Clinicopathologic characteristics, therapeutic modalities and survival outcomes of plasmablastic lymphoma: a real-world study

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Abstract

Introduction: Plasmablastic lymphoma (PBL), an extremely rare subtype of B-cell non-Hodgkin lymphoma (NHL), is characterized by aggressiveness, rapid progression and a bleak prognosis. Neither a standardized regimen nor a consensus for PBL treatment has been established.

Material and methods: We retrospectively analyzed the clinicopathologic characteristics, therapeutic modalities and survival outcomes of 418 patients registered in the Surveillance, Epidemiology, and End Results (SEER) database from 2008 to 2016 and 21 (19 treated) patients in our institution. Kaplan-Meier survival curves and the log-rank test for overall survival (OS) and disease-specific survival (DSS) were performed to compare each variable. Variables with statistical significance in the univariate Cox regression were incorporated into the multivariate Cox model to determine the independent prognostic factors.

Results: In the patient cohort from the SEER database, PBL has a striking male predilection. The median OS for all PBL patients was 17 months. The 1-year, 3-year and 5-year OS rates were 54.4%, 40.4% and 37.2% respectively. Patients who suffered from previous malignancy had a significant survival disadvantage compared to those without previous cancer. Patients with a higher Ann Arbor stage at diagnosis were at higher risk of death than those with a lower stage. Chemotherapy alone or chemotherapy combined with radiotherapy could significantly reduce the risk of death and extend the patients' survival, yielding a HR of 0.209 (95% CI: 0.152–0.288) and 0.187 (95% CI: 0.089–0.394), respectively. Radiation alone seemed useless. All patients from our institution were HIV-negative. The main therapeutic regimens were CHOP or CHOPE, DA-EPOCH, DHAP and ESHAP. A complete response (CR) was achieved in only 3 patients, while a partial response was achieved in 10 patients. The median OS was 7 months. Fourteen patients later died due to disease progression.

Conclusions: Previous malignancy history, Ann Arbor stage and therapeutic modality were independent prognostic factors. Bortezomib combined with DA-EPOCH may serve as an effective regimen for PBL. The optimal therapeutic modality necessitates further exploration.

Key words: plasmablastic lymphoma, therapeutic modality, prognosis, Surveillance, Epidemiology, and End Results.

Introduction

Plasmablastic lymphoma (PBL) is an extremely rare and distinct subtype of B-cell non-Hodgkin lymphoma (NHL) [1, 2]. PBL exhibits mixed morphological characteristics of diffuse large B-cell lymphoma (DLBCL) and multiple myeloma (MM) with its highly aggressive course and plasmacytic differentiation [3]. The cell origin of PBL is considered the post-germinal center B-lymphocyte or plasmablast. Although PBL cells usually express classic biomarkers of plasmacytic differentiation (CD38, CD138 and MUM1) such as MM and seldomly express B-lymphocyte differentiation markers (CD19, CD20, and PAX5), PBL bears a striking resemblance to DLBCL via genomic profiling [4]. It is often believed that PBL afflicts immunocompromised individuals, including those infected with human immunodeficiency virus (HIV), those receiving intense chemotherapy or radiotherapy for cancers, those undergoing organ or stem cell transplantation and those receiving immunosuppressive drugs [5–7]. Plasmablastic lymphoma was once regarded as a tumor that predominantly arose in patients with HIV-infection [8]. However, Castillo *et al.* reported 71 HIV-negative PBL patients with unique clinicopathological characteristics markedly distinct from their HIV-positive counterparts [9].

Plasmablastic lymphoma is notorious for resistance to chemotherapy, invasiveness and rapid progression. The CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone) serves as the first-line choice for the treatment of NHL. However, the National Comprehensive Cancer Network (NCCN) guidelines stipulate that standard CHOP seems 'inadequate and less intense' for PBL [10]. Despite the use of various regimens, the prognosis of PBL remains bleak. Owing to the rarity of PBL, previous publications mainly focus on clinical case reports or case series with a small sample size. Little is known about this rare hematological malignancy. What is worse, neither a standardized regimen nor a consensus for PBL treatment has been established yet. The objective of our study is to further explore the clinical characteristics, prognostic factors and therapeutic modality of PBL on a larger scale. Patients in our study derived from the Surveillance, Epidemiology, and End Results (SEER) database and our institution. We also discussed the recent therapeutic approaches and advances in PBL.

Material and methods

Patient data from the SEER database

Patient selection

Initially constructed by the National Cancer Institute of United States (US), the SEER database accounts for nearly 30% of the US population across 18 cancer registries and is completely available to the public via formal application. We obtained authorization to have access to the unidentified individual information. According to the International Classification of Disease for Oncology, 3rd edition (ICD-O-3), we retrieved the SEER database for PBL patients from 2008 to 2016 using the "9735/3: plasmablastic lymphoma" histology code in the "site and morphology ICD-O-3 histology/behavior, malignant" field. The patient data were downloaded using SEER*Stat Software (Version 8.3.6, http://www.seer.cancer.gov/seerstat).

The patient data include age at diagnosis, gender, race, primary anatomical site, Ann Arbor stage, previous malignancy history, survival months, vital status, cause of death and the first round of treatment modalities (chemotherapy or not, radiation or not). However, the detailed HIV infection status, immunohistochemical results, chemotherapy regimens, types of surgery, drug dosage and radiation dosage were not recorded in the SEER database. Patients without pathologically confirmed diagnosis or sufficient follow-up information were excluded.

Statistical analysis

Overall survival (OS) was determined from the time of diagnosis to death from any cause or the last follow-up. Disease-specific survival (DSS) was calculated from diagnosis to the date of death caused by PBL. Kaplan-Meier curves and the log-rank test for OS and DSS were conducted to compare each potential variable related to the prognosis. Variables with a p-value < 0.1 in the univariate Cox regression model were incorporated into the multivariate Cox model to determine the independent prognostic factors, with a hazard ratio (HR) > 1 indicating adverse factors. All tests were two-sided, with a p-value < 0.05 regarded as statistically significant. All statistical analyses were performed with SPSS Software (Version 26.0, IBM Corp., USA).

Patient group from our institution

We then retrospectively identified 21 PBL patients in our institution between Aug 2009 and Aug 2018. In accordance with the 2008 WHO classification of tumors of hematopoietic and lymphoid tissues, the pathological diagnosis was made through hematoxylin-eosin staining and immunophenotyping results.

Relevant clinical information of 21 PBL patients included age at diagnosis, gender, HIV infectious status, Eastern Cooperative Oncology Group performance status (ECOG-PS), Ann Arbor stage, international prognostic index (IPI), primary tumor locations, immunochemistry results, specific ther-

apeutic regimen, the best response to therapy and the final survival outcomes. Immunohistochemical studies were conducted on formalin-fixed, paraffin-embedded tissue sections by utilizing antibodies including CD138, CD38, CD10, CD20, CD79, PAX5, MUM1, CD30, CD56, BCL6, CD5, CD3, CD45 and Ki67. In situ hybridization (ISH) for EB virus-encoded small RNA (EBER) was also detected by employing a fluorescein-labeled peptide nucleic acid probe on the tissue sections.

Given the rarity of PBL and the small sample size from our institution, we consider it unreasonable to conduct a log-rank test or Cox regression analysis. Therefore, we only plotted an OS curve to demonstrate the patient survival outcomes.

Results

Patients from the SEER population registries

After rigorous identification, a total of 418 eligible patients were ultimately enrolled in our study. The flow diagram of the selection process is presented in Figure 1. The demographic and clinical characteristics of PBL patients are summarized in Table I. The median age at diagnosis was 56 years. PBL has a striking gender predilection for males, with the ratio of male to female patients being 3.5 : 1. Patients with B symptoms accounted for 23.68%. Nearly 18.7% of the patients had a previous history of other malignancies. However, the SEER database did not record the information on the HIV infection status. Only 6% of the patients received both chemotherapy and radiation at the initial diagnosis, while 66% received chemotherapy alone and 26.8% of patients were untreated.

The distribution of primary anatomical sites is presented in Table II. Of all the patients, 185 (44.26%) cases were detected within the lymph nodes and 233 (55.74%) cases suffered from extranodal infiltration. The most frequently involved extranodal site was the gastrointestinal tract

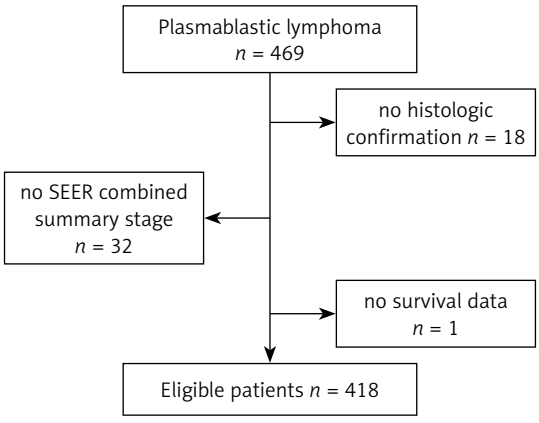

Figure 1. Flow chart of the selection process for the eligible patient cohort

Table I. Demographic and clinical characteristics of 418 patients from SEER database

Characteristics	Number	Percentage (%)
Age [years] (median):	56 (9–95)	
0–20	3	0.72
20–40	75	17.94
40–60	175	41.87
60–80	134	32.06
> 80	31	7.42
Gender:		
Male	325	77.75
Female	93	22.25
Race:		
White	323	77.27
Black	66	15.79
Others	29	6.94
Marital status:		
Married	166	39.71
Single	172	41.15
Divorced/separated/ widowed	56	13.40
Unknown	24	5.74
Primary site:		
Nodal	185	44.26
Extranodal	233	55.74
Ann Arbor stage:		
I	93	22.25
II	66	15.79
III	43	10.29
IV	153	36.60
Unknown	63	15.07
B symptoms:		
Yes	99	23.68
No	197	47.13
Unknown	122	29.19
Previous malignancy history:		
Yes	78	18.66
No	340	81.34
Therapeutic modality:		
Chemotherapy alone	276	66.03
Radiation alone	5	1.20
Chemotherapy + radiation	25	5.98
No treatment	112	26.79

(20.10%), followed by nasal cavity/paranasal sinuses (11.72%) and oral cavity, mouth and tongue (5.50%).

Some patients died promptly after the initial diagnosis due to the high aggressiveness and rapid progression of PBL. Therefore the follow-up time is very short. Other patients survived several years after the diagnosis. The follow-up time of patients varied considerably. As was revealed in the Kaplan-Meier curves of OS (Figure 2 A) and DSS (Figure 2 B), the median OS for all PBL patients was 17 months (95% CI: 10.3–23.7). The 1-year, 3-year and 5-year OS rates were 54.4%, 40.4% and 37.2%, respectively. The median DSS was not reached, and the 1-year, 3-year and 5-year DSS rates were 69%, 58.6% and 55%, respectively.

In the univariate assessment, marital status (p = 0.015), previous malignancy history (p = 0.003), primary site (p = 0.009), Ann Arbor stage (p = 0.001), therapeutic modality (p < 0.001) are the possible predictive factors of OS (Table III). Age, gender and race were not found to influence PBL prognosis. The predictors of DSS were similar to those of OS (Table III). Kaplan-Meier survival curves gave a vivid description of the association between various factors and OS (Figure 3) and DSS (Figure 4) of PBL patients. As revealed in Table IV, multivariate analysis verified that previous malignancy history, Ann Arbor stage and therapeutic modality were independent prognostic factors. Patients who suffered from previous malignancy had a significant survival disadvantage (HR = 1.444, 95% CI: 1.037–2.001) compared to those without previous cancer. Patients with a higher Ann Arbor stage at diagnosis were at higher risk of death than those with a lower stage. In terms of therapeutic modalities, chemotherapy alone or chemotherapy combined with radiotherapy could significantly reduce the risk of death and extend the patients' survival, yielding HR of 0.209 (95% CI: 0.152–0.288, p < 0.001) and 0.187 (95% CI: 0.089–0.394, p < 0.001), respectively. However, radiation alone without chemotherapy seemed useless.

Table II. Distribution of primary anatomic sites of plasmablastic lymphoma

Primary anatomic sites	Number	Percentage (%)
Nodal	185	44.26
Extranodal	233	55.74
Oral cavity, mouth, tongue	23	5.50
Nasal cavity and sinus	49	11.72
Gastrointestinal tract:	84	20.10
Stomach and esophagus	22	5.26
Small intestine	11	2.63
Colon, rectum, anus, cecum	51	12.20
Skin and connective tissue	19	4.55
Lung and pleura	8	1.91
Urogenital system	11	2.63
Bone	7	1.67
Central nervous system	9	2.15
Bone marrow	11	2.63
Other organs	12	2.87

Patients from our institution

We enrolled altogether 21 patients including 12 males and 9 females. The median age at diagnosis was 52 years. Clinical features and immunopheno-

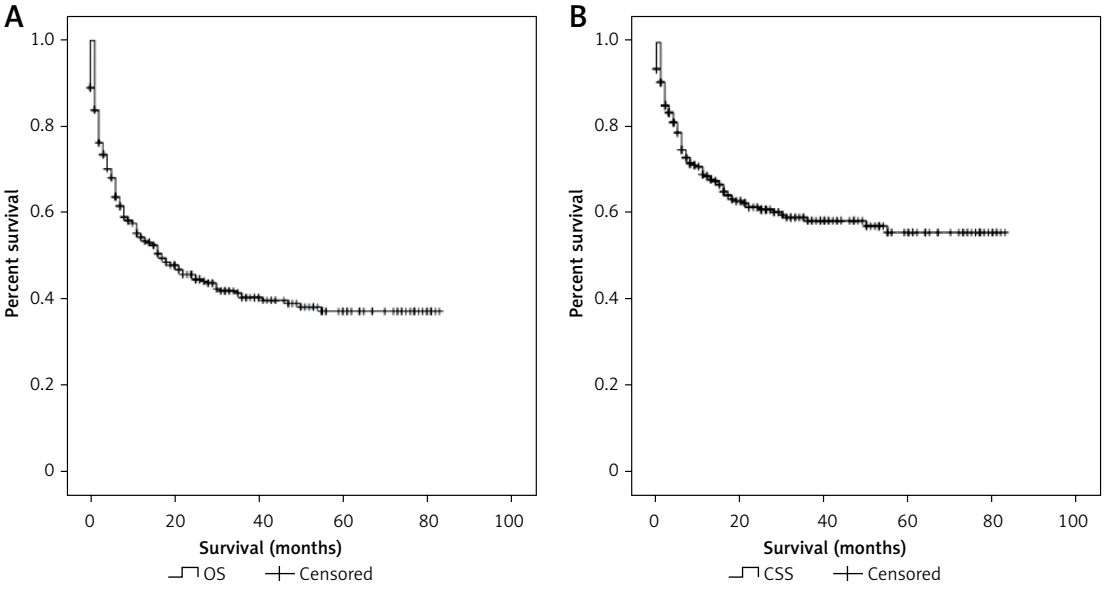

Figure 2. Kaplan-Meier curves of the whole eligible cohort: **A** – overall survival, **B** – disease-specific survival

Table III. Univariate Cox regression analysis of overall survival and disease-specific survival

Variables	Overall survival			Disease-specific survival		
	Median survival (95% CI)	Hazard ratio (95% CI)	*P*-value	Median survival (95% CI)	Hazard ratio (95% CI)	*P*-value
Age [years]:						
< 60	22 (12.7–31.3)	Reference	0.052	NA	Reference	0.718
> 60	11 (4.7–17.3)	1.3 (0.998–1.695)		NA	0.937 (0.66–1.332)	
Sex:						
Male	18 (9.6–26.4)	Reference		NA	Reference	
Female	13 (1.6–24.4)	1.13 (0.83–1.54)	0.43	NA	0.721 (0.46–1.13)	0.153
Race:			0.364			0.938
White	30 (17.5–NA)	Reference		NA	Reference	
Black	17 (7.3–41.1)	1.13 (0.80–1.60)	0.493	NA	1.229 (0.799–1.89)	0.349
Others	21.8 (4–55.2)	1.32 (0.80–2.18)	0.283	NA	0.879 (0.409–1.892)	0.742
Marital status:			**0.015**			**0.039**
Married	35 (8.2–61.8)	Reference		NA	Reference	
Single	21 (9.8–32.2)	1.192 (0.879–1.615)	0.258	NA	1.566 (1.055–2.325)	0.026
Divorced/ separated/ widowed	7 (4.4–9.6)	1.815 (1.232–2.674)	0.003	13	2.094 (1.261–3.478)	0.004
Previous malignancy history:						
No	21 (11.1–30.9)	Reference		NA	Reference	
Yes	8 (3.8–12.2)	1.61 (1.18–2.20)	**0.003**	NA	0.04 (0.006–0.285)	**0.001**
Primary site:						
Nodal	11 (6.5–15.5)	Reference		NA	Reference	
Extranodal	30 (18.5–41.5)	0.7 (0.54–0.91)	**0.009**	NA	0.68 (0.485–0.953)	**0.025**
Ann Arbor stage:			**0.001**			**0.044**
I	NA	Reference		NA	Reference	
II	16 (6.2–25.8)	1.69 (1.087–2.627)	0.02	NA	1.86 (1.048–3.299)	0.034
III	11 (3.6–18.4)	1.738 (1.064–2.840)	0.027	55	1.705 (0.884–3.288)	0.111
IV	8 (2.8–13.2)	2.005 (1.384–2.903)	< 0.001	30	2.245 (1.382–3.647)	< 0.001
B symptoms:						
No	25 (11.6–38.4)	Reference		NA	Reference	
Yes	15 (6.0–24.0)	1.256 (0.912–1.730)	0.163	NA	1.279 (0.857–1.909)	0.229
Therapeutic modality:			< 0.001			< 0.001
No treatment	2 (1.2–2.8)	Reference		6 (4.1–7.9)	Reference	
Chemotherapy alone	30	0.277 (0.21–0.367)	< 0.001	NA	0.282 (0.197–0.403)	< 0.001
Radiation alone	18 (0–39.5)	0.461 (0.169–1.259)	0.131	NA	0.191 (0.026–1.386)	0.102
Combined therapy	NA	0.151 (0.073–0.312)	< 0.001	NA	0.19 (0.081–0.444)	< 0.001

typical results of patients from our institution are presented in Table V. All patients were HIV-negative and were not in immunocompromised status. The tumor arose extranodally in 16 (76.2%) cases. Plasma cell marker positivity including CD38, CD138, and MUM1 was universally detected (81%, 90% and 85.7%, respectively), while CD20 and PAX5 negativity was detected in most cases (90.5% and 86.7%, respectively). The proliferation index Ki-67 was commonly high, ranging from 40% to 95% with 16 cases > 80%. EBER positivity was detected in 5 out of 17 cases (29.4%).

Detailed information on therapeutic regimen and survival outcomes is summarized in Table VI. The Kaplan-Meier plot for the whole group revealed that median OS was 7 months (Figure 5). The CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone) or CHOPE regimen

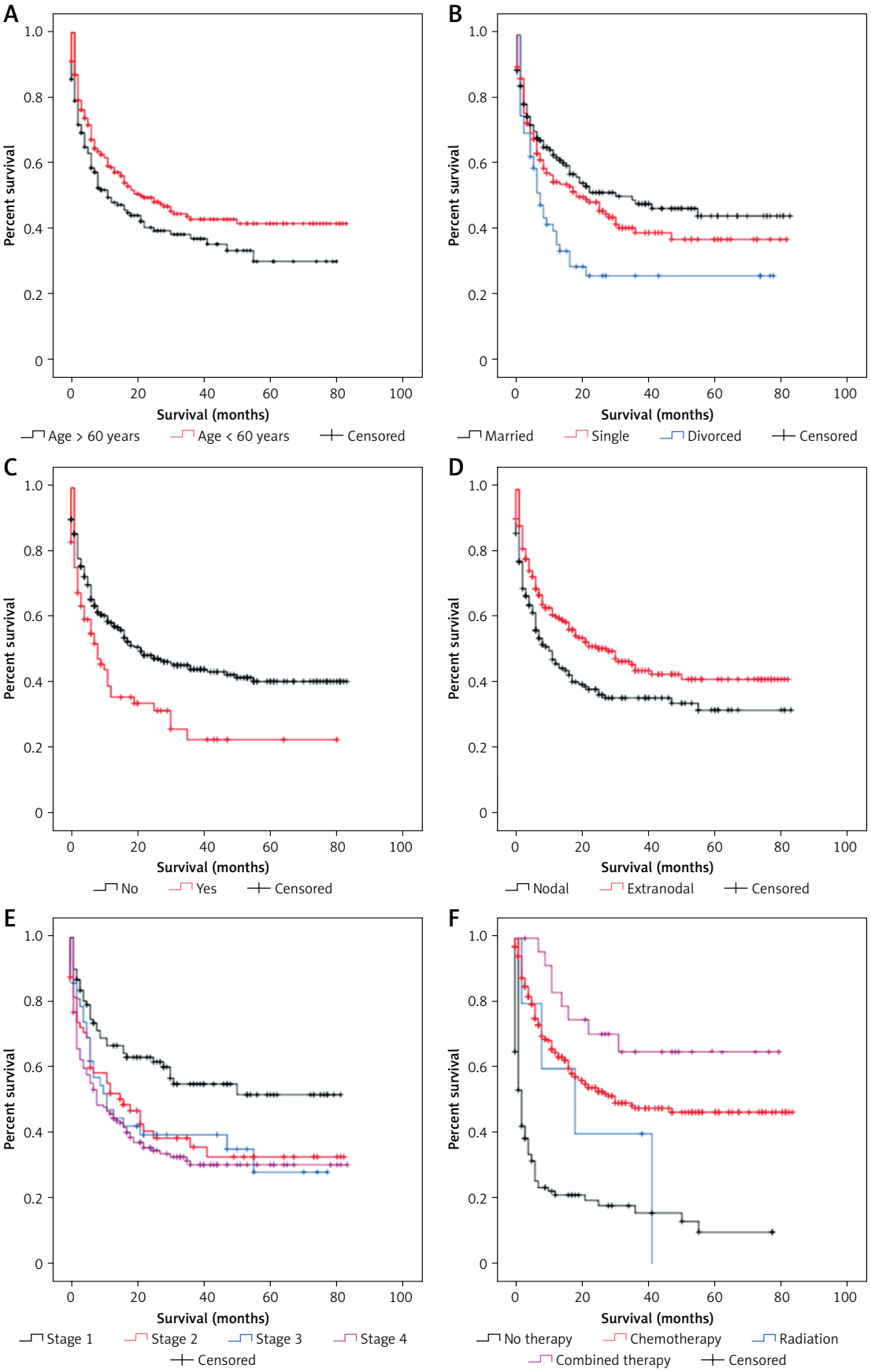

Figure 3. Kaplan-Meier estimate of overall survival by subgroup analysis: **A** – age, **B** – marital status, **C** – previous malignancy history, **D** – primary site, **E** – Ann Arbor stage, **F** – therapeutic modality

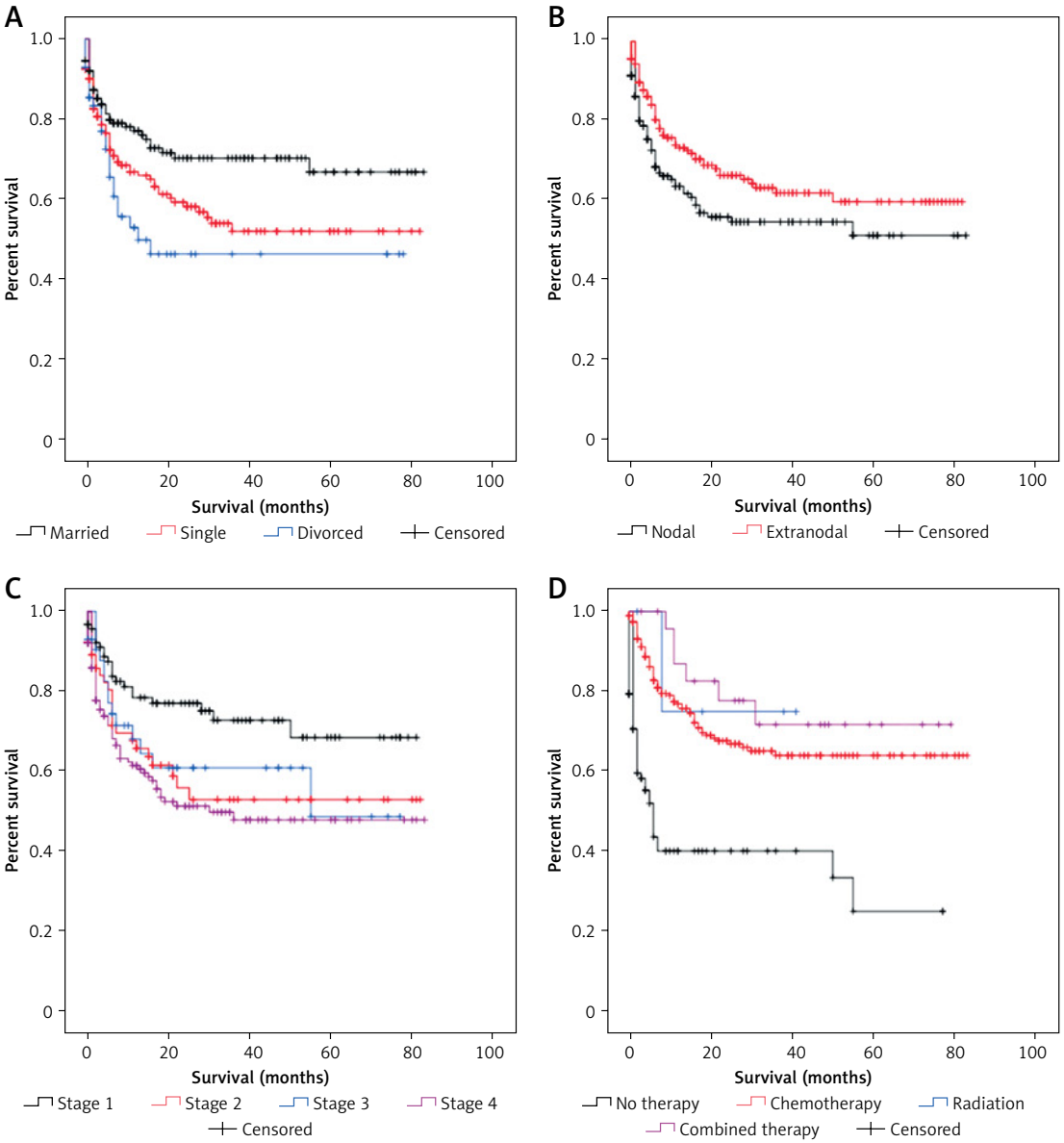

Figure 4. Kaplan-Meier estimate of disease-specific survival by subgroup analysis: **A** – marital status, **B** – primary site, **C** – Ann Arbor stage, **D** – therapeutic modality

(CHOP + etoposide) was selected as the first-line therapy for most patients. DA-EPOCH (dose-adjusted etoposide + doxorubicin + vincristine + cyclophosphamide + prednisone), DHAP (cisplatin + high-dose cytarabine + dexamethasone), DICE (cisplatin + ifosfamide + etoposide + dexamethasone), ESHAP (etoposide + methylprednisolone + high-dose cytarabine + cisplatin), GDP (gemcitabine + cisplatin + dexamethasone) and HyperCVAD/high-dose MTX/Ara-C (hyper-fractionated cyclophosphamide + vincristine + doxorubicin + dexamethasone alternating with methotrexate and cytarabine) were reasonable options. Regimens for the treatment of MM such as PAD (bortezomib + doxorubicin + dexamethasone), PCD (bortezomib + cyclophosphamide + dexamethasone), TAD (thalidomide + doxorubicin + dexamethasone), and MPT (melphalan + prednisone + thalidomide) were also administered. Only 1 patient who received autologous stem cell transplantation (ASCT) with thalidomide maintenance was still alive at the end of our study. A complete response (CR) was achieved in only 3 patients who were still alive at the study endpoint. A partial response (PR) was obtained in 10 patients. Efficacy was limited and transient in most patients. Fourteen patients later died due to disease progression.

Discussion

Initially described in the oral cavity of HIV-infected patients in 1997, PBL is characterized by

Table IV. Multivariate Cox regression analysis of overall survival and disease-specific survival

Variables	Overall survival		Disease-specific survival	
	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Marital status:				
Married	Reference		Reference	
Single	1.227 (0.875–1.720)	0.236	1.513 (1.003–2.282)	0.048
Divorced/separated/widowed	1.477 (0.987–2.209)	0.058	2.107 (1.253–3.544)	0.005
Previous malignancy history:				
No	Reference		/	
Yes	1.444 (1.037–2.011)	0.029	/	
Primary site:				
Nodal	Reference		Reference	
Extranodal	0.798 (0.598–1.065)	0.126	0.702 (0.483–1.019)	0.063
Ann Arbor stage:				
I	Reference		Reference	
II	1.54 (0.974–2.437)	0.065	1.651 (0.916–2.976)	0.096
III	1.644 (1.002–2.802)	0.048	1.614 (0.79–3.297)	0.189
IV	2.555 (1.688–3.867)	< 0.001	3.005 (1.745–5.173)	< 0.001
Therapeutic modality:				
No treatment	Reference		Reference	
Chemotherapy alone	0.209 (0.152–0.288)	< 0.001	0.188 (0.127–0.279)	< 0.001
Radiation alone	0.444 (0.16–1.233)	0.119	0.173 (0.023–1.275)	0.085
Combined therapy	0.187 (0.089–0.394)	< 0.001	0.201 (0.084–0.483)	< 0.001

male predominance, predilection for extranodal involvement and higher incidence among immunocompromised patients [8]. Highly active antiretroviral therapy (HAART) is oriented to kill HIV, which mainly includes stavudine in combination with lamivudine and nevirapine, zidovudine in combination with lamivudine and efavirenz, and emtricitabine in combination with tenofovir and Kaletra [11, 12]. Some case reports depicted the spontaneous regression of HIV-related PBL after use of HAART. However, a sustained CR could not be achieved and patients experienced early relapse [13, 14]. A study from the LYmphoma Study Association (LYSA) Group also verified that HAART alone without chemotherapy could not achieve a sustained CR [15]. The administration of HAART combined with chemotherapy is preferably recommended in HIV-positive patients.

With the increased understanding of PBL, we have come to realize that PBL also occurs in HIV-negative or other immunocompetent patients. All patients from our institution were HIV-negative and previously immunocompetent with a normal CD4+T cell count. HIV-positive and HIV-negative PBL are two strikingly distinct subentities with different clinicopathological characteristics. HIV-negative patients bore a bleaker prognosis, worse response to chemotherapy and shorter OS than HIV-positive patients [9, 15, 16]. Some cases with oral cavity involvement are associated with EB virus (EBV). The criteria for PBL diagnosis have varied over time. Some researchers rigorously defined coexistence of a lesion in the oral cavity and presence of HIV or EBV. But now the classification of PBL has been defined in a broader sense, in which morphology and immunophenotype correspond to B immunoblasts or plasma cells with EBV-negativity and extranodal involvement in other parts of the body [17].

We should make a reasonable differential diagnosis to tell apart anaplastic lymphoma kinase-positive large B-cell lymphoma (ALK+ LBCL), primary effusion lymphoma (PEL), Epstein-Barr virus-positive DLBCL, human herpes virus 8-positive DLBCL, intravascular large B-cell lymphoma (IVLBCL) and other specific variants of DLBCL [2, 18]. PBL is not always associated with EBV positivity. PBL exhibits a 'terminal B-cell differentiation' phenotypical feature with upregulation of plasma cell markers (CD138, CD38) and downregulation of B-cell markers. ALK-positive large B-cell lymphoma (ALK + LBCL) exhibits immunoblast-like or plasmablast-like features with prominent overexpression of ALK protein due to ALK translocation and prevalent positivity of plasma cell-associated markers [19, 20].

There has been no standard therapeutic regimen for PBL. Arora's *et al.* study reported that

Table V. Clinical features and immunophenotypical results of 21 patients with plasmablastic lymphoma in our institution

Patient	Gender	Age at diagnosis	ECOG-PS	Ann Arbor Stage	IPI score	Localization	HIV	ISH	Immunohistochemistry												
								EBER	CD138	CD38	CD10	CD20	CD79	PAX5	MUM1	CD30	CD56	BCL6	CD5	CD3	CD45	Ki67
1	Male	17	1	III A	1	Small intestine	–	+	+	+	–	–	–	–	+	–	–	ND	ND	–	ND	70
2	Female	37	1	IV B	2	Appendix	–	–	+	+	ND	–	–	ND	+	+	–	ND	ND	ND	ND	80
3	Male	77	1	II A	1	LN	–	–	+	+	–	–	–	–	+	–	–	–	ND	ND	–	60
4	Male	28	1	IV A	2	LN, spleen, bone marrow	–	–	–	+	–	–	+	+	–	ND	–	–	ND	ND	–	90
5	Male	46	1	IV B	3	LN, bone, bone marrow	–	–	+	+	–	+	+	–	+	ND	–	–	+	ND	+	40
6	Male	65	1	IV B	4	Oral cavity, bone marrow	–	+	+	+	–	–	+	–	+	ND	+	ND	ND	ND	–	90
7	Female	43	1	IV A	2	LN, nasal sinus and cavity, mediastinum	–	+	+	–	–	–	ND	–	+	ND	+	–	ND	+	–	80
8	Female	57	1	IV A	1	LN	–	–	+	+	–	–	–	–	+	–	ND	–	–	–	ND	75
9	Female	53	1	IV A	2	Vagina, liver, right kidney, pancreas,	–	ND	–	–	ND	–	–	–	+	–	–	ND	ND	–	–	70
10	Female	51	1	III B	2	LN	–	–	+	+	+	–	–	–	+	+	–	+	ND	–	+	83
11	Female	27	1	IV A	3	Stomach, lymph nodes	–	ND	+	+	ND	–	–	ND	+	ND	ND	ND	ND	–	–	80
12	Female	53	2	IV B	2	LN, breast	–	ND	+	+	–	–	+	–	+	–	–	ND	ND	–	+	80
13	Male	24	3	IV A	3	Vertebral column	–	–	+	–	+	–	–	+	–	–	–	ND	ND	–	–	90
14	Female	32	0	IV A	2	Stomach	–	ND	+	+	–	–	+	ND	+	ND	–	–	ND	–	ND	80
15	Female	62	3	IV B	4	Right kidney and adrenal gland, ureter	–	–	+	–	–	–	–	–	+	–	–	–	–	–	ND	95
16	Male	52	1	IV A	1	Right adrenal gland	–	+	ND	+	–	–	–	–	+	ND	–	ND	ND	–	–	90
17	Male	73	1	I A	1	Throat	–	–	+	+	+	–	–	–	+	–	+	ND	ND	–	+	80
18	Male	75	3	II A	3	Pleura	–	–	+	+	–	+	–	ND	–	–	–	ND	ND	–	ND	95
19	Male	67	1	IEA	1	Stomach	–	–	+	+	ND	–	–	ND	+	ND	+	ND	ND	ND	ND	90
20	Male	45	1	IVA	1	LN, gingiva	–	+	+	+	+	–	+	+	+	ND	–	–		–	–	95
21	Male	60	3	IV B	5	LN, kidney	–	–	+	+	ND	–	–	ND	+	+	–	ND	ND	–	ND	95

ECOG-PS – Eastern Cooperative Oncology Group performance score, LN – lymph nodes, ISH – in situ hybridization, ND – not determined.

Table VI. Therapeutic regimen and survival outcomes of 19 treated patients with plasmablastic lymphoma in our institution

Patient	Therapeutic regimen	Radiation	Surgery	Best response	Progression	Survival (months)	Status at last follow-up
1	CAD × 2 + CHOPE × 7	–	–	CR	CR	94	Alive
2	CHOPE × 6 + PAD × 3 + ASCT + TAD + Thal (maintenance)	–	–	CR	CR	89	Alive
3	CHOPE × 8 + MINE × 1 + TAD × 1	–	–	PR	PD	41	Dead of disease
4	CHOPE × 2 + ESHAP × 1 + VAD × 1	–	–	PD	PD	3	Dead of disease
5	HyperCVAD × 2 + CHOP × 1	–	–	PR	PD	3	Dead of disease
6	CHOP × 2 + MPT × 1	–	–	PD	PD	2	Dead of disease
7	CHOP × 2 + CHOPE × 4	–	–	PR	PD	6	Dead of disease
8	CHOP × 1 + CHOPE × 2 + DICE × 3	–	–	PR	PD	7	Dead of disease
9	CHOPE × 6 + Radiotherapy + MOPE × 1	+	–	PR	PD	10	Dead of disease
10	CHOPE × 9	–	–	PR	PD	7	Dead of disease
11	CHOP × 4 + CHOPE × 1 + ESHAP × 3 + DHAP × 1	–	–	PR	PD	9	Dead of disease
12	CHOPE × 2	–	–	PD	PD	2	Dead of disease
13	CHOP × 2	–	–	PD	PD	2	Dead of disease
14	CHOPE × 11 + MOPE × 1	–	–	PR	PD	12	Lost to follow-up
15	CVE × 1 + DA-EPOCH × 2 + PAD × 1 + VCD × 1	–	–	PD	PD	5	Dead of disease
16	No therapy in our center	NA	NA	NA	NA	NA	Lost to follow-up
17	No therapy in our center	NA	NA	NA	NA	NA	Lost to follow-up
18	CHOPE × 3 + CHOP × 3	–	–	PR	PD	6	Dead of disease
19	CHOP × 8 + Thal (maintenance)	–	–	CR	CR	50	Alive
20	CDOP × 5 + CHOPE × 3 + GDP × 1 + Thal (maintenance)	–	–	PR	PR	48	Alive
21	CHOP × 3	–	–	PD	PD	3	Dead of disease

ASCT – autologous stem cell transplantation, CAD – cyclophosphamide + doxorubicin + dexamethasone, CDOP – cyclophosphamide + liposomal doxorubicin + vincristine + prednisone, CHOP – cyclophosphamide + doxorubicin + vincristine + prednisone, CHOPE – cyclophosphamide + doxorubicin + vincristine + prednisone + etoposide, CVE – cyclophosphamide + vincristine + etoposide, DA-EPOCH – dose-adjusted etoposide + doxorubicin + vincristine + cyclophosphamide + prednisone, DHAP – cisplatin + high-dose cytarabine + dexamethasone, DICE – cisplatin + ifosfamide + etoposide + dexamethasone, ESHAP – etoposide + methylprednisolone + high-dose cytarabine + cisplatin, GDP – gemcitabine + cisplatin + dexamethasone, HyperCVAD – cyclophosphamide + doxorubicin + vincristine + dexamethasone, MINE – mitoxantrone + ifosfamide + etoposide, MOPE – mitoxantrone + vincristine + prednisone + etoposide, MPT – melphalan + prednisone + thalidomide, PAD – bortezomib + doxorubicin + dexamethasone, PCD – bortezomib + cyclophosphamide + dexamethasone, TAD – thalidomide + doxorubicin + dexamethasone, Thal – thalidomide, VAD – vincristine + doxorubicin + dexamethasone, CR – complete response, PD – progressive disease, PR – partial response, NA – not available.

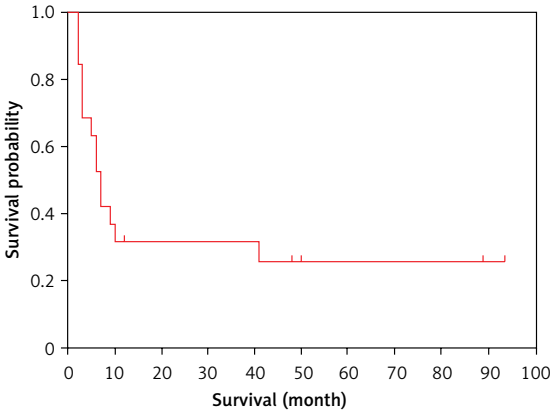

Figure 5. Overall survival of 19 plasmablastic lymphoma patients treated in our institution

median OS of the entire cohort was 15.9 months. The median OS for treated and untreated patients was 17.9 months and 0.9 months, respectively [21]. Despite the fact that the most commonly used regimen is CHOP or CHOP-like at present, the NCCN guidelines state that CHOP is 'inadequate and inefficient' and propose more intensive regimens including DA-EPOCH, HyperCVAD and CODOX-M/IVAC (cyclophosphamide, vincristine, doxorubicin, methotrexate/ifosfamide, etoposide, cytarabine) [10]. The MD Anderson center reported that patients who underwent the CHOP regimen tended to enjoy better OS compared with those who underwent the hyper-CVAD regimen (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone), which can be explained by the fact that hyper-CVAD is much more intense and possesses more "toxicity" than the CHOP regimen [22]. The efficacy of adding rituximab (a kind of anti-CD20 monoclonal antibody) to conventional chemotherapy remains obscure. We speculate that the addition of rituximab is unlikely to achieve clinical benefit as PBL cells scarcely express CD20 antigen. Several studies have shown that EPOCH displayed better efficacy and survival outcomes than CHOP, especially in highly aggressive B-cell NHL [23, 24]. Castillo *et al.* reported that 3 PBL patients achieved a durable CR to V-DAEPOCH (bortezomib in combination with dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) with OS of 12, 18, 24 months respectively [25]. Dittus *et al.* reported that the V-DAEPOCH regimen was efficacious and well tolerated in 8 PBL patients, achieving a CR rate of 100% and 2-year OS rate of 50% [26]. In 2018, Castillo *et al.* reported that among 16 patients who received the V-DAEPOCH regimen (range: 4–6 cycles), CR was observed in 15 patients and PR in 1 patient. The 5-year OS rate was 65%. Of the 5 dead patients, 3 died due to PBL progression and 2 died of infection [27]. The infusional EPOCH regimen resulted in long-lasting remission in 13 patients with extranodal involvement [28]. The above observations indicate that V-DAEPOCH is an effective and frontline therapeutic regimen for PBL.

Lenalidomide is a kind of immunomodulatory agent, which is widely used for MM treatment. The RCD regimen (lenalidomide in combination with cyclophosphamide and dexamethasone) was reported to successfully treat a stage IE HIV-negative PBL patient, achieving an at least 24 months' durable CR [29]. Similarly, an HIV-positive PBL was effectively treated with lenalidomide combined with CHOP [30].

A case-control study suggested that there was no significant difference in non-relapse mortality, 2-year disease-free survival and OS between HIV-positive and HIV-negative NHL patients who received ASCT. That is to say, HIV status does not influence the long-term outcome of ASCT for NHL [31]. Autologous stem cell transplantation during first CR after intensive induction therapy is a feasible solution to improve the PBL outcome [32]. Infusional EPOCH with subsequent consolidation ASCT in the eligible patients was recommended for treating HIV-associated PBL [33]. The European Society for Blood and Marrow Transplantation registry reported 24 PBL patients who underwent ASCT. Those who were autografted in CR showed a significantly decreased relapse risk and overall mortality risk [34]. ASCT warrants to be further investigated as first-line consolidation and salvage therapy for both HIV-positive and negative PBL patients especially in the absence of effective therapeutic options [35]. Nishi *et al.* reported that an HIV-negative woman with chemotherapy-refractory PBL had disease-free survival of more than 18 months after umbilical cord stem cell transplantation (UBSCT) [36].

PRDM1 gene mutation was frequently found in PBL and greatly augmented the oncogenicity of the MYC gene to enhance the proliferative activity by inducing MYC translocation or amplification. In a sense, PRDM1 mutations can be genetically regarded as a second hit in PBL and may become a therapeutic target in the future [37]. A recent study found that CD30 expression was pronounced in PBL tissue and will become a target with the potential use of brentuximab vedotin [38].

There were several inevitable defects in our study mainly owing to the inherent drawbacks of the SEER database. Firstly, the SEER registry is a population-based registry and does not record some important individual information, such as ECOG-PS, IPI, tumor size, immunohistochemistry results, FISH results, cytogenetic abnormalities, virus infection status and lactate dehydrogenase (LDH). Secondly, information concerning comorbidities, disease progression and relapse was not documented. Thirdly, the specific drug dosage and

radiation dose were not recorded in the SEER database. Whether PBL patients received ASCT was unknown from the SEER. What is more, dates of information retrieval spanned a long period of time, which witnessed the variations in diagnostic criteria and the advancement of therapeutic approaches. The high heterogeneity of PBL cannot be neglected as well. Lastly, research on patients from our institution involved a small sample size due to the scarcity of PBL.

In conclusion, PBL is an extremely rare and aggressive entity of B-cell NHL. Despite being initially reported in HIV-infected patients, PBL has also been identified in other immunocompetent patients. PBL has a male predilection. The cohort from the SEER database revealed that previous malignancy history, Ann Arbor stage, and therapeutic modality were independent prognostic factors. Bortezomib combined with DA-EPOCH may serve as an effective and frontline therapeutic regimen for PBL. Prospective clinical trials should also be further conducted to explore the efficacy and safety of novel agents including chimeric antigen receptor T cell (CAR-T) therapy, immune checkpoint inhibitors and other monoclonal antibodies for the treatment of PBL.

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Ethical approval

Before commencing this study, we obtained informed consent from patients or their next of kin (if the patients were dead) and official ethical approval from the institutional review board of the Fourth Military Medical University. The SEER database provides unidentified individual information and is totally available to the public after formal application. We received permission from the SEER program funded by the National Cancer Institute of the United States to gain access to the patient information.

Conflict of interest

The authors declare no conflict of interest.

References

1. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2016; 127: 2375-90.
2. Grimm KE, O'Malley DP. Aggressive B cell lymphomas in the 2017 revised WHO classification of tumors of hematopoietic and lymphoid tissues. Ann Diagn Pathol 2019; 38: 6-10.
3. Montes-Moreno S, Montalbán C, Piris MA. Large B-cell lymphomas with plasmablastic differentiation: a biological and therapeutic challenge. Leuk Lymphoma 2012; 53: 185-94.
4. Chang CC, Zhou X, Taylor JJ, et al. Genomic profiling of plasmablastic lymphoma using array comparative genomic hybridization (aCGH): revealing significant overlapping genomic lesions with diffuse large B-cell lymphoma. J Hematol Oncol 2009; 2: 47.
5. Morscio J, Dierickx D, Nijs J, et al. Clinicopathologic comparison of plasmablastic lymphoma in HIV-positive, immunocompetent, and posttransplant patients: single-center series of 25 cases and meta-analysis of 277 reported cases. Am J Surg Pathol 2014; 38: 875-86.
6. Castillo J, Pantanowitz L, Dezube BJ. HIV-associated plasmablastic lymphoma: lessons learned from 112 published cases. Am J Hematol 2008; 83: 804-9.
7. Liu M, Liu B, Liu B, et al. Human immunodeficiency virus-negative plasmablastic lymphoma: a comprehensive analysis of 114 cases. Oncol Rep 2015; 33: 1615-20.
8. Delecluse HJ, Anagnostopoulos I, Dallenbach F, et al. Plasmablastic lymphomas of the oral cavity: a new entity associated with the human immunodeficiency virus infection. Blood 1997; 89: 1413-20.
9. Castillo JJ, Winer ES, Stachurski D, et al. Clinical and pathological differences between human immunodeficiency virus-positive and human immunodeficiency virus-negative patients with plasmablastic lymphoma. Leuk Lymphoma 2010; 51: 2047-53.
10. Zelenetz AD, Gordon LI, Abramson JS, et al. NCCN guidelines insights: B-cell lymphomas, version 3.2019. J Natl Compr Canc Netw 2019; 17: 650-61.
11. Koizumi Y, Uehira T, Ota Y, et al. Clinical and pathological aspects of human immunodeficiency virus-associated plasmablastic lymphoma: analysis of 24 cases. Int J Hematol 2016; 104: 669-81.
12. Wang D, Zheng Y, Zeng D, et al. Clinicopathologic characteristics of HIV/AIDS-related plasmablastic lymphoma. Int J STD AIDS 2017; 28: 380-8.
13. Nasta SD, Carrum GM, Shahab I, Hanania NA, Udden MM. Regression of a plasmablastic lymphoma in a patient with HIV on highly active antiretroviral therapy. Leuk Lymphoma 2002; 43: 423-6.
14. Armstrong R, Bradrick J, Liu YC. Spontaneous regression of an HIV-associated plasmablastic lymphoma in the oral cavity: a case report. J Oral Maxillofac Surg 2007; 65: 1361-4.
15. Tchernonog E, Faurie P, Coppo P, et al. Clinical characteristics and prognostic factors of plasmablastic lymphoma patients: analysis of 135 patients from the LYSA group. Ann Oncol 2017; 28: 843-8.
16. Liu JJ, Zhang L, Ayala E, et al. Human immunodeficiency virus (HIV)-negative plasmablastic lymphoma: a single institutional experience and literature review. Leuk Res 2011; 35: 1571-7.
17. Cesarman E. Gammaherpesviruses and lymphoproliferative disorders. Annu Rev Pathol 2014; 9: 349-72.
18. Sukswai N, Lyapichev K, Khoury JD, Medeiros LJ. Diffuse large B-cell lymphoma variants: an update. Pathology 2020; 52: 53-67.
19. Pan Z, Hu S, Li M, et al. ALK-positive large B-cell lymphoma: a clinicopathologic study of 26 cases with review of

additional 108 cases in the literature. Am J Surg Pathol 2017; 41: 25-38.
20. Qunaj L, Castillo JJ, Olszewski AJ. Survival of patients with CD20-negative variants of large B-cell lymphoma: an analysis of the National Cancer Data Base. Leuk Lymphoma 2018; 59: 1375-83.
21. Arora N, Eule C, Gupta A, Li HC, Sadeghi N. Clinicopathologic features, management, and outcomes of plasmablastic lymphoma: a 10-year experience. Am J Hematol 2019; 94: E127-9.
22. Loghavi S, Alayed K, Aladily TN, et al. Stage, age, and EBV status impact outcomes of plasmablastic lymphoma patients: a clinicopathologic analysis of 61 patients. J Hematol Oncol 2015; 8: 65.
23. Barta SK, Lee JY, Kaplan LD, Noy A, Sparano JA. Pooled analysis of AIDS malignancy consortium trials evaluating rituximab plus CHOP or infusional EPOCH chemotherapy in HIV-associated non-Hodgkin lymphoma. Cancer 2012; 118: 3977-83.
24. Petrich AM, Gandhi M, Jovanovic B, et al. Impact of induction regimen and stem cell transplantation on outcomes in double-hit lymphoma: a multicenter retrospective analysis. Blood 2014; 124: 2354-61.
25. Castillo JJ, Reagan JL, Sikov WM, Winer ES. Bortezomib in combination with infusional dose-adjusted EPOCH for the treatment of plasmablastic lymphoma. Br J Haematol 2015; 169: 352-5.
26. Dittus C, Grover N, Ellsworth S, Tan X, Park SI. Bortezomib in combination with dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) induces long-term survival in patients with plasmablastic lymphoma: a retrospective analysis. Leuk Lymphoma 2018; 59: 2121-7.
27. Castillo JJ, Guerrero-Garcia T, Baldini F, et al. Bortezomib plus EPOCH is effective as frontline treatment in patients with plasmablastic lymphoma. Br J Haematol 2019; 184: 679-82.
28. Jayachandran PK, Rajan AK, Karunakaran P, et al. Plasmablastic lymphoma – single centre experience with infusional EPOCH chemotherapy. Leuk Res 2020; 95: 106391.
29. Schmit JM, DeLaune J, Norkin M, Grosbach A. A case of plasmablastic lymphoma achieving complete response and durable remission after lenalidomide-based therapy. Oncol Res Treat 2017; 40: 46-8.
30. Yanamandra U, Sahu KK, Jain N, Prakash G, Saikia U, Malhotra P. Plasmablastic lymphoma: successful management with CHOP and lenalidomide in resource constraint settings. Ann Hematol 2016; 95: 1715-7.
31. Krishnan A, Palmer JM, Zaia JA, Tsai NC, Alvarnas J, Forman SJ. HIV status does not affect the outcome of autologous stem cell transplantation (ASCT) for non-Hodgkin lymphoma (NHL). Biol Blood Marrow Transplant 2010; 16: 1302-8.
32. Al-Malki MM, Castillo JJ, Sloan JM, Re A. Hematopoietic cell transplantation for plasmablastic lymphoma: a review. Biol Blood Marrow Transplant 2014; 20: 1877-84.
33. Dunleavy K, Wilson WH. How I treat HIV-associated lymphoma. Blood 2012; 119: 3245-55.
34. Cattaneo C, Finel H, McQuaker G, Vandenberghe E, Rossi G, Dreger P. Autologous hematopoietic stem cell transplantation for plasmablastic lymphoma: the European Society for Blood and Marrow Transplantation experience. Biol Blood Marrow Transplant 2015; 21: 1146-7.
35. Balsalobre P, Díez-Martín JL, Re A, et al. Autologous stem-cell transplantation in patients with HIV-related lymphoma. J Clin Oncol 2009; 27: 2192-8.
36. Nishi K, Mitani S, Hatanaka K, Imada K. Successful cord blood transplantation for an HIV-negative patient with refractory plasmablastic lymphoma. Ann Hematol 2017; 96: 1057-8.
37. Montes-Moreno S, Martinez-Magunacelaya N, Zecchini-Barrese T, et al. Plasmablastic lymphoma phenotype is determined by genetic alterations in MYC and PRDM1. Mod Pathol 2017; 30: 85-94.
38. Witte HM, Hertel N, Merz H, et al. Clinicopathological characteristics and MYC status determine treatment outcome in plasmablastic lymphoma: a multi-center study of 76 consecutive patients. Blood Cancer J 2020; 10: 63.