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Factors associated with survival among patients with AIDS-related primary central nervous system lymphoma

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Abstract

Objective—AIDS-related primary central nervous system lymphoma (AR-PCNSL) has a poor prognosis. Improved understanding of specific patient, infectious, diagnostic, and treatment-related factors that affect overall survival (OS) are required to improve outcomes.

Design—Population-based registry linkage study.

Methods—Adult cases from the San Francisco AIDS registry (1990–2000) were matched with the California Cancer Registry (1985–2002) to ascertain AR-PCNSL data. Survival time was assessed through 31 December 2007. Risk factors and temporal trends for death were measured using two-sided Kaplan–Meier and Cox analyses.

Results—Two hundred and seven AR-PCNSL patients were identified: 68% were white, 20% Hispanic, 10% African–American, and 2% Asian. Nineteen percent of patients had central nervous system (CNS) opportunistic infections diagnosed prior to AR-PCNSL. Fifty seven percent of patients received radiation and/or chemotherapy and 12% used HAART prior to or within 30 days of AR-PCSNL diagnosis. One hundred and ninety-nine patients died (34 deaths/100 person-years). In adjusted analysis, prior CNS opportunistic infections diagnosis increased risk of death (hazard ratio 1.9, $P = 0.0006$) whereas radiation and/or chemotherapy decreased risk (hazard ratio 0.6, $P < 0.0001$). AR-PCNSL diagnosis 1999–2002 had a lower mortality risk (hazard ratio = 0.4, $P = 0.02$) compared to 1990–1995. African–Americans had an increased risk of death compared to whites or Asians (hazard ratio = 2.0, $P = 0.007$).

Conclusion—OS among AR-PCSNL patients improved over time but remains poor, especially among African–Americans. Prospective evaluation of curative therapy in AR-PCNSL is urgently needed. Accurate diagnosis of CNS mass lesions in patients with AIDS is required and for those with AR-PCNSL, antiretroviral therapy with concomitant AR-PCNSL therapy, and antimicrobial supportive care may improve OS.

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Conflicts of interest

There are no conflicts of interest.

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S.S. and N.A.H. conceived the San Francisco AIDS Surveillance – California Cancer Registry Link Study, wrote the grant application, and received the funding. T.S.U. and N.A.H. conceived and designed this study, and directed the analyses. S.P. designed and performed analyses. All authors contributed to writing the manuscript.

Keywords

AIDS; AIDS-related lymphoma; brain neoplasms; HAART; prognosis; risk factors; time factors

Introduction

AIDS-related primary central nervous system lymphoma (AR-PCNSL) is a rare B-cell non-Hodgkin lymphoma (NHL). Prior to the use of HAART for treatment of HIV, a large proportion of PCNSL occurred in patients with advanced AIDS [1–3]. Established early in the epidemic, the primary treatment for AR-PCNSL was palliative whole brain radiotherapy (WBRT). However, without HAART, the median survival was less than 3 months [4–6].

Patients with AIDS are also at risk for life-threatening central nervous system (CNS) infections, especially toxoplasmosis, which cannot be reliably differentiated from AR-PCNSL by computed tomography (CT) or MRI. Given the poor outcomes in AR-PCNSL treated with WBRT alone, AIDS patients with ring-enhancing brain masses by conventional imaging, especially those with high-titer *Toxoplasma* serology, are sometimes treated with empiric antibiotics for toxoplasmosis before biopsy is attempted [7,8].

Although biopsy is the gold standard for CNS malignancies, minimally invasive diagnostic methods have also been evaluated in AIDS patients with CNS masses. Nuclear medicine imaging can help differentiate infectious from malignant CNS masses [7,9,10]. Furthermore, the association of AR-PCNSL with Epstein–Barr virus (EBV) [11] has led to evaluation of cerebral spinal fluid (CSF) for EBV DNA [12,13]. A combination of detectable EBV in the CSF [12,13] and increased Thallium-201 (201Tl) uptake on single-photon emission CT in patients with advanced AIDS and CNS masses was found to have a 100% positive predictive value for AR-PCNSL in one study [10]. These advances led to clinician acceptance of minimally invasive diagnostic techniques to establish an accurate diagnosis of AR-PCNSL.

The prognosis for AR-PCNSL has modestly improved in the HAART era [14–18], due in part to improved immune function [19–21] in those taking HAART [22]. However, clinical trial data are lacking for treatment for AR-PCNSL. Heterogeneity in reported overall survival (OS) in the HAART era suggests patient-related factors, delayed diagnosis, and diagnostic as well as treatment-related factors may influence long-term outcomes [17,18,23–25]. Despite the availability of HAART, the prognosis for AR-PCNSL remains extremely poor; in both an AIDS cohort study [26] and an analysis of Surveillance, Epidemiology, and End Results (SEER) data [24,27], 2-year mortality was more than 84%. We hypothesized that evaluation of specific factors associated with OS may identify areas for improvement in the clinical approach to AR-PCNSL.

Methods

Study population

Adult AIDS cases (ages 16–86 years) diagnosed between 1990 and 2000 and reported in the San Francisco AIDS surveillance registry were computer-matched to cancer cases diagnosed 1985–2002 and reported in the California Cancer Registry (CCR) as previously described [22]. AIDS surveillance in San Francisco is estimated to be 95–98% complete [28]. Additionally, individual patient demographics, the date when antiretroviral therapy began, type of therapy used, opportunistic infections, and $CD4^+$ cell count results were recorded from medical records at the time of initial case report and every 12–18 months thereafter. Opportunistic infections diagnoses were classified as presumptive or definitive, the later

requiring microbiologic confirmation, using the 1993 *Morbidity and Mortality Weekly Report* Revised HIV and AIDS case definition [29]. Guidelines for presumptive diagnosis of toxoplasmosis included recent onset focal neurologic abnormality, brain imaging with ring-enhancing mass, and a positive serum antibody to toxoplasmosis, or successful response to toxoplasmosis therapy. Survival was followed through 31 December 2007, with vital statistic information ascertained from local and national databases.

CNS lymphoma cases were identified using the SEER site recoding scheme, which is based on International Classification of Diseases for Oncology (ICD-O)-2 and ICD-O-3. The CCR was considered 100% complete at time of the match. CCR data include tumor histopathology, diagnostic methods (pathologic diagnosis obtained by histology or cytopathology versus clinical diagnosis), and the initial cancer therapy administered [no therapy, radiation alone, and chemotherapy-based treatment (either alone or in combination with radiation)]. We included AR-PCNSL cases occurring within 5 years of initial AIDS diagnosis or anytime thereafter [30–34] and excluded patients with non-B-cell histology [35] or history of systemic NHL diagnosed within 2 years prior to AR-PCNSL diagnosis.

The University of California Committee on Human Research and the National Institutes of Health Clinical Center Office for Human Research Protections each reviewed and approved this study.

Statistical considerations

Independent variables evaluated included race, AIDS-related factors, comorbidities, diagnostic, and treatment-related factors, and era. Race/ethnicity was classified as non-Hispanic white and Asian/Pacific Islander (combined given very few Asian/Pacific Islanders), Hispanic, or African–American. $CD4^+$ cell count prior to AR-PCNSL was categorized as 0–49 cells/μl, 50+cells/μl, or unknown. Opportunistic infections diagnosed prior to diagnosis of AR-PCNSL were categorized as either opportunistic infections that often have CNS manifestations (toxoplasmosis, *Cryptococcus*, histoplasmosis, and extrapulmonary tuberculosis) or other common opportunistic infections that do not typically have CNS manifestations (*Pneumocystis* pneumonia and *Mycobacterium avium* complex). AR-PCNSL diagnostic modality was categorized as pathology-based or clinical. HAART use was defined as prescription of a regimen that contained either a protease inhibitor or nonnucleoside reverse transcript inhibitor, prior to or within 30 days of AR-PCNSL diagnosis. Treatment of AR-PCNSL was categorized as no lymphoma-directed therapy, radiation-only, or chemotherapy-based treatment. Year of AR-PCNSL diagnosis was categorized as pre-HAART era (1990–1995), early HAART era (1996–1998), or later HAART era (1999–2002). Survival time was calculated from date of cancer diagnosis to date of death or, if alive, censored at 31 December 2007, whichever occurred first. Kaplan–Meier methods were used to evaluate survivor functions from AR-PCNSL diagnosis to death, stratified by different factors and with the log-rank test used to assess statistical differences in survival. Individual risk factors for death were evaluated in unadjusted Cox proportional hazard analyses, and those considered statistically significant (P <0.1) were included in multivariate Cox models. All tests of statistical significance were two-sided. To address the potential uncertainty of the clinically defined AR-PCNSL cases in the CCR, univariate and multivariate sensitivity analyses were repeated in only the pathology-confirmed cases. Statistical analyses were performed using SAS software version 9.2 (SAS Institute Inc., Cary, North Carolina, USA).

Results

Patient characteristics

A total of 17 709 adults were diagnosed with AIDS in San Francisco from 1990 to 2000 and 207 AR-PCNSL cases were identified (Fig. 1). AR-PCNSL represented 5% of all AIDS-defining malignancies in this time period. A decreased number of San Francisco AR-PCNSL cases were observed in the HAART era [15,22,36]; 140 participants (68%) were diagnosed during 1990–1995, 52 (25%) during 1996–1998, and 15 (7%) during 1999–2002.

The majority of patients were non-Hispanic white, MSM, and not prescribed HAART prior to their AR-PCNSL diagnosis (Table 1). One hundred and six AR-PCNSL cases (51%) were pathologically confirmed. Forty patients (19%) had a diagnosis of a CNS infection prior to their diagnosis of AR-PCNSL, 106 patients (51%) had a diagnosis of another prior opportunistic infections, and 89 patients (43%) had no opportunistic infections history. The median time from diagnosis of toxoplasmosis to diagnosis of AR-PCNSL was 1 month. The median time from diagnosis of other opportunistic infections to AR-PCNSL ranged from 10 to 26 months.

HAART use increased over time: two (1%) 1990–1995, 15 (29%) 1996–1998, and seven (58%) 1999–2002 were prescribed HAART prior to or within 30 days of AR-PCNSL diagnosis. AR-PCNSL therapy was comparatively stable over time: 74 (53%) 1990–1995, 35 (67%) 1996–1998, and nine (60%) 1999–2002 received WBRT and/or chemotherapy. Of patients receiving AR-PCSL therapy, 97% received therapy within 1 week of diagnosis.

Risk factors for death

During study follow-up, 199 of the 207 patients died (34 deaths/100 person-years). In unadjusted Cox analyses among all AR-PCNSL patients (Table 2, Column A), significant factors associated with shorter cancer survival time included CNS infections diagnosed before AR-PCNSL (hazard ratio = 2.2, P <0.0001), no AR-PCNSL-directed therapy (compared to no therapy, hazard ratio of death with radiation and/or chemotherapy 0.6, P <0.0001), and not receiving HAART within 30 days of diagnosis (hazard ratio for those receiving HAART 0.5, P = 0.005). When evaluated separately, both radiation alone (hazard ratio 0.6, P = 0.0005) and chemotherapy-based treatment (hazard ratio 0.4, P = 0.001) decreased risk of death compared to no therapy. There were improved outcomes for patients diagnosed after 1998 compared to those diagnosed before 1996 (hazard ratio 0.4, P = 0.0008). Compared to non-Hispanic white and Asian/Pacific Islanders, African–Americans had an increased risk of death (hazard ratio = 2.3, P = 0.0007). Of the 106 patients with pathology-confirmed AR-PCNSL, 103 died (36 deaths/100 person-years.) There was no difference in OS between AR-PCNSL clinically diagnosed and those with pathologic confirmation (Table 2, Column A). The unadjusted Cox model results were similar when risk factor analyses were limited to these 106 patients. (Table 2, Column B).

In the adjusted Cox model among all 207 AR-PCNSL cases (Table 3, Column A), the significant prognostic factors included history of CNS infection (hazard ratio = 1.9, P = 0.0006), treatment of AR-PCNSL (hazard ratio = 0.6, P <0.0001), year of diagnosis (hazard ratio = 0.4 for years 1999–2002, P = 0.02), and African–American race (hazard ratio = 2, P = 0.007). HAARTuse was no longer significant after controlling for these other factors. Kaplan–Meier survival curves for significant prognostic factors are noted in Fig. 2a–d. Restricting the analysis to the 106 patients with pathology-confirmed AR-PCNSL led to similar results (Table 3, Column B).

In multivariate Cox analyses evaluating the benefit of lymphoma therapy, stratified by cancer diagnosis time period, HAART, or CNS infection, and corrected for the other

variables, a benefit of treatment of AR-PCNSL was seen in each stratum (data not shown). Stratified analysis showed that the hazard ratio for death in patients with a history of CNS opportunistic infections diagnosis prior to AR-PCNSL diagnosis increased over time from 1.6 (1990–1995, $P = 0.03$), 5.5 (1996–1998, $P < 0.0001$) to 12.4 (1999–2002, $P = 0.07$).

Discussion

Prevention of immunodeficiency-associated cancers is a major benefit of HAART. AR-PCNSL incidence decreased 80% in the United States with the broad availability of HAART [22,37]. Although AR-PCNSL has become an increasingly rare disease, there remains a need for an evidence-based approach for managing patients, as diagnostic and treatment practices vary by institution [16,27,38,39]. Importantly, AR-PCNSL occurs mainly in younger patients [2] whose survival time could benefit substantially if curative therapy for lymphoma were achieved.

Several studies have evaluated either calendar period [15,27] or HAART use [16–18,23,40] as prognostic factors. Building on our previous work, this is the first study to independently evaluate calendar period and individual HAART data in strictly defined AR-PCNSL cases. Our study provides additional evidence of a temporal improvement in OS in patients with AR-PCNSL [15,27]. Most improvement was observed after 1998, likely reflecting improved HIV therapeutics and/or less HIV resistance in this later time period [22]. However, HAART use per se was not associated with improved survival in multivariate analysis that included time period. These findings may be because HAARTuse was confounded by indication, whereby those prescribed HAART were likely to have more advanced HIV-related disease. Alternatively, HAART prescribed more than 30 days after initial diagnosis may have provided a survival benefit. A limitation of the current study is incomplete data on additional HIV-related factors that could differentiate these possibilities. We were unable to evaluate plasma HIV viral load, which is a more sensitive measure of effective HAART, and $CD4^+$ cell count, a measure of degree of immunodeficiency, was available on only 42% of patients.

Although WBRT is commonly used in AR-PCNSL patients, some patients with AR-PCNSL also are treated with chemotherapy. For example, between 1994 and 2002, 14% of Medicare patients with AR-PCNSL received chemotherapy either alone or in combination with WBRT [27]. Importantly, the current study demonstrates a survival benefit of lymphoma-directed treatment in AR-PCNSL that is independent of HAART prescription, CNS infections, and time period. Despite small numbers of patients, there was a survival benefit for chemotherapy-based treatment of AR-PCNSL compared to no therapy. A limitation of this study is that we do not have data on patient performance status, which may have been a confounding factor [17].

An important new finding is that prior diagnosis of CNS infection was strongly associated with death in this patient population. Previous studies did not show prior opportunistic infections as a poor prognostic factor [18], likely due to combining opportunistic infections with CNS manifestations with other common opportunistic infections or not including patients with CNS infections [40]. The diagnosis of CNS infections may be associated with a worse prognosis either because patients carry clinical diagnoses of CNS infections that are treated empirically with antibiotics, introducing a deleterious lag time before subsequent AR-PCNSL diagnosis, or patients with AR-PCNSL may have concurrent life-threatening CNS infections. This study suggests that AIDS patients who present with ring-enhancing masses may benefit from expedited evaluation utilizing minimally invasive techniques [10]. CSF cytology and flow cytometry can detect leptomeningeal involvement of B-cell lymphomas [41–43] and may establish a diagnosis. In many cases, a stereotactic needle

biopsy is required [44]. Empiric antibiotic therapy is outdated in the HAART era. Progressive neurologic symptoms that may develop in this time period would likely lead to a worsening performance status and worse long-term outcomes [17,40,45]. Furthermore, outcomes for patients treated for CNS opportunistic infections have improved in the HAART era [46,47] and CNS infections and AR-PCNSL are potentially manageable concurrently.

HIV/AIDS continues to disproportionately affect African–Americans [48], and in the general population the increased incidence of PCNSL in African–Americans ages 20–49 (compared to whites) [49] is likely due to HIV. Diagnostic and treatment advances in AR-PCNSL may be limited by healthcare disparities [50,51], and our study provides evidence that African–Americans who developed AR-PCSNL had worse outcomes than other racial/ethnic groups. Shorter AR-PCSNL survival time may be related to delayed initial diagnosis, although additional factors such as lag time from diagnosis to initiation of therapy may also affect survival. Further study is needed to identify patient and physician-related factors [26,52–56], and barriers to cancer therapy [57,58] that disproportionately affect African–Americans.

Our study of patients with AR-PCNSL is unique and has several strengths. By using the San Francisco AIDS registry data, we were able to assess the impact of several AIDS-specific variables at the individual level, including prescription of HAART, $CD4^+$ cell count, and history of opportunistic infections. Additionally, the CCR provided data on treatment and diagnosis. As such, this study population is the largest to date to incorporate both HIV and AR-PCNSL treatment variables. Importantly, our methodology also excluded patients with a history of systemic NHL who were later diagnosed with CNS disease, as these patients are better classified as recurrent lymphoma than AR-PCNSL. This study also had a minimum of 5 years follow-up for all AR-PCNSL patients, reducing bias due to right truncation.

In conclusion, our study is the first to identify prior diagnosis of CNS opportunistic infections as a risk factor for death in patients with AR-PCNSL. This finding has important implications for the evaluation and management of neurologic comorbidities in patients with AR-PCNSL. This investigation is also the first to demonstrate inferior outcomes for African–American patients with AR-PCNSL, suggesting healthcare disparities may contribute to poor outcomes. This study provides evidence of a strong independent benefit for broad availability of HAART (based on HAART era) and lymphoma-directed therapy in AR-PCNSL. Encouragingly, AR-PCNSL-directed therapy, including chemotherapy-containing regimens, appears to improve OS. Continued monitoring of AR-PCNSL mortality trends is important, as further improvements are achievable.

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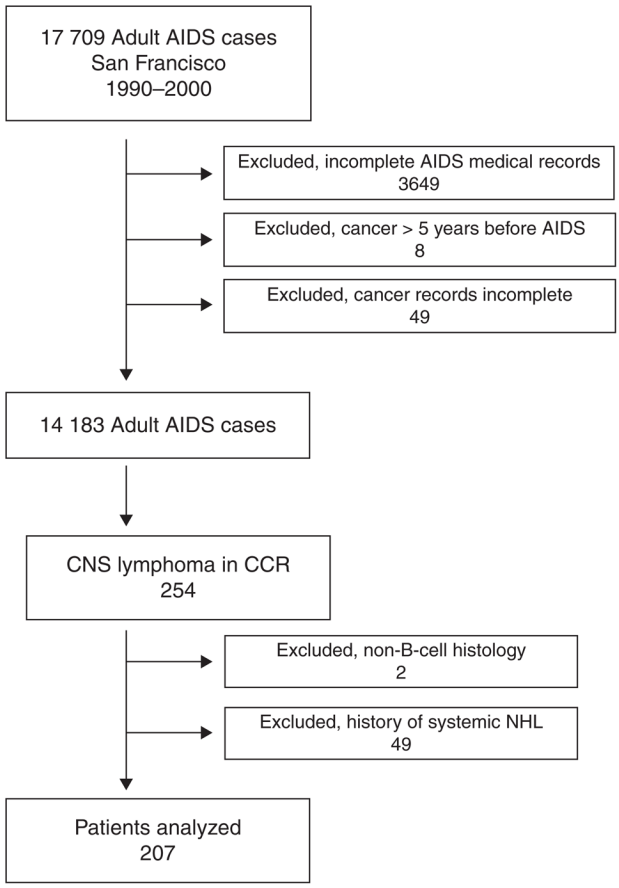

Fig. 1. Patient selection

CCR, California Cancer Registry; CNS, central nervous system; NHL, non-Hodgkin lymphoma.

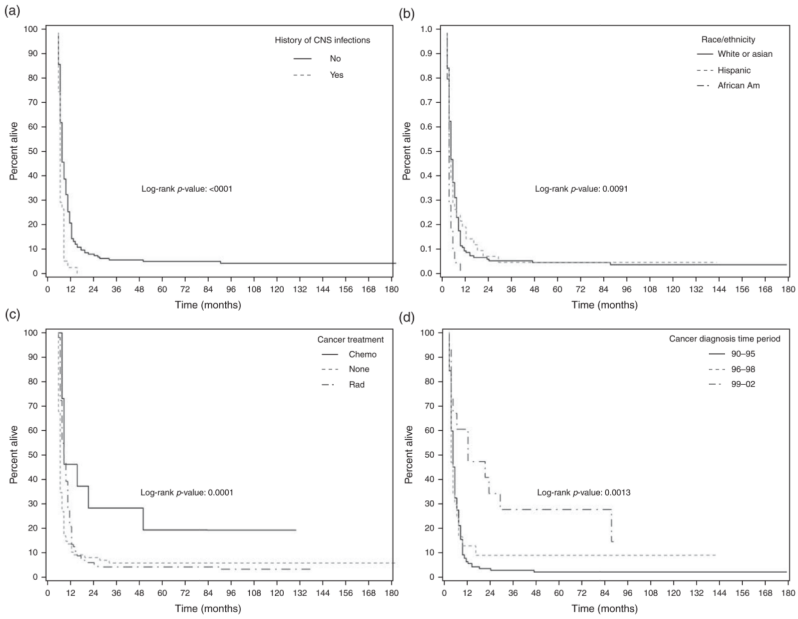

Fig. 2. Kaplan–Meier survival curves for AIDS-related primary central nervous system lymphoma (AR-PCNSL) cases diagnosed in San Francisco, California, from 1990 to 2002, by four prognostic factors significant in multivariate analysis

(a) OS by prior diagnosis of central nervous system (CNS) infection. (b) OS by race: white or Asian, non-Hispanic white, or Asian/Pacific Islander; Hispanic; or African Am, African–American. (c) OS by PCNSL therapy: Chemo, chemotherapy-containing therapy; None, no therapy or unknown; Rad, radiation therapy. (d) OS by year of AR-PCNSL diagnosis: 1990–1995, pre-HAART era; 1996–1998, early HAART era; 1998–2002, later HAART era. OS, overall survival.

Table 1

Characteristics of 207 cases of AIDS-related primary central nervous system lymphoma diagnosed in San Francisco, California, 1990–2002.

Patient characteristic	*n* (%) or median (interquartile range)
Race	
Non-Hispanic white	140 (68%)
African–American	21 (10%)
Hispanic	41 (20%)
Asian/Pacific Islander	5 (2%)
Sex	
Men	198 (96%)
Women	9 (4%)
Age	39 (35–46)
HIV risk group	
MSM	164 (79%)
IVDU	17 (8%)
MSM/IVDU	19 (9%)
Other/not specified	7 (3%)
$CD4^+$ cell count (cells/μl)	20 (6–53)
Prior CNS infections	
Toxoplasmosis	17 (8%)
Definitive	4 (2%)
Presumptive	13 (6%)
Cryptococcosis[a]	19 (9%)
Histoplasmosis[a]	2 (1%)
Extrapulmonary tuberculosis[a]	2 (1%)
Other prior OI (PCP/MAC)	106 (51%)
No prior OIs	89 (43%)
AR-PCNSL diagnosis	
Pathology based	106 (51%)
Clinical	39 (19%)
Not specified	62 (30%)
AR-PCNSL therapy	
None or unknown	89 (43%)
Radiation only	107 (52%)
Chemotherapy[b]	11 (5%)
HAART	
Yes	24 (12%)
No	183 (88%)

AR-PCNSL, AIDS-related primary central nervous system lymphoma; IVDU, intravenous drug use; MAC, *Mycobacterium avium* complex; OI, opportunistic infection; PCP, *Pneumocystis* pneumonia.

[a] Cryptococcosis, histoplasmosis, and tuberculosis are considered definitive diagnoses based on microbiology confirmation by microscopy, culture, or direct evidence of antigen in a specimen collected from affected tissues or fluids.

[b] Chemotherapy only (5/13), chemotherapy and radiotherapy (6/13), and chemotherapy and immunotherapy (2/13).

Table 2

Univariate Cox analysis modeling hazard of death in adult patients with AIDS-related primary central nervous system lymphoma from the California Cancer Registry and San Francisco AIDS Registry, 1990–2002.

	Column A; all cases (*n* = 207)				Column B; pathology confirmed cases (*n* = 106)			
	Deaths (*n* = 199)				Deaths (*n* = 103)			
Risk factor	***N***	**Unadjusted hazard ratio**	**95% Confidence interval**	***P***	***N***	**Unadjusted hazard ratio**	**95% Confidence interval**	***P***
History of central nervous system infections[a]								
No	170	1.0	Reference group	–	89	1.0	Reference group	–
Yes	37	2.2	1.5–3.2	<0.0001	17	2.7	1.6–4.6	0.0003
Other OIs[b]								
No	101	1.0	Reference group	–	59	1.0	Reference group	–
Yes	106	1.1	0.9–1.5	0.34	47	1.3	0.9–1.9	0.21
Diagnosis								
Pathology	106	1.0	Reference group	–	106	–	–	–
Clinical	39	1.3	0.9–2.0	0.12	0	–	–	–
Unknown	62	1.4	1.0–1.9	0.06	0	–	–	–
AR-PCNSL therapy								
None	89	1.0	Reference group	–	21	1.0	Reference group	–
Radiation and/or chemotherapy	118	0.6	0.4–0.7	<0.0001	85	0.3	0.2–0.5	<0.0001
HIV therapy								
No HAART	183	1.0	Reference group	–	94	1.0	Reference group	–
HAART	24	0.5	0.3–0.8	0.005	12	0.5	0.3–1.0	0.04
$CD4^+$ cell count (cells/μl)								
0–49	62	1.0	Reference group	–	36	1.0	Reference group	–
50+	24	1.1	0.7–1.7	0.77	12	0.9	0.5–1.8	0.78
Unknown	121	1.3	0.9–1.8	0.1	58	1.1	0.8–1.8	0.52
Cancer diagnosis time period								
1990–1995	140	1.0	Reference group	–	73	1.0	Reference group	–
1996–1998	52	0.9	0.7–1.3	0.67	26	0.8	0.5–1.2	0.24
1999–2002	15	0.4	0.2–0.7	0.0008	7	0.3	0.1–0.8	0.01
Race/ethnicity								

	Column A; all cases (*n* = 207)				Column B; pathology confirmed cases (*n* = 106)			
	Deaths (*n* = 199)				Deaths (*n* = 103)			
Risk factor	***N***	**Unadjusted hazard ratio**	**95% Confidence interval**	***P***	***N***	**Unadjusted hazard ratio**	**95% Confidence interval**	***P***
White or API[a]	145	1.0	Reference group	–	75	1.0	Reference group	–
Hispanic	41	1.0	0.7–1.4	0.91	23	1.1	0.7–1.7	0.76
African–American	21	2.3	1.4–3.6	0.0007	8	2.7	1.3–5.7	0.009

AR-PCNSL, AIDS-related primary central nervous system lymphoma; N, number; white, non-Hispanic white; API, Asian/Pacific Islander; OI, opportunistic infection.

[a]Includes OIs that often have CNS manifestations; Toxoplasmosis, *Cryptococcus*, histoplasmosis, and extrapulmonary tuberculosis.

[b]Includes *Pneumocystis* pneumonia and *Mycobacterium avium* complex.

Table 3

Multivariate Cox analysis of risk factors for death in adult patients with AIDS-related primary central nervous system lymphoma from the California Cancer Registry and San Francisco AIDS Registry, 1990–2002, using variables significant ($P < 0.1$) in unadjusted analyses.

	Column A; all cases (n = 207)				Column B; pathology confirmed cases (n = 106)			
	Deaths (n = 199)				Deaths (n = 103)			
Risk Factor	***N***	**Adjusted hazard ratio**	**95% Confidence interval**	***P***	***N***	**Adjusted hazard ratio**	**95% Confidence interval**	***P***
History of central nervous system infections[a]								
No	170	1.0	Reference group	–	89	1.0	Reference group	–
Yes	37	1.9	1.3–2.8	0.0006	17	2.0	1.1–3.6	0.02
AR-PCNSL therapy								
None	89	1.0	Reference group	–	21	1.0	Reference group	–
Radiation and/or chemotherapy	118	0.6	0.4–0.7	<0.0001	85	0.3	0.2–0.5	<0.0001
HIV therapy								
No HAART	183	1.0	Reference group	–	94	1.0	Reference group	–
HAART	24	0.8	0.5–1.5	0.59	12	0.9	0.4–2.0	0.89
Cancer diagnosis time period								
1990–1995	140	1.0	Reference group	–	73	1.0	Reference group	–
1996–1998	52	1.0	0.7–1.4	0.99	26	0.7	0.4–1.1	0.11
1999–2002	15	0.4	0.2–0.9	0.02	7	0.4	0.1–1.0	0.05
Race/ethnicity								
White or API	145	1.0	Reference group	–	75	1.0	Reference group	–
Hispanic	41	1.0	0.7–1.4	0.9	23	0.9	0.5–1.5	0.64
African–American	21	2.0	1.2–3.3	0.007	8	3.0	1.3–6.8	0.008

API, Asian/Pacific Islander; AR-PCNSL, acquired immunodeficiency syndrome-related primary central nervous system lymphoma; N, number; white, non-Hispanic white; OI, opportunistic infection.

[a]Includes OIs that often have CNS manifestations; Toxoplasmosis, Cryptococcus, histoplasmosis, and extrapulmonary tuberculosis.