Appendix 1

Methods

Study design

This is a retrospective, single-center analysis which had been approved by the institutional review board at Montefiore Einstein Cancer Center, NYC. Consecutive patients treated at our tertiary care cancer center from 06/01/2000 to 04/05/2022 aged 18 or older with diagnosis of PCNSL were included in the study. The diagnosis was suggested through magnetic resonance imaging, and definitive diagnosis of PCNSL was made by a histopathological examination of a tumor specimen obtained through a stereotactic biopsy or a tumor resection. At the initial diagnosis, all patients underwent staging with computed tomography of the chest, abdomen and pelvis. All patients with involvement outside the central nervous system at the time of diagnosis were excluded from this study. For analyses of SES, we used a measure of neighborhood disadvantage called the Area Deprivation Index (ADI), a composite of 17 measures of education, employment, housing quality, and poverty validated across a range of diseases (12). We also compared outcomes with various induction and consolidation regimens in this cohort. Outcomes like overall survival and overall response rates were compared between HIV positive and HIV negative patients.

To identify subjects with PCNSL, we used structured language to query our Enterprise Data Warehouse for ICD 10 code C85.89. We reviewed electronic health records and collected the pertinent data, including patient demographics, address, HIV status, treatment details, performance status at the time of diagnosis, date of birth, and date of death or last contact. In those who were HIV positive, we collected information about CD4 counts and HIV viral loads at diagnosis, HCT-CI (hematopoietic cell transplantation-comorbidity index) and if they received HAART. In those who received ASCT, information about the date of stem cell infusion and conditioning regimen used was also collected. We determined the reason for patients who did not receive ASCT after reviewing oncology notes. ADIs were obtained by geocoding subjects' addresses using an online tool (https://geocoding.geo.census.gov/) and matching census block groups to ADI 2019 national percentiles. For categorical variables, χ^2 statistics were used, and the Mann-Whitney test was used for continuous variables. The Kaplan-Meier method was used to calculate the probabilities of overall survival (OS). For survival analyses, when there was an interval between the last date known to be alive and the first date known to have died, death was assumed at the end of the interval. Univariate analyses were done using Gray's test for cumulative incidence functions and the log rank test for OS. A Cox proportional hazards model was used for multivariate regression, and results were expressed as hazard ratios (HRs) with a 95% confidence interval (CI). All tests were two-sided. The type I error rate was fixed at 0.05 for the determination of factors associated with time-to-event outcomes. All analyses were performed using R version 3.4.0. (R Core Team, R: A Statistical Computing Language, 2014. R Foundation for Statistical Computing, Vienna, Austria).

Results

Clinical characteristics

Fifty-three patients with PCNSL were identified in our tertiary center. Out of the 53 patients, 10 (19%) were HIV-positive, 40 were HIV negative and the results of HIV testing for 3 patients were not available (HIV status unknown). Fifty-one percent (n=27/53) were males in the overall cohort as opposed to 60% (n=6/10) in HIV-positive patients. The PCNSL patients living with HIV (PLWH) in our cohort were significantly younger than their HIV-negative counterparts (median age in years; 45 *vs.* 64, P=0.006). Racial/ethnic distribution of our population: Asian (n=4) 7%, Black (n=18) 34%, Hispanic (n=17) 32%, White (n=7) 13%, and other/unknown (n=7) 13%. 17/53 (32%) patients received consolidative ASCT in the entire cohort. Our population had a higher poverty index than the national average (median NY state ADI 5th percentile, range 1–10, standard deviation 1.5 after median imputation.)

Forty-four patients received methotrexate-based induction regimens, the most common being RMV (Rituximab, Methotrexate, Vincristine) 47% (n=25); MPV (Methotrexate, Procarbazine, Vincristine) +/– Rituximab was used in 23% patients (n=12). Consolidation therapies were as follows, ASCT (n=17), WBRT (n=10), cytarabine-based chemotherapy (n=3), WBRT after cytarabine (n=1), and no consolidation (n=21).

Analysis of the treatment characteristics and its outcomes among patients living with HIV (PLWH)

Ninety percent (n=9) of the PLWH were receiving HAART.

60% (n=6) of PLWH were EBV positive by plasma antibody test and/or biopsy. The PLWH were significantly less likely to receive any induction treatment [60% vs. 95%, P=0.01] and more likely to receive WBRT for induction (OR =9, P=0.09) than their HIV-negative counterparts. 20% of PLWH did not receive any treatment while all of their HIV negative counterparts did. Among PLWH, that did receive treatment, 50% got methotrexate-based regimens (RMV/RMPV) for induction. Sixty percent of PLWH did not get any consolidation. PLWH were more likely to get WBRT for consolidation than their HIV negative counterparts (40% vs. 25% OR: 1.6, P=0.4). None of the PLWH received ASCT for consolidation, while 39.5% (17/43) of patients whose HIV status was negative/unknown underwent ASCT (P=0.01).

Overall, in our cohort, those receiving ASCT after a methotrexate-based induction regimen for consolidation had a significantly better mean/median overall survival of 170 month/not reached compared with 128 months/80 months in those receiving other consolidative treatments such as WBRT or chemotherapy (P=0.01). We observed that one-year overall survival favored autologous stem cell transplant over WBRT (87% vs. 76%, P=0.08). Out of all the patients receiving consolidation with ASCT, 87.5% were alive at the time of the last visit (range time from transplant: 161 to 2 months, median survival after ASCT 30 months). Notably, WBRT had a remarkable benefit with 75% alive at last follow-up. Patients not receiving consolidative therapy had a worse outcome with mean overall survival of 58 months and 14/21 alive at last follow-up (66.6%). The addition of Rituximab or procarbazine to induction regimens did not result in improved outcomes in survival (median overall survival 87 vs. 131 months, P=0.9 and median overall survival 147 vs. 122 months, P=0.23 respectively).

Since HIV-positive patients did not get ASCT, we compared their overall survival with HIV negative/unknown status patients and did not observe any significant differences. One-year OS was 63% in HIV-positive compared with 83% in HIV-negative/unknown status. The overall response rate (ORR) was 70% in the HIV negative patients and 40% in the HIV-positive patients (P=0.544). The mean OS for those who received methotrexate-based regimens with WBRT was 34.7 months in the entire cohort, but in PLWH it was a meagre 10.7 months. At the time of PCNSL diagnosis, 60% of the patients had uncontrolled HIV infection (CD4 T cell count <200 cells/microlitre and HIV RNA >500 copies/mL). There was no statistically significant difference in 1-year overall survival (65.5% vs. 80%, P=0.5) and early mortality (20% vs. 10%, P=0.6) than their HIV-negative/unknown counterparts. Seventy percent (n=7; 7/10) of the patients with HIV were alive at the last follow-up compared to the 81.4% (35/43) of the HIV-negative/unknown cohort.

Outcomes by demographic characteristics and access to ASCT

The median OS in males was 90 months, which was not reached in females. The difference in OS amongst the genders was reaching significance (P=0.07). No significant difference in OS was found between different races/ethnicity. ECOG ≥2 was significantly associated with poor survival probability (P=0.02). We analyzed the factors that can affect access to ASCT, as shown in *Table S1*. We found that age, gender, race/ethnicity and ADI (a measure of socioeconomic status) did not significantly decrease the likelihood of receiving ASCT. In a logistic regression model, HIV-positive status was significantly associated with decreased likelihood of receiving ASCT (P=0.01) in multivariate analysis. Poor performance status was the major reason impairing ASCT in PLWH and the overall cohort. We also calculated the hematopoietic cell transplantation-Comorbidity Index (HCT-CI) in PLWH, it was two or more in 7 patients, <2 in two patients and not available in one patient. The ECOG performance status at diagnosis was ≤2 in 82% of the patients who underwent ASCT, while only 53% of those who did receive ASCT had ECOG ≤2. The Karnofsky score was >90 in 44% of those who underwent ASCT, while only 22% of the patients who did not receive consolidative ASCT had a Karnofsky performance status score >90 (P=0.04). Hence poor performance status significantly limited utilization of ASCT in multivariate analysis.

References

12. Kind AJH, Buckingham WR. Making Neighborhood-Disadvantage Metrics Accessible - The Neighborhood Atlas. N Engl J Med 2018;378:2456-8.

Table S1 Analysis of the factors affecting access to ASCT in PCNSL (comparison of patient and transplant characteristics between those who received ASCT and those who did not)

Patient and transplant characteristics	ASCT (n=17)	No ASCT (n=36)	P value
Median follow up	36 (9–179) [21–42]	12 (0–186) [4.5–57]	0.3
Age (years)	63 (49–70) [55–66]	61 (23–84) [54–71.5]	0.45
Gender			
Male	8 (47%)	20 (56%)	0.56
Female	9 (53%)	16 (44%)	
Ethnicity			
Black	8 (47%)	10 (27.7%)	0.38
Hispanic	6 (35.2%)	11 (30.5%)	
White	2 (11.7%)	5 (13.8%)	
Asian	1 (5.8%)	3 (8.3%)	
Other/unknown	0	7 (19.4%)	
ECOG			
0	2 (12%)	3 (8%)	0.12
1	11 (65%)	10 (28%)	
2	1 (6%)	6 (17%)	
3	1 (6%)	2 (6%)	
4	1 (6%)	3 (8%)	
Missing	1 (6%)	12 (33%)	
Karnofsky score			
≥90	8 (47%)	8 (22%)	0.045
<90	7 (41%)	12 (33%)	
Missing	2 (12%)	16 (44%)	
HIV			
HIV+	0 (0%)	10 (28%)	0.01
HIV–	17 (100%)	23 (64%)	
Unknown	0 (0%)	3 (8%)	
Reason for no transplant			
Functional status	NA	14 (38.9%)	NA
Trial		2 (5.5%)	
Refused		4 (11%)	
Lost to follow up		1 (3%)	
Death		2 (5.5%)	
Compliance		3 (8%)	
Decline		1 (3%)	
Unknown		9 (25%)	
Diagnosis to transplant	6 (5–19) [5–7]	NA	NA
Conditioning[†]			
TBC	10 (59%)	NA	NA
BCNU/TT	1 (6%)		
BEAM	5 (29%)		
Overall survival (in months)	170	128	0.01

Data are shown as N (%)/median (range) [interquartile range]. [†], conditioning regimen information not available for one ASCT recipient. ASCT, autologous stem cell transplant; PCNSL, primary central nervous system lymphoma; Eastern Cooperative Oncology Group; HIV, human immunodeficiency virus; TBC, Thiotepa, busalfan and cyclophosphamide; BCNU, Bis-chloroethylnitrosourea, carmustine; TT, thiotepa; BEAM, etoposide, cytarabine, melphalan; NA, not applicable.