Racial differences in primary central nervous system lymphoma incidence and survival rates

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To determine racial and ethnic differences in incidence and survival in patients with primary central nervous system lymphoma (PCNSL), NCI Surveillance, Epidemiology, and End Results (SEER) program data from 1992 to 2002 were queried. Data were substratified by age (20–49 years vs. 50 or above) and race (White, Black, Asian/Pacific Islander [A/PI], American Indian/Alaskan Native [AI/AN]). Incidence of PCNSL and survival were calculated by SEER*Stat software. The incidence rates were 0.94 per 100,000 per year (95% confidence interval [CI] 0.90–0.98) for Whites, 1.10 (95% CI 0.98–1.22) for Blacks, 0.51 (95% CI 0.28–0.74) for AI/AN, and 0.64 (95% CI 0.56–0.72) for A/PI. In patients aged 20–49 years the rates were 0.72 (95% CI 0.68–0.76) for Whites, 1.43 (95% CI 1.27–1.59) for Blacks, 0.58 (95% CI 0.30–0.86) for AI/AN, and 0.21 (CI 0.15–0.27) for A/PI. In patients over 49 years, the rates were 1.30 (95% CI 1.22–1.38) for Whites, 0.56 (95% CI 0.40–0.72) for Blacks, 0.34 (95% CI 0–0.70) for AI/AN, and 1.31 (95% CI 1.00–1.53) for A/PI. PCNSL incidence for ages 20–49 years for Black patients was twice that for Whites. Incidence for ages over 49 years for Whites was twice that for Blacks. Survival at 12 months, 24 months, and 60 months was higher among Whites than Blacks. Research is needed to determine the origin of these differences. *Neuro-Oncology 11, 318–322, 2009 (Posted to Neuro-Oncology [serial online], Doc. D08-00121, March 9, 2009. URL http://neuro-oncology.dukejournals.org; DOI: 10.1215/15228517-2008-103)*

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Primary central nervous system lymphoma (PCNSL) is a rare primary brain tumor characterized by perivascular accumulation of neoplastic cells with lymphoid characteristics. PCNSL is seen in two age groups: a younger group frequently associated with viral (human immunodeficiency virus [HIV]) or iatrogenic immunosuppression and a group age 50 or older, generally without any other known systemic disease. The age-adjusted incidence is 0.48 per 100,000[1] and appears to be increasing over time.[2] Approximately 1,000 new cases are diagnosed annually in the United States. Unlike the situation in immunocompromised patients, where a component of pathogenesis is known, the pathogenesis of PCNSL in the older immunocompetent patients is unknown.

Though there is a slight male preponderance, the racial and ethnic associations of PCNSL have never been determined.[1–3] Our clinical impression was that PCNSL in presumed immunocompetent patients was less commonly diagnosed in Blacks than in Whites and rarely in Asian/Pacific Islanders (A/PI) and American Indians/Alaskan

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natives (AI/AN). To determine whether there was a racial difference in incidence and survival we used the National Cancer Institute (NCI) Surveillance, Epidemiology and End Results (SEER) program data.[4] SEER collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 26% of the U.S. population. The SEER program is the only comprehensive source of population-based information in the United States that includes stage of cancer at the time of diagnosis and patient survival data.

Methods

Incident malignancies were classified using the second edition of the International Classification of Disease Oncology (ICD-O). PCNSL was defined by cancer diagnoses in the spinal cord, cranial nerves, and other parts of the CNS (ICD-O codes C70.0–C72.9) and specified non-Hodgkin lymphoma (NHL) morphologies (ICD-O codes 9590–9595 and 9670–9723). The codes queried were for PCNSL (site and morphology, primary site = 700–729 meshed with site and morphology histologic type ICD-O 9590–9595, 9670–9723).

Data were stratified to ages 20–49 years and 50 or older. To minimize the impact of HIV on the data (because of the strong association with HIV), patients with a diagnosis of both PCNSL and an AIDS-associated cancer such as Kaposi sarcoma were excluded.[1–3] Cases with a post-transplant lymphoproliferative disorder were similarly excluded. We made no exclusions based on SEER registry site or gender.

The categories selected for subgroup analysis reflect the four racial groups recognized by SEER—White, Black, A/PI, and AI/AN. Because minority representation was limited in the initial SEER data from 1973 to 1992, only data for the expanded 13 SEER sites (available beginning in 1992) were used. Age-adjusted incidence rates were calculated using SEER*Stat, a statistical software program for the analysis of SEER and other cancer-related databases[4] (available at www.seer.cancer.gov/seerstat). Rates were age-adjusted to the 2000 U.S. standard million population and reported per 100,000 person-years. Ninety-five percent confidence intervals (CI) were calculated based on properties of the Poisson distribution. All analyses were restricted to persons age 20 years.

Absolute and relative survival rates among PCNSL cases and corresponding standard errors were calculated using the actuarial method as implemented by the SEER*Stat software. Relative survival is defined as "the ratio of the proportion of observed survivors (all causes of death) in a cohort of cancer patients to the proportion of expected survivors in a comparable cohort of cancer-free individuals." Only cases of known age were included in survival estimates. Expected rates were generated using survival probabilities from the general U.S. population, matched to the PCNSL cases by race, sex, age, and calendar period. We compared differences in survival across race using standard two-sample *t*-tests.

Results

The initial evaluation assessed the incidence of PCNSL in all persons aged 20 years in 1992–2002. Whites had a PCNSL incidence of 0.94 per 100,000 per year (95% CI 0.90–0.98); Blacks had an incidence of 1.10 (95% CI 0.98–1.22, Table 1). The AI/AN and A/PI subgroups had much lower PCNSL incidence of 0.51 (95% CI 0.28–0.74) and 0.64 (95% CI 0.56–0.72), respectively. The small number of cases in the AI/AN group caused the estimated incidence to be less concise.

A subanalysis for patients aged 20–49 years at diagnosis demonstrated that the PCNSL incidence in Blacks (1.43, 95% CI 1.27–1.59) was twice that of similarly aged Whites (0.72, 95% CI 0.68–0.76). The AI/AN and A/PI subgroups had rates of 0.58 (95% CI 0.30–0.86) and 0.21 (CI 0.15–0.27), respectively. For those aged 50 or over, the incidence ratio between the two racial groups was reversed; the PCNSL incidence was 1.30 (95% CI 1.22–1.38) in Whites and 0.56 (95% CI 0.40–0.72) in Blacks. Incidence was 0.34 (95% CI 0–0.70) in AI/AN and 1.31 (95% CI 1.00–1.53) in A/PI.

Absolute survival for all races and ages at 12 months, 2 years, and 5 years was 33%, 25%, and 16%, respectively. Only Whites and Blacks were evaluated by subgroup analysis since there were not enough cases in the AI/AN or A/PI groups to merit statistical analysis. Among all persons aged 20 years and older, absolute survival at 12 months, 24 months, and 60 months was significantly higher among Whites than Blacks (Table 2). However, for subsets of individuals aged 20–49 at diagnosis, only 12-month and 5-year survival were statistically different in the two racial groups ($p = 0.03$, $p = 0.05$, respectively). No statistically significant differences in survival were found for individuals aged 50 and older, perhaps due in part to small race-specific sample sizes. Patterns of relative survival across age and race were similar to those for absolute survival (data not shown).

Table 1. Incidence rates of primary central nervous system lymphoma per 100,000 person-years and race, 1992–2002

	Incidence Rate (95% Confidence Interval)					
Race	***n***	**Age 20+**	***n***	**Age 20–49**	***n***	**Age 50+**
White	2118	0.94 (0.90–0.98)	1055	0.72 (0.68–0.76)	1063	1.30 (1.22–1.38)
Black	355	1.10 (0.98–1.22)	305	1.43 (1.27–1.59)	50	0.56 (0.40–0.72)
American Indian/Alaskan Native	19	0.51 (0.28–0.74)	16	0.58 (0.30–0.86)	3	0.34 (0–0.70)
Asian/Pacific Islander	173	0.64 (0.56–0.72)	45	0.21 (0.15–0.27)	128	1.31 (1.09–1.53)

Table 2. Absolute survival rates among subjects with primary central nervous system lymphoma by race, 1992–2002[a]

	Age 20+			Age 20–49			Age 50+		
Survival Time	White	Black	*p*-Value[b]	White	Black	*p*-Value[b]	White	Black	*p*-Value
12 months	34.1 (1.2)	19.1 (2.3)	<0.001	23.3 (1.5)	16.9 (2.4)	0.02	44.1 (1.7)	31.8 (7.2)	0.10
2 years	24.7 (1.1)	15.6 (2.2)	<0.001	17.2 (1.4)	13.8 (2.2)	0.19	31.7 (1.6)	26.0 (7.0)	0.43
5 years	15.9 (1.0)	9.2 (1.9)	0.002	12.7 (1.3)	8.2 (1.9)	0.05	18.8 (1.5)	15.1 (6.3)	0.57

[a]Survival percent (corresponding standard error).

[b]*t*-Test comparing survival rates in Whites to those in Blacks.

Discussion

The hypothesis under investigation was whether there were statistically significant differences in PCNSL incidence and survival rates between U.S. Whites and Blacks. Our data demonstrated that such differences did exist. Black patients had twice the incidence of PCNSL as Whites in ages 20–49 years. However, in those aged 50 years or older, incidence in Whites was twice that in Blacks. In the other racial groups, the number of cases was too low to make definite statements. That said, the pattern for A/PI was similar to that in Whites, with older individuals at higher risk than younger individuals.

The incidence rates identified in this study are higher than reported rates. We have no satisfactory explanation for this observation. The 0.48 per 100,000 estimate may be an underestimate of the true rate.[1,2] Even if accurate, it may only reflect the time period in which the cases were collected. Both the Eby et al. study[5] and the Olson et al. study[2] also used SEER data. However, the study period for the former ended in 1988, and that for the latter ended in 1997. A plausible explanation is that the data that informed our study included cases from more recent calendar months, a different racial mixture, and different SEER sites.

Racial disparities have been noted in primary brain tumors; meningiomas are more common in Blacks, gliomas more common in Whites, and germ cell/pineal region tumors more common in Asians.[6] The reasons for these observed disparities are not known. Similarly, an explanation for the observed racial difference in PCNSL incidence is not obvious.

PCNSL risk is closely associated with immunocompetence. The SEER data excluded cases following solid organ transplantation (CNS posttransplant lymphoproliferative disorder [CNS-PTLD]), but could not cull out cases associated with HIV infection. In fact, there is no accepted strategy to account for HIV infection as it relates to SEER data. Cases in the San Francisco (SF) SEER site have been determined to be problematic surrogates partly because of the rise in HIV infection rates in women and heterosexual men[7] and the influence of highly active antiretroviral therapy (HAART) on disease phenotype.[8] Thus, our observations could reflect a difference in HIV infection rates in the two populations among those younger than 50, or a more profound effect of HIV infection on immunocompetence among Blacks versus Whites.

There are compelling recent data that HIV infection is rising in the U.S. Black population, independent of gender and sexual orientation.[9] The rate of HIV infection in American Blacks was 4.9 cases per 1,000 persons, compared with 0.22 cases per 1,000 in other racial/ethnic groups.[10, 11] Stated another way, more than three-quarters of persons under 25 years diagnosed with HIV/AIDS are American Black or Hispanic.[12] Among persons aged 25 to 34 years, HIV is the sixth leading cause of death among non-Hispanic whites and Hispanics, the third leading cause among American Blacks, and the leading cause among American Black women.[13]

The incidence of HIV infection in people over age 50 is just beginning to evolve, so we cannot exclude the possibility that both younger (<50) and older (>50) Blacks with PCNSL may have a higher proportion of HIV cases than non-Blacks. The rate of HIV infection and its impact on the observed difference in survival could not be assessed in this study and is a limitation of SEER data overall.[14] Regardless of the HIV concern, the data still show a major difference in age distribution and survival with PCNSL between Blacks and Whites.

In some settings, race may be a surrogate for socioeconomic status (SES). An earlier paper from our group suggested an association between PCNSL and low SES.[15] In other words, earlier acquisition of PCNSL in Black populations could reflect environmental factors separate from HIV infection and genetic risks.[16] Socioeconomic access to cancer screening and early detection is not relevant for PCNSL or other primary brain tumors. Even in tumors where early detection is available and reliable, a recent Southwestern Oncology Group (SWOG) study showed no difference in outcome once patients had access to tertiary medical centers.[17]

The other important finding in this study was the consistent difference in survival rates between the two races regardless of age. Twelve-month survival was 34% for Whites compared to 19% for Blacks. The gap in survival narrowed over time but was still present at 5 years, at which time survival was 16% for Whites but only 9% for Blacks. Stratification into age group categories reduced the statistical power to detect differences between the racial groups. However, survival was always higher for Whites than for Blacks at all time periods in all age groupings.

Possible explanations for these differences include disparate access to health care, pharmacogenetic differences in treatment between races, and the effect of co-morbidity on cancer treatment. The SWOG experience suggested that the observed differences in mortality between Black and White patients could not be attributed to treatment if patients were given comparable regimens at comparable times after diagnosis.[17] Relative survival accounts for differences in overall life expectancy across race. Although PCNSL is a disease of older persons, we had to be certain that the observed data did not reflect a difference in life expectancy between Blacks and Whites. Over the time of this study, PCNSL patients tended to be treated in clinical trials, and more recent clinical trials have clearly resulted in improved outcomes.[18] We cannot address the treatments these patients received, the breakdown by race, or the venues.

The role of SES on outcome is still under debate. Survival in patients with cancer correlates with SES overall.[19] Nevertheless, SES has not proved to affect survival in a related hematologic malignancy, multiple myeloma.[17] In that study, the median overall survival of patients was similar in Blacks and Whites. Incidence was not addressed in that study. Furthermore, race, distance traveled, and socioeconomic status were not independent prognostic factors for overall survival. Whether this result represents an inherent difference in patients with solid versus hematologic malignancies is not apparent.[20]

Exploring incidence patterns by racial group may generate new etiologic hypotheses and identify high-risk groups for further study. There is clearly a precedent for racial influences on myeloma, leukemia, and adult T-cell lymphoma/leukemia incidence.[21] The data presented here suggest a racial influence on PCNSL incidence and mortality. Quality of SEER data for racial groups was judged to be excellent. Nevertheless there are two limitations to the current study. First, the American population is becoming increasingly multiracial. Thus the impact of the African genome on tumorigenesis risk may become diluted. Second, racial classification uses self-selection of race. Thus patients might actually fall into different groups from those described by SEER. Because of the African diaspora, a larger retrospective series of international cases would increase power and diminish these two influences in order to determine whether there are demographic factors separate from race.

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