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ORIGINAL PAPER

Primary central nervous system lymphoma in patients with and without HIV infection: a multicenter study and comparison with U.S national data

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Abstract

Purpose Primary central nervous system lymphoma (PCNSL) in patients living with HIV (PLWH) is a distinct entity; however, the management is adopted from patients without HIV. The study aims to examine the differences in presentation, treatment, and outcomes of PCNSL patients with or without HIV.

Methods We retrospectively compared the characteristics of 144 patients with PCNSL with and without HIV, and analyzed factors associated with overall and progression-free survival. Results were compared to the Central Brain Tumor Registry of the United States (CBTRUS) and the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) system.

Results Among all patients with PCNSL, 19% had HIV. PLWH were younger (38 vs. 63 years; $p < 0.01$) and more likely to be African American (59% vs. 7%; $p < 0.01$) and male (74% vs. 49%; $p = 0.02$) than patients without HIV. PLWH were more likely to have multiple lesions (67% vs. 43%; $p = 0.02$), hemorrhage (59 vs. 37%; $p = 0.03$), and peripheral rim enhancement (57% vs. 7%; $p < 0.01$) on imaging; to receive palliative care (15% vs. 2%) or whole brain radiation (63% vs. 3%); and less likely to receive chemotherapy (22% vs. 95%) ($p < 0.01$). Twenty-four patients, none PLWH, underwent stem cell transplant. Not receiving transplant was an independent factor in mortality and disease progression. Our cohort of patients, compared to the national database, were younger (60 vs. 65 years), 58% were white vs. 75%, and had longer median overall survival 43 vs. 25 months.

Conclusion Epidemiology, imaging, and treatment options for patients with PCNSL with and without HIV differ, but HIV was not an independent factor of mortality or disease progression. More efforts are needed to improve access to research and treatment options for PLWH with PCNSL.

Keywords Primary central nervous system lymphoma · HIV · Stem cell transplant · Incidence · Prognosis · Treatment

Introduction

Primary central nervous system lymphoma (PCNSL) is a rare form of non-Hodgkin lymphoma confined to the central nervous system (CNS). The majority (90–95%) of PCNSLs are classified as diffuse large B-cell lymphoma (DLBCL). The incidence of PCNSL has increased in recent years in the United States (US) [1]. Most of the cases are sporadic. A subset of cases is attributable to immunosuppressed states, including human immunodeficiency virus (HIV) infection or iatrogenic immunosuppression [2]. HIV-associated PCNSL is a distinct entity, almost exclusively associated with Epstein-Barr virus (EBV) in the cerebrospinal fluid (CSF) or brain tissue. The incidence inversely correlates with CD4 cell counts and has declined with the increased use of antiretroviral therapy (ART) [3].

The diagnosis of PCNSL is challenging, especially in patients living with HIV (PLWH) [4]. EBV-DNA testing by polymerase chain reaction (PCR) in the CSF or by immunohistochemistry has a sensitivity of 58–100% and a specificity of 93–100% [5–7]. The features of PCNSL on neuroimaging might overlap with those of malignant and

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non-malignant brain tumors as well as other CNS lesions [8, 9]. Histopathologic examination of tissue obtained through biopsy is essential for definitive diagnosis [10].

Many prognostic markers have been reported in patients with PCNSL. The most relevant are poor performance status and advanced age [11]. Male sex, HIV infection, and African American race have been reported as independent predictors of mortality [12]. Other potential prognostic factors include B-symptoms (fever, weight loss, or night sweats) and CSF cytology positive for lymphoma [11]. High-expression of biomarkers BCL2, BCL6, and Ki67 proliferation index by immunohistochemistry has also been reported to correlate with poor clinical outcomes [13]. In HIV-associated PCNSL, survival correlates with CD4 count and HIV RNA viral load [14]. There are two prognostic score tools for PCNSL, the International Extranodal Lymphoma Study Group Experience (IELSG), and the Memorial Sloan Kettering Cancer Center (MSKCC). These have not been validated in patients with HIV-associated PCNSL.

The optimal treatment for PCNSL is still not defined. High-Dose methotrexate (MTX)-based polychemotherapy regimen has prolonged survival and is currently considered the most effective treatment and the standard of care [10]. The role of intrathecal chemotherapy and whole brain radiation therapy (WBRT) is unclear. Most recently, high-dose chemotherapy followed by autologous stem cell transplant (SCT) as consolidative therapy has shown promising results [2, 15]. Given that HIV infection is typically an exclusion criterion for most prospective treatment trials of patients with PCNSL, therapy for PLWH has been empirically adopted from the treatment of PCNSL in immunocompetent patients [16]. Some previous studies have shown that chemotherapy combined with ART is feasible and safe and has prolonged the survival of patients with HIV and PCNSL. However, these studies were limited by their design and by small sample sizes [17]. Moreover, despite evidence suggesting that patients with systemic non-Hodgkin lymphoma might have a different prognosis than patients with PCNSL, the overall survival (OS) was similar between HIV-positive and HIV-negative patients after the introduction of ART [6, 18]. Several small studies reported successful outcomes with autologous SCT for the treatment of AIDS-related lymphomas [19]. No recent study has examined the differences in clinical characteristics, prognosis, and clinical outcomes between patients with PCNSL with or without HIV infection in the era of widespread use of ART. In addition, it is unclear whether having an HIV infection should influence the treatment options for patients PCNSL.

The study aimed to compare the presentation, treatment, and outcomes of PCNSL patients with or without HIV. To accomplish this, we evaluated the clinical characteristics, magnetic resonance imaging (MRI) findings, prognostic markers, management, and clinical outcomes in patients with PCNSL with and without HIV infection. We also compared our study results to PCNSL cases during the period 2000 to 2014 from the Central Brain Tumor Registry of the United States (CBTRUS) and the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) system.

Materials and methods

Study design and patient population

We conducted a retrospective study of patients in whom PCNSL was diagnosed at The University of Texas MD Anderson Cancer Center between March 2000 and May 2017 or Ben Taub Hospital (BTH), the largest publicly funded hospital in Houston, Texas, between January 2012 and December 2016. PCNSL patients at MD Anderson were identified by utilizing the garglab search engine [20] and at BTH by utilizing discharge and radiology diagnostic reports. The study cohort comprised adult patients aged 18 years and older with PCNSL presenting to MD Anderson or BTH during the respective study period. We reviewed the medical records to verify that the study patients had no evidence of systemic lymphoma as confirmed by whole-body computed tomography (CT) or positron emission tomography (PET) scan and bone marrow biopsy. Patients with diffuse lymphoma with CNS involvement or relapse in the CNS, patients with no biopsy-proven CNS lymphoma, and patients who had no preoperative brain MRI for analysis were excluded.

Study variables

We reviewed medical records and collected information on the following variables: socio-demographic characteristics, HIV status, CD4 count, HIV RNA viral load, ART received (when applicable), hepatitis C virus antibody and RNA viral load, date of PCNSL diagnosis, presenting symptoms, laboratory data, results of CSF analysis, and ophthalmologic findings. The results of the biopsy, histologic examination, and immunohistochemistry were noted. Radiographic characteristics at the time of diagnosis were recorded and verified by a neuro-radiologist. The IELSG prognostic score includes age more than 60 years, Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2, elevated lactate dehydrogenase (LDH) level, high CSF protein, and location of any lesion within the deep brain structures (periventricular, basal ganglia, brainstem, and/or cerebellum). Because of wide variability in treatment modalities, we divided therapeutic strategies into five groups: (i) supportive care, (ii) WBRT only, (iii) MTX monotherapy,

(iv) MTX-based combination therapy, and (v) MTX-based chemotherapy and WBRT. We also reported whether the patient had undergone autologous SCT.

Clinical outcomes

We analyzed two primary endpoints for patients from MD Anderson and BTH: the OS in months as the time from the date of PCNSL diagnosis to death of any cause and the progression-free survival (PFS) in months from the date of PCNSL diagnosis to progression, relapse, or death from any cause. Date of death and date of the last follow-up were recorded from the medical records. Patients who survived or were lost to follow-up were censored at the time of last follow-up visit.

Comparison with the national data

To compare our results with the national data, we retrieved PCNSL cases during the period from 2000 to 2014 from the CBTRUS and the SEER systems [21, 22]. CBTRUS data are derived from 51 central cancer registries (50 state registries and the District of Columbia) and represent ~ 99.9% of the US population, including Texas. SEER data are a subset of the registries covered by CBTRUS and represent ~ 28% of the US population, including California, Connecticut, Hawaii, Georgia, Iowa, New Mexico, Kentucky, Louisiana, Utah, New Jersey, Seattle-Puget Sound, and Detroit [21, 23, 24]. Survival data are not available for CBTRUS, and thus only SEER data were used for survival analyses. PCNSL cases were identified using the International Classification of Diseases for Oncology (ICD-O), 3rd edition. Cases with ICD-O-3 site codes C71 (Brain only) and ICD-O-3 histology codes 9590, 9591, 9596, 9670, 9671, 9673, 9675, 9680, 9684, 9687, 9690, 9691, 9695, 9698, 9699, 9701, 9702, 9705, 9714, 9719, 9728, or 9729 were selected as PCNSL. Since the CBTRUS and SEER databases do not include HIV status, it was not possible to stratify these patients by HIV status. Therefore, all PCNSL cases from MD Anderson and BTH were pooled for comparison with SEER data, regardless of HIV status. SEER cases were limited to those with histologically confirmed diagnosis and excluded those diagnosed at autopsy.

Statistical analysis

Frequencies were used to describe categorical data. Continuous measures were reported as medians and interquartile ranges (IQR). Patients with and without HIV infection were compared by using the Chi-square and Fisher exact tests when applicable. For continuous variables, we used the independent-samples *t* test or Mann–Whitney *U* test to evaluate the difference between the two groups. The accompanying *p* value was used to evaluate statistical significance, defined as $p < 0.05$. Kaplan–Meier survival analyses and Cox proportional hazards models were used to identify predictors of OS and PFS. The significance of predictors in Kaplan–Meier analyses was assessed using log-rank tests. In the Cox proportional hazards model, factors with a p value ≤ 0.1 in univariate analysis were included. Statistical analyses were done using SPSS version 24 (IBM SPSS, Inc. Chicago, IL), R 3.4.3, and SEER*Stat 8.3.5 [25, 26].

The study protocol, including a waiver of individual consent for medical record review, was approved by the institutional review boards of MD Anderson Cancer Center and Baylor College of Medicine and affiliated hospitals, which include BTH.

Results

Patient demographic characteristics

We identified 144 patients with PCNSL who met all the inclusion criteria, 38 (26%) from BTH and 106 (74%) from MD Anderson. Among this cohort, 27 patients (19%) had HIV infection. The median age at presentation was 60 years (IQR 49–68) and 77 (53%) were males. Eighty-three patients (58%) were non-Hispanic white, 31 (22%) were Hispanic, 24 (17%) were African American, and 5 (3%) were Asian. PLWH were significantly younger (median age 38 years vs. 63 years; $p < 0.01$) and were more likely to be African American (59% vs. 7%; $p < 0.01$), male (74% vs. 49%; $p = 0.02$), and to have their PCNSL diagnosed at BTH (89% vs. 12%; $p < 0.01$) than patients without HIV (Table 1).

Clinical, radiographic, and prognostic characteristics

At the time of diagnosis, the most common presenting symptoms and signs were focal neurological deficits ($n = 42$; 29%), cognitive and behavior changes ($n = 41$; 28%), and signs of increased intracranial pressure ($n = 31$; 21%). In addition, 21 patients (15%) had B-symptoms (weight loss, fever, or night sweats), 13 (9%) had ocular involvement, and only 2 (1%) had leptomeningeal involvement. There was no significant difference in clinical presentation between patients with or without HIV infection. The ECOG score was the most widely used evaluation of performance status at presentation; PLWH had a significantly higher rate of ECOG scores ≥ 2 (81% vs. 30%; $p < 0.01$) (Table 1).

Among PLWH ($n = 27$), only 8 patients were on ART, 23 patients (85%) had an initial CD4 count < 200 cells/μL, and 20 patients (74%) had a detectable HIV viral load at the time of PCNSL diagnosis. Seventeen of the patients with HIV infection underwent EBV PCR analysis of the CSF; of those, 10 had a positive result (59%). PLWH were significantly

Table 1 Baseline characteristics of all patients, HIV-positive patients, and HIV-negative patients with PCNSL at MD Anderson/BTH ($N=144$) in comparison with the national data (CBTRUS/SEER)

Variable	MDA/BTH				National data	
	All patients ($N=144$)	HIV positive ($n=27$, 19%)	HIV negative ($n=117$, 81%)	p value	CBTRUS ($n=16{,}783$)	SEER ($n=4693$, 28% of CBTRUS)
Treatment location				0.001	–	–
BTH	38 (26%)	24 (89%)	14 (12%)		–	–
MD Anderson	106 (74%)	3 (11%)	103 (88%)		–	–
Median age at PCNSL diagnosis, years (IQR)	60 (49–68)	38 (33–49)	63 (55–70)	0.001	65 (53–74)	65 (52–75)
Sex						
Male	77 (53%)	20 (74%)	57 (49%)	0.02	8,735 (52%)	2,505 (53%)
Female	67 (47%)	7 (26%)	60 (51%)		8,048 (48%)	2,188 (47%)
Race/ethnicity				0.001		
Non-Hispanic white	83 (58%)	3 (11%)	80 (69%)		12,580 (75%)	3115 (66%)
African American	24 (17%)	16 (59%)	8 (7%)		1562 (9%)	384 (8%)
Hispanic	31 (22%)	8 (30%)	23 (20%)		1694 (10%)	689 (15%)
Asian	5 (3%)	0	5 (4%)			
Clinical presentation				0.15		
Focal neurologic deficit	42 (29%)	7 (26%)	35 (30%)		–	–
Cognitive and/or behavior changes	41 (28%)	9 (33%)	32 (28%)		–	–
Signs of increased ICP[a]	31 (22%)	3 (11%)	28 (24%)		–	–
Seizure	8 (6%)	4 (15%)	4 (3%)		–	–
Other or mixed symptoms	22 (15%)	4 (15%)	18 (15%)		–	–
B-symptoms[b]				0.55		
Yes	21 (15%)	5 (18%)	16 (14%)		–	372 (13%)
No	123 (85%)	22 (82%)	101 (86%)		–	2,517 (87%)
Not documented	0 (%)	0 (%)	0 (%)		–	681 (23%)
ECOG performance status				0.001		
< 2	86 (60%)	5 (19%)	81 (70%)		–	–
≥ 2	57 (40%)	22 (81%)	35 (30%)		–	–
Imaging findings						
Number of brain lesions						
Solitary lesion	76 (53%)	9 (33%)	67 (57%)	0.02	–	–
Multiple lesions	68 (47%)	18 (67%)	50 (43%)		–	–
Median number of lesions (IQR)	1 (1–3)	3 (1–6)	1 (1–2)	0.04	–	–
Mean size of the tumor, cm (SD)[c]	3.7 (1.5)	3.6 (1.7)	3.7 (1.5)	0.7	–	–
Involvement of deep brain structures[d]	69 (48%)	14 (52%)	55 (47%)	0.6	3,340 (20%)	938 (20%)
Location brain, NOS	–	–	–		5237 (31%)	1455 (31%)
Solid enhancement	122 (85%)	12 (44%)	110 (94%)	0.001	–	–
Rim enhancement	23 (16%)	15 (57%)	8 (7%)	0.001	–	–
Presence of hemorrhage	59 (41%)	16 (59%)	43 (37%)	0.03	–	–
IELSG prognostic score[e]				0.26		
0–1	23 (24%)	2 (11%)	21 (27%)		–	–
2–3	66 (67%)	16 (84%)	50 (63%)		–	–
4–5	9 (9%)	1 (5%)	8 (10%)		–	–

BTH Ben Taub Hospital, *ECOG* Eastern Cooperative Oncology Group, *ICP* intracranial pressure, *IELSG* International Extranodal Lymphoma Study Group Experience, *NOS* not otherwise specified, *PCNSL* primary CNS lymphoma

[a]Signs of increased ICP (headache, vomiting, and papilledema)

[b]B-symptoms (fever, weight loss > 10% in 6 months, drenching night sweats). SEER data are available for cases after 2004 only

[c]In patients with multiple lesions, the size of the largest lesion was included in the analysis

[d]Deep brain structures include periventricular regions, basal ganglia, brainstem, and/or cerebellum

[e]IELSG score was calculated only if all values of the score were available ($n=98$)

more likely to have elevated serum LDH level than patients without HIV based on the upper limit at each institution (68% vs. 36%; $p < 0.01$). CSF cytology was positive for malignancy in 15% of patients in whom it was measured ($n = 14/96$); CSF protein concentration was elevated in 59% ($n = 59/100$); these proportions did not differ significantly between the groups with and without HIV infection.

Histopathologic diagnosis was obtained by stereotactic brain biopsy in most cases (67%), by partial resection (26%), or by complete resection of the brain tumor (7%). The most common histopathologic diagnosis was DLBCL, in 93% of the cases. Thirty patients (21%) had overexpression of BCL2, 45 (31%) had overexpression of BCL6, and 33 (23%) had a Ki67 index ≥ 90. PLWH were less likely to have BCL6 overexpression than patients without HIV (11% vs. 36%; $p = 0.01$). There was no significant difference between the two groups for expression of BCL2 and Ki67 index.

The most common location of brain lesions was the cerebral hemisphere ($n = 85$, 59%), followed by cerebellum and brain stem ($n = 20$, 14%), basal ganglia and thalamus ($n = 19$, 13%), corpus callosum ($n = 14$, 10%), and other locations ($n = 6$, 4%). PLWH were more likely to have multiple lesions by imaging than patients without HIV infection (67% vs. 43%; $p = 0.02$). Additionally, PCNSL lesions in PLWH were more likely to demonstrate hemorrhage (59 vs. 37%; $p = 0.03$) and peripheral rim enhancement (57% vs. 7%; $p < 0.01$) on imaging, whereas PCNSL lesions in patients without HIV infection more often exhibited solid enhancement (94% vs. 44%; $p < 0.01$). The tumor location and the size of the tumor were not significantly different in patients with or without HIV infection (Table 1).

Sixty-six patients (67%) had an IELSG score of 2–3. IELSG prognostic scores did not differ significantly between patients with or without HIV infection (Table 1).

Management

After diagnosis, 24 of 27 patients with HIV (89%) were started on ART; among those, 13 (50%) achieved viral suppression within a 6-month follow-up period. Among all, 144 patients identified with PCNSL, 6 patients (4%) presented with advanced disease and received only supportive care, 21 patients (15%) received only WBRT because they were deemed not candidates for systemic chemotherapy, and 117 patients (81%) had MTX-based chemotherapy, as monotherapy (7%), MTX-based combination chemotherapy (62%), or in combination with WBRT (12%) (Fig. 1a). PLWH were more likely to receive palliative care (15% vs. 2%) or WBRT as sole treatment (63% vs. 3%) and less likely to receive chemotherapy (22% vs. 95%) ($p < 0.01$) (Fig. 1b, c). Twenty-four patients (21%), all without HIV infection, underwent high-dose induction chemotherapy followed by autologous SCT.

Predictors of clinical outcomes

In univariate analysis, patients with poor performance status at presentation (ECOG score ≥ 2 as compared to < 2) and patients with higher IELSG prognostic scores had significantly shorter PFS as well as shorter median OS. Other factors associated with significantly shorter median OS included identification of hemorrhage on imaging, positive HIV status, and the institution where treatment was received (Table 2). Survival outcome and disease progression were also significantly associated with treatment modalities. Median OS was 1 month for patients who did not receive treatment, 24 months for patients who received WBRT alone, as compared to 47 months for patients who received chemotherapy ($p < 0.01$). Median PFS was 1 month for patients who received only supportive care, 18 months with WBRT alone, and 36 months for patients who had chemotherapy ($p < 0.01$). Patients who underwent SCT as compared to no transplant had significantly longer OS and PFS (Table 2).

After adjusting for age, HIV status, treatment site, ECOG and IELSG scores, initial treatment, autologous SCT, and presence of hemorrhage on imaging in the Cox proportional hazards model, only treatment modalities had an impact on clinical outcomes. Not receiving SCT (hazard ratio 3.4, 95% confidence interval [CI] 1.2–11.4; $p = 0.04$) was an independent factor in mortality and the only predictor of disease progression after controlling for other variables (hazard ratio 4.9, 95% CI 1.5–16.8; $p = 0.01$). The hazard ratios of death were for WBRT, 0.06 (95% CI 0.01–0.7; $p = 0.02$), and for chemotherapy with or without WBRT, 0.05 (95% CI 0.01–0.5; $p = 0.01$), as compared to no treatment. HIV infection was not associated with shorter OS or PFS in multivariate analysis (Table 3). Kaplan–Meier plots are presented in Fig. 2. In a subset analysis, excluding patients who did not receive treatment, patients who received a SCT were less likely to die (hazard ratio 0.3, 95% CI 0.08–0.83; $p = 0.04$) and to have disease progression (hazard ratio 0.2, 95% CI 0.1–0.7; $p = 0.01$). There was no difference in overall and progression-free survival in patients who received chemotherapy with or without WBRT when compared to WBRT alone.

Comparison with the SEER and CBTRUS data

A total of 16,783 CNS lymphoma cases were identified in CBTRUS between 2000 and 2014, and 4,693 of these cases (28%) had outcome data available in SEER. Overall annual average age-adjusted incidence (IR) of PCNSL during the period 2000–2014 was 0.48 per 100,000 population (95% CI 0.48–0.49), with an average of 1,199 cases diagnosed per year. Incidence was higher in males than in females (IR = 0.55, 95% CI 0.54–0.56 vs. IR = 0.42, 95% CI 0.42–0.43, incidence

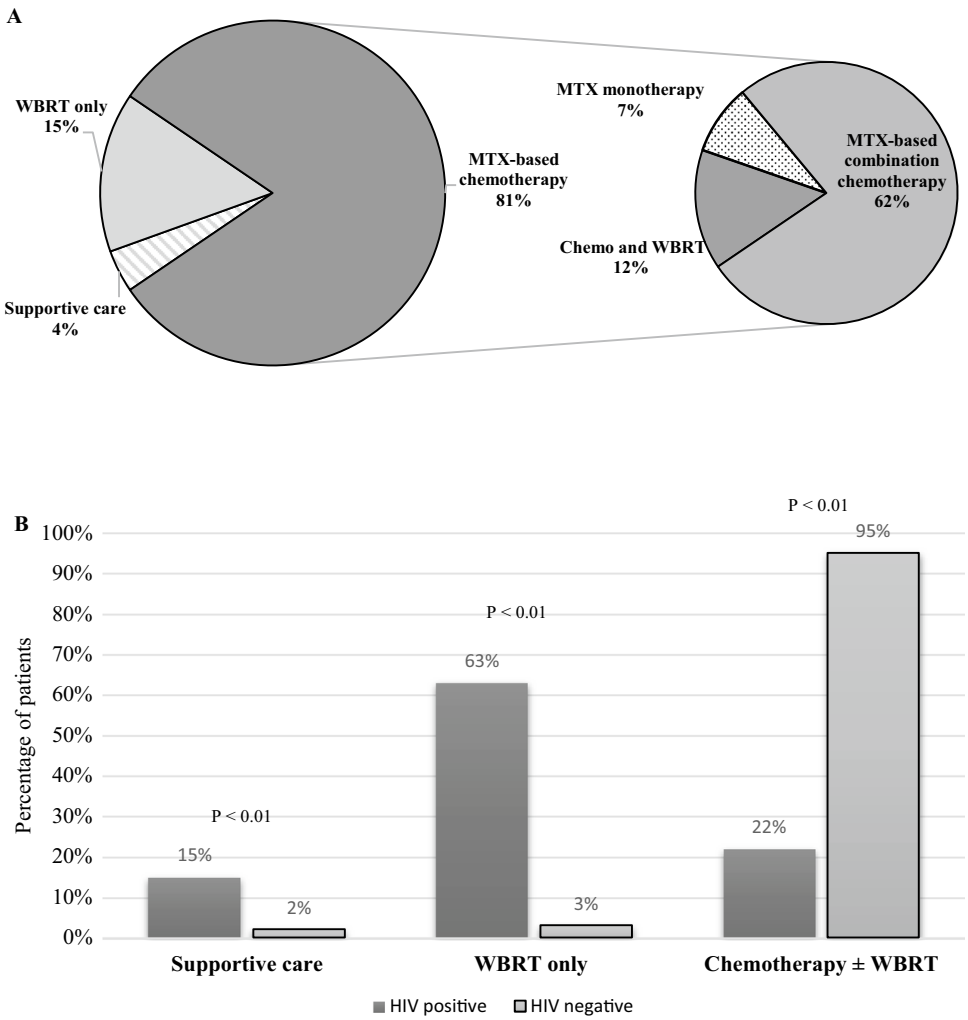

Fig. 1 Initial induction therapy: **a** initial induction therapy for all patients ($N=144$); **b** comparison of initial induction therapy for PLWH ($n=27$) and for patients not known to have HIV ($n=117$). *MTX* methotrexate, *WBRT* whole brain radiation therapy

rate ratio [IRR] = 1.31). Hispanic persons had the highest incidence of CNS lymphoma (IR = 0.53, 95% CI 0.50–0.56), higher than non-Hispanic white and African American persons (IR = 0.47, 95% CI 0.46–0.47, IRR = 1.13 and IR = 0.41, 95% CI 0.39–0.43, IRR = 1.29, respectively). National median age at diagnosis was 65 years, and 52% of cases were in men, as compared to 60 years and 53% men in our study cohort. Nationally, non-Hispanic white persons represented the majority of cases (75%), while 9% of cases were in African American and 10% were in Hispanic persons; in our cohort, 58% were non-Hispanic white, 17% African American, and 22% Hispanic (Table 1). Data on B-symptoms were available for SEER cases diagnosed in 2004 or later. For cases with available data ($n=3,570$; 76%), 13% were reported to have B-symptoms, which is slightly lower than the 15% observed in our cohort (15%); however, 23% of the patients in our cohort had no documentation of B-symptoms. Similarly, deep brain structures were involved in 3,340 cases (20%) in the CBTRUS data and 938 (20%) in the SEER data, as compared to 48% in our study cohort. However, in both registries around 30% of cases were reported as brain location, not otherwise specified.

Two-year observed survival rate was higher in our study population (58%) than in the SEER data (50%). Median OS duration in the SEER18 was 25 months (95% CI 22–28), whereas it was 43 months (95% CI 27–76) in our study cohort; however, this difference was not statistically significant ($p=0.14$) (Table 4).

Discussion

Our study is one of the largest multicenter studies comparing patients with PCNSL with or without HIV infection. In this study of a cohort of patients with PCNSL, we found demographic differences across the two groups. Patients with HIV-associated PCNSL were younger, more likely to be African American, and male as compared to patients with HIV-negative PCNSL. Patients with or without HIV

Table 2 Predictors of overall survival and progression-free survival among all patients with PCNSL ($n = 144$)

Variable	Number of events/patients (n/N)	Median OS months (95% CI)	p value	Median PFS months (95% CI)	p value
HIV status			0.02		0.17
HIV positive	16/27	6 (1–21)		6 (1–17)	
HIV negative	60/117	45 (33–57)		33 (14–51)	
Treatment location			0.007		0.05
BTH	24/38	24 (7–41)		12 (1–24)	
MD Anderson	52/106	52 (24–80)		39 (14–64)	
Age			0.47		0.25
≤ 60 years	36/73	47 (33–61)		37(16–58)	
> 60 years	40/71	29 (11–47)		18 (5–31)	
Sex			0.16		0.19
Male	44/77	37 (21–52)		15 (5–25)	
Female	32/67	100 (16–184)		41 (21–61)	
Race			0.51		0.48
African American	15/24	9 (1–31)		6 (3–9)	
White	46/83	45 (33–57)		21 (1–43)	
Hispanic	13/31	43 (31–55)		41 (7–75)	
B-symptoms[a]			0.66		0.95
Yes	12/21	41 (20–62)		36 (9–63)	
No	64/123	43 (28–58)		24 (3–45)	
ECOG performance status			0.001		0.001
<2	34/86	76 (23–129)		52 (17–55)	
≥2	41/57	8 (5–11)		5 (2–8)	
Number of brain lesions			0.89		0.67
Solitary lesion	42/76	43 (27– 58)		21 (5–37)	
Multiple lesions	34/68	41 (19–63)		36 (8–64)	
Size of primary tumor			0.53		0.66
≤ 3 cm	33/65	43 (1–98)		36 (8–64)	
> 3 cm	43/79	41 (30–52)		26 (6–46)	
Deep brain involvement			0.94		0.72
Yes	40/69	47 (15–80)		21 (6–72)	
No	36/75	41 (31–51)		39 (5–37)	
Solid enhancement			0.29		0.45
Yes	63/122	43 (33–53)		33 (9–57)	
No	13/22	37 (1–90)		24 (1–51)	
Rim enhancement			0.24		0.35
Yes	14/23	16 (1–53)		15 (1–52)	
No	61/121	43 (33–53)		33 (10–58)	
Presence of hemorrhage			0.01		0.05
Yes	37/59	21 (1–47)		11 (1–22)	
No	39/85	47 (7–87)		37 (21–53)	
Treatment			0.001		0.001
Supportive care	5/6	1 (0–1)		1 (0–1)	
WBRT only	13/21	24 (1–60)		18 (17–55)	
Chemotherapy ± WBRT	58/117	47 (36–58)		36 (1–44)	
Auto-SCT			0.001		0.001
Yes	4/24	121 (75–123)		73 (60–85)	
No	72/120	26 (7–45)		11 (2–20)	
IELSG prognostic score			0.01		0.04
0–1	8/23	101 (22–180)		42 (33–60)	
2–3	33/66	41 (1–66)		36 (11–61)	
4–5	8/9	9 (5–13)		11 (4–18)	

Auto-SCT autologous stem cell transplant, *BTH* Ben Taub Hospital, *ECOG* Eastern Cooperative Oncology Group, *IELSG* International Extranodal Lymphoma Study Group Experience, *WBRT* whole brain radiation therapy

[a]B-symptoms (fever, weight loss > 10% in 6 months, drenching night sweats)

Table 3 Multivariate Cox proportional hazards model examining the adjusted hazard ratio for study outcomes. ($n = 144$)

	Overall survival		Progression-free survival	
	Adjusted HR (95% CI)	*p* value	Adjusted HR (95% CI)	*p* value
HIV status				
HIV positive	1.0 (reference)	–	1.0 (reference)	–
HIV negative	1.4 (0.4–4.7)	0.61	1.7 (0.5–5.2)	0.36
Treatment location				
BTH	1.0 (reference)	–	1.0 (reference)	–
MD Anderson	0.5 (0.2–1.1)	0.09	0.4 (0.2–1.1)	0.08
ECOG performance status				
< 2	1.0 (reference)	–	1.0 (reference)	–
≥ 2	1.3 (0.6–2.9)	0.53	1.0 (0.5–2.3)	0.93
Presence of hemorrhage				
Yes	1.0 (reference)	–	1.0 (reference)	–
No	1.6 (0.8–2.9)	0.15	1.2 (0.7–2.3)	0.46
Treatment				
Supportive care	1.0 (reference)	–	1.0 (reference)	–
WBRT only	0.06 (0.01–0.7)	0.02	0.2 (0.02–1.7)	0.13
Chemotherapy ± WBRT	0.05 (0.01–0.5)	0.01	0.1 (0.02–1.2)	0.07
Auto-SCT				
Yes	1.0 (reference)	–	1.0 (reference)	–
No	3.4 (1.2–11.4)	0.04	4.9 (1.5–16.8)	0.01
IELSG prognostic score				
0–1	1.0 (reference)	–	1.0 (reference)	–
2–3	1.7 (0.7–4.1)	0.23	1.6 (0.7–3.8)	0.29
4–5	3.3 (1.1–11.4)	0.56	2.7 (0.8–8.9)	0.11

Auto-SCT autologous stem cell transplant, *BTH* Ben Taub Hospital, *ECOG* Eastern Cooperative Oncology Group, *HR* hazard ratio, *IELSG* International Extranodal Lymphoma Study Group Experience, *WBRT* whole brain radiation therapy

infection had a similar clinical presentation, however, significantly different MRI findings. When adjusted for other variables, clinical outcomes were associated with primary treatment modalities and were not associated with HIV status.

Although there were no major differences in clinical presentation between HIV-positive and HIV-negative PCNSL patients, there are some distinct features in patients with HIV-associated PCNSL. PLWH were more likely to have a higher LDH level and worse performance status on presentation. HIV-associated PCNSL is almost universally associated with EBV infection, but the sensitivity of positive EBV PCR was only 59% among patients with HIV in our study. Another study showed a similar sensitivity of 58% [6]. The radiologic features were strikingly different between patients with and without HIV infection. HIV-associated PCNSL was significantly more likely to present with multiple lesions, strong rim enhancement, and bleeding within the lesion; this is concordant with the literature [27–29]. The direct association of these radiographic findings with clinical outcomes and prognosis is not clearly defined. In our study, the only predictors of poor outcome were the choice of primary therapy and consolidative therapy with SCT. Our finding that prognosis, when controlled for other factors, was not significantly different by HIV status is inconsistent with earlier findings that HIV-associated PCNSL had a worse prognosis than PCNSL not associated with HIV [6], but some of these previous studies were limited by a small sample size or were done prior to widespread use of ART.

MTX-based chemotherapy, either as monotherapy or in combination with other agents, has been the standard of care. WBRT is associated with high risk of neurotoxicity without clear survival benefit [2]. Several studies have demonstrated favorable outcomes in patients treated with high-dose chemotherapy followed by SCT [30–32]. In our study, PLWH were significantly more likely to be treated with supportive care or WBRT as the sole treatment. Several ongoing randomized controlled trials are investigating the optimal treatment regimens for PCNSL and the role of SCT. All of these studies have HIV infection as an exclusion criterion. As an example, the PRECIS trial is a multicenter, randomized study comparing PFS among HIV-negative patients younger than 60 years with newly diagnosed PCNSL receiving MTX-based chemotherapy followed by WBRT or MTX-based chemotherapy followed by high-dose

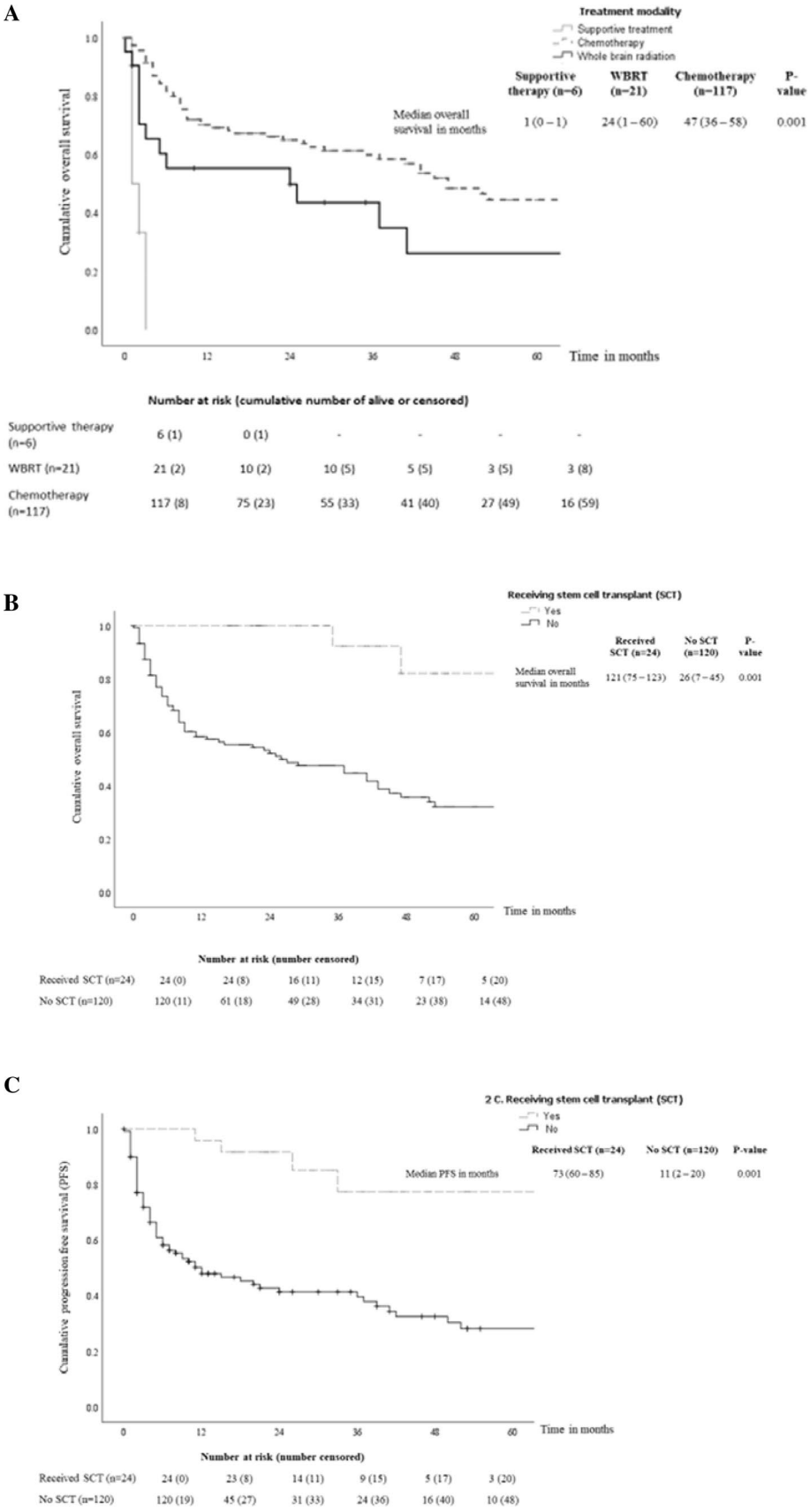

Fig. 2 Kaplan–Meier analysis: **a** overall survival in months by initial treatment for primary central nervous system lymphoma; **b** overall survival in months for patients who did or did not undergo autologous stem cell transplant; **c** progression-free survival in months for patients who did or did not receive autologous stem cell transplant. *p* value was calculated by the log-rank test

Table 4 Survival duration for SEER18 and study hospitals, overall and by HIV status

	N	1-year survival	2-year survival	5-year survival
SEER 18 (overall)	4098	58.5% (56.9–60.1%)	50.2% (48.5–51.9%)	37.7% (35.9–39.6%)
MD Anderson/BTH (overall)	144	65.6% (58.1–74.0%)	60.4% (52.7–69.3%)	40.4% (31.5–51.6%)
HIV positive	27	49.2% (33.1–73.2%)	39.4% (23.8–65.1%)	–
HIV negative	117	69.3% (61.3–78.3%)	65.2% (61.3–78.3%)	42.53% (32.7–55.3%)

BTH Ben Taub Hospital

chemotherapy and SCT [33]. One case has been reported of a patient with HIV infection with PCNSL who was treated with chemotherapy and immunotherapy followed by SCT who showed complete remission at 4 months after transplant with no major complications [34]. To answer the question about safety and effectiveness of SCT in PLWH in the era of effective, widely available ART, PLWH might benefit from being included in prospective clinical trials for PCNSL treatment.

Median age at diagnosis in the SEER18 was higher than that observed in our multicenter study, and the racial, age, and gender distributions were closer to those in our HIV-negative group of patients. A possible explanation is that the proportion of patients with HIV among our group could be different from the overall proportion across the United States [35]. A prior analysis of a subset of the SEER data (including Connecticut, New Mexico, Utah, Hawaii, Atlanta, Detroit, San Francisco-Oakland, and Seattle-Puget Sound) estimated that, from 2005 to 2012, HIV-positive individuals accounted for 36.3% of incident PCNSL cases and 17.6% of PCNSL deaths among those with known HIV status, though 52.6% of cases had no HIV status information [36]. HIV prevalence in non-Hodgkin lymphoma cases varied by SEER registry, with the highest prevalence in Atlanta and San Francisco-Oakland. This proportion is likely inflated by a large number of individuals with unknown status but suggests that the contribution of HIV to PCNSL varies geographically. The prevalence of HIV infection in the Houston Metropolitan Statistical Areas is 415.8/100,000 (vs 305.4/100,000 in the US overall).

Our study has several limitations; it is a retrospective study, and a number of patients were lost to follow-up [4 out of 27 patients (15%) in the HIV-positive group, and 21 out of 117 patients (18%) in the HIV-negative group]. The induction regimens, treatment protocols, and radiation doses varied widely. The small sample size prohibited a more detailed analysis of the effect of these differences on the outcomes. However, there is no strong evidence to suggest the superiority of a particular treatment regimen beyond the general treatment category groups that we used. As the number of patients with HIV is small, the analysis is likely underpowered to detect a difference in outcome between patients with or without HIV infection. However, the study does highlight the major difference in treatment modalities among the two groups. The national data included in this manuscript represent the most complete and up-to-date reporting of patterns of CNS lymphoma incidence and survival in the US [37]. No mechanism currently exists for central pathology review of cases within the US cancer registry system, and histology code assignment at case registration is based on histologic information contained in the patient's medical record. This means that incomplete, incorrect, or alternatively stated diagnoses included in a medical record can result in an incorrect reporting of the details of an individual case. These datasets do not include HIV status information in the public data releases, and as a result, it is not possible to assess the prevalence of HIV in these population-based resources or estimate the effect that HIV infection has on survival outcomes. US cancer registration requires the reporting of cases that are confirmed by diagnostic procedure, either histologic confirmation or radiographic confirmation. As a result, the cases included in these analyses may include those that were diagnosed by imaging only, though these cases were excluded from survival comparisons. SEER registries are specifically funded to collect active follow-up data on patients, and as a result, have highly accurate survival data for patients whose disease is diagnosed within the geographic regions covered by these registries. The SEER18 population dataset used for the survival analyses is a subset of the larger CBTRUS dataset used to generate incidence, and as a result, survival estimates based on the SEER dataset may be less reliable as representations of "real" relative survival rates for the US than if they were based on data from a larger portion of the population.

In conclusion, epidemiology, imaging features, and treatment options vary for PCNSL with HIV infection and PCNSL without HIV infection. Receiving MTX-based chemotherapy and SCT as a consolidative therapy is strongly associated with better clinical outcome. HIV infection was not an independent factor in mortality or disease progression. With the advances made in the treatment of HIV, PLWH with PCNSL can benefit from inclusion in clinical research to evaluate the safety and efficacy of new treatment modalities on clinical outcomes and survival.

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Compliance with ethical standards

Conflict of interest All authors have read and approved this manuscript and have no conflicts of interest to declare.

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