass					0.385
+		8		64	
–		40		224	
Extranodal sites involved					**0.014**
≤1		15		145	
>1		33		143	
Extranodal sites					
paranasal		1		17	0.276
breast		1		8	0.783
pleura		3		26	0.526
stomach		1		24	0.133
small intestine		3		12	0.518
liver		2		10	0.81
spleen		2		12	0.696

Table 3 (continued)

	CD25+		CD25-		*p* value
	Median (range)	No. (%)	Median (range)	No. (%)	
kidney		1		3	0.538
adrenal gland		4		8	0.055
testis		2		6	0.351
ovary/uterus		1		4	0.684
bladder		1		2	0.323
bone		18		16	**<0.01**
bone marrow		10		32	0.059
peripheral blood		9		28	0.062
Treatment outcome					**0.018**
CR		13		121	
PR		25		90	
NR/SD		10		77	
Local irradiation					0.589
+		9		42	
–		39		246	
Intrathecal prophylaxis					***p* < 0.001**
+		22		56	
–		26		232	
CNS relapse					***p* < 0.001**
+		26		6	
–		22		282	

Bold values indicates $p < .05$

WBC white blood cells, *Hb* hemoglobin, *Plt* platelets, *Alb* albumin, *LDH* lactate dehydrogenase, *β2MG* beta-2 microglobulin, *sIL2R* soluble interleukin-2 receptor, *R-IPI* revised-international prognostic index, *CNS-IPI* central nervous system international prognostic index, *CR* complete response, *PR* partial response, *NR* non response, *SD* stable disease

with CD25+ than in those with CD25-. No significant differences were observed in the rates of local radiation between patients with CD25+ and those with CD25-, and the rates of intrathecal prophylaxis were higher in patients with CD25+ than in those with CD25-. CNS relapse was more frequently observed in patients with CD25+ than in those with CD25-.

A number of prognostic indicators were found to be significant in univariate and multivariate analyses (Table 4). The univariate analysis showed that an advanced stage, high-risk R-IPI, high-risk CNS-IPI, bone involvement, and CD25+ were associated with shorter OS. The multivariate analysis confirmed that CD25+ and high-risk CNS-IPI were independent adverse prognostic factors for shorter OS .

The median follow up time from diagnosis of DLBCL was 32 months. The estimated 5-years OS rate was significantly lower in patients with than in those without CNS relapse (47% vs.71%, $p = 0.007$) (Fig. 1). In patients with CNS relapse, the 5-years OS rate was significantly lower in CD25+ patients than in CD25- patients (23% vs. 68%, $p = 0.021$) (Fig. 2a). The 5-years OS rate was significantly lower in high risk CNS-

Table 4 Analysis of prognostic factors for worse OS in patients with CNS relapse

	univariate		multivariate	
	HR (95%CI)	*p value*	HR (95%CI)	*p value*
Stage (3, 4 vs. 1, 2)	3.26 (2.67–7.32)	**0.021**		NS
R-IPI (3–5 vs. 0–2)	2.42 (1.14–3.21)	**0.036**		NS
CNS-IPI (4–6 vs. 0–3)	2.72 (1.33–5.54)	**<0.001**	1.37 (1.18–2.85)	**0.018**
Bone involvement (yes vs. no)	1.20 (1.05–2.17)	**0.011**		NS
CD25 (positive vs. negative)	2.36 (1.10–3.67)	**<0.001**	1.58 (1.14–3.24)	**0.005**

Bold values indicates $p < .05$

R-IPI revised-international prognostic index, *CNS-IPI* central nervous system international prognostic index

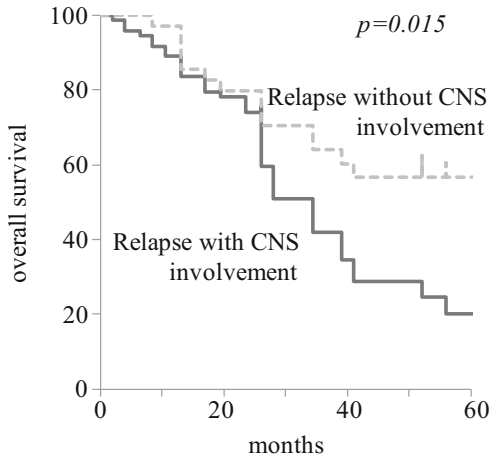


Fig. 1 Kaplan-Meier analysis of overall survival (OS) of patients with and those without CNS relapse. The estimated 5-years OS rate was significantly lower in patients with than in those without CNS relapse (47% vs.71%, $p = 0.007$)

IPI patients than in low/intermediate CNS-IPI patients (18% vs. 57%, $p = 0.045$) (Fig. 2b).

Discussion

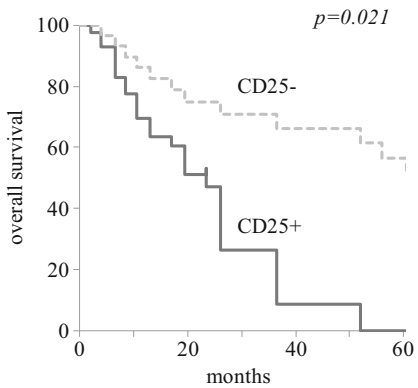
The presence of CNS relapse is a detrimental clinical feature because remission is rare and <10% of patients remain alive at 1 year [22]. In the present study, an advanced stage, higher R-IPI, higher CNS-IPI, and the presence of B symptoms were identified as predictive poor prognosis of DLBCL patients with CNS relapse. CNS-IPI was recently shown to be a robust and readily calculable risk estimate in patients with DLBCL; however, this model is not entirely accurate and has a low positive value (10–12%) [8]. Other factors including the involvement of other specific anatomic sites and biological factors, such as rearrangements in MYC and Bcl2/Bcl6, have been reported in separate studies as being predictive of CNS relapse and warrant specific consideration [8]. Although difficulties were associated with the analysis of data due to the small number of cases (3 cases of double- or triple-hit lymphomas) in the present study, previous studies suggested that the use of CNS prophylaxis is associated with the suppression of CNS progression and longer OS [23, 24].

The present results showed that CD25 expression was associated with poor prognosis of DLBCL patients with CNS relapse treated with R-CHOP. The univariate and multivariate analyses identified CD25+ and high-risk CNS-IPI as independent adverse prognostic factors for OS. CD25 is expressed in several hematological diseases and previous studies showed that the expression of CD25 was associated with aggressive clinical features and a poor prognosis in lymphoma [19, 20]. In the present study, an advanced stage, higher R-IPI, higher CNS-IPI, presence of B symptoms, and bone involvement correlated with CD25+. Furthermore, CD25+ was associated with an aggressive clinical course in DLBCL patients with CNS relapse.

The addition of rituximab to the CHOP regimen has been suggested to reduce the incidence of CNS relapse; however, other studies did not confirm these findings [25–27]. Although the present study from the R era cannot be directly compared with previous studies, we presumed that the incidence of CNS relapse has not decreased in the R era.

The intrathecal administration of methotrexate or cytarabine is a well-accepted method for CNS prophylaxis. The efficacy of CNS prophylaxis has been confirmed in patients with testicular involvement, but not at other extranodal sites [28, 29]. In the present study, the addition of rituximab and IT prophylaxis were inadequate strategies for the prevention of CNS relapse, particularly in CD25+ patients.

Optimal methods for the administration of CNS-directed prophylaxis have not yet been established. CNS relapse in DLBCL has a parenchymal component and the limited ability



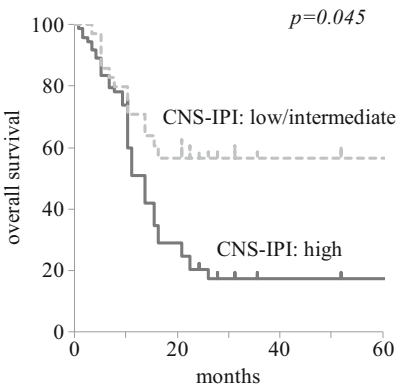


Fig. 2 **a** Kaplan-Meier analysis of overall survival (OS) in groups of DLBCL patients with CNS relapse based on risk stratifications by CD25 expression; the 5-years OS rate was significantly lower in CD25+ patients than in CD25- patients (23% vs. 68%, $p = 0.021$). **b** Kaplan-Meier analysis of overall survival (OS) in groups of DLBCL patients with CNS relapse based on risk stratification by CNS-IPI; the 5-years OS rate was significantly lower in high risk CNS-IPI patients than in low/intermediate CNS-IPI patients (18% vs. 57%, $p = 0.045$)

of cytotoxic drugs administered by IT injection to penetrate deep brain tissue is an issue, with information obtained to date suggesting a minimal impact on CNS progression [30, 31]. Phillips et al. showed a potential benefit from the early inclusion of high-dose MTX in the regimen for high-risk DLBCL [32]. Ibrutinib and lenalidomide were recently reported to cross the BBB and be active in CNS lymphomas [33, 34]. The addition of anti-CD25 immunotherapy may be useful for CD25+ patients. Further studies are needed to identify high-risk patients and develop better prophylactic strategies.

In conclusion, the present study showed that the expression of CD25 in DLBCL patients with CNS relapse was associated with patient prognosis independent of other prognostic factors. The establishment of a treatment strategy for patients with CD25+ lymphoma cells is needed to improve poor outcomes. Further studies are warranted to clarify the role of these markers in the pathogenesis of DLBCL with CNS relapse.

Compliance with Ethical Standards

Conflict of Interest Satoko Oka declares that she has no conflicts of interest in the present study.

Kazuo Ono declares that he has no conflicts of interest in the present study.

Masaharu Nohgawa declares that he has no conflicts of interest in the present study.

Human Studies This article does not contain any studies with human participants performed by any of the authors.

Informed Consent These patients provided their written informed consent to receive each regimens, and treatments were administered according to the principles of the Declaration of Helsinki and this study was approved by the institutional ethics committee.

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