Letter to the Editor

Primary central nervous system lymphoma: treatment access and outcomes in HIV positive patients in a minority rich cohort

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Primary central nervous system lymphoma (PCNSL) is an aggressive acquired immune deficiency syndrome (AIDS) defining malignancy with poor prognosis. Historically PCNSL patients living with HIV (PLWH) had poorer outcomes compared with those without HIV, however the use of highly active antiretroviral therapy (HAART) has improved physicians' capacity to prescribe chemotherapy but there is limited data on how this progress affected the outcomes of PCNSL PLWH and their ability to undergo autologous stem cell transplantation (ASCT) which is a potentially curative treatment (1-4). We studied the patient characteristics and outcomes for PCNSL in the Bronx, which has a high prevalence and one of the highest rates of HIV infection (about 2.5 times the national average), particularly among women and minorities (5-7). Minorities comprise 89% of the Bronx population with 29% living below the poverty line (5-7).

The main objective was to compare differences in access to ASCT in patients who had HIV versus those who did not. Multiple methotrexate (M)-based induction regimens including rituximab (R), vincristine (V), procarbazine (P), etc. have been described in literature and used clinically but there is a dearth of studies describing the benefit of addition of procarbazine to these regimens (8).

This is a single center retrospective cohort study of 53 PCNSL patients treated between 2000–2020, whose characteristics were compared by using χ^2 statistics and Mann-Whitney test. Overall survival (OS) was calculated using Kaplan Meir. For analyses of socioeconomic status (SES), we used a measure of neighborhood disadvantage called the Area Deprivation Index (ADI), a composite of 17 measures validated across a range of diseases (9). High ADI indicates worse SES.

In our cohort, 19% (10/53) patients had HIV which is three times the global prevalence of HIV in patients with PCNSL (6.1%) (10). The HIV status of three patients was not available, hence they were excluded from the study. Although 32% of the patients received ASCT, they were all HIV negative. None of the patients with HIV (0/10) received ASCT. PCNSL PLWH were significantly younger than those without HIV (45 *vs.* 64 years, P=0.006) and were predominantly males (60% males in PLWH). Comparison of clinical characteristics of PLWH with patients without HIV is given in *Table 1*. Females had a better OS compared to males, a trend that was reaching statistical significance (90 months *vs.* not reached, P=0.07, *Figure 1*). Racial/ethnic distribution of our population was as follows: Asian (7%), Black (34%), Hispanic (32%), White (13%), and other/unknown (13%). Our population had a higher poverty index than the national average [median New York (NY) state ADI

Table 1 Comparison of clinical characteristics of HIV positive and negative patients

Demographics	†HIV positive (n=10)	HIV negative (n=40)	P value
Age (years)			0.006*
<30	2	0	
30–60	7	14	
>60	1	26	
Sex			0.736
Male	6	21	
Female	4	19	
Race			0.478
White	0	7	
Black	4	14	
Hispanic	5	12	
Asian	0	3	
Other	1	4	
ECOG at diagnosis			0.574
0	2	5	
1	2	18	
2	2	9	
3	1	4	
4	3	4	
Karnofsky at diagnosis			0.53
≥90	5	17	
<90	5	23	
ECOG after treatment			0.369
0	2	8	
1	3	9	
2	0	3	
3	0	10	
4	5	10	
Karnofsky post treatment			0.901
≥90	5	13	
<90	5	27	
ASCT for consolidation			0.01*
Received	0	17	
Not received	10	23	

Table 1 (*continued*)

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Demographics	†HIV positive (n=10)	HIV negative (n=40)	P value
WBRT for consolidation			0.405
Received	4	7	
Not received	6	33	
Best response			0.544
CR	3	23	
PD	5	7	
PR	1	5	
SD	1	5	
Survival probability			0.538
Overall, 1-year survival	63%	82%	
Median OS	Not reached	111 months	
Early mortality (within 3 months of PCNSL diagnosis)	20%	10%	0.6
Reasons for not receiving ASCT	(I) Poor performance status (60%); (II) refused ASCT (20%); (III) different consolidation therapy chosen in view of poor compliance to prior oncological treatment (20%)	(I) Poor performance status (31.9%); (II) refused ASCT (12.8%); (III) different consolidation therapy chosen in view of poor compliance to prior oncological treatment (15.9%); (IV) unknown (27.7%); (V) decline in functional status after induction therapy (6.4%); (VI) lost to follow up (5.3%)	–

†, the HIV status of three patients could not be found, hence they have not been described in the table above; *, statistical significance. HIV, human immunodeficiency virus; ECOG, Eastern Cooperative Oncology Group; ASCT, autologous stem cell transplantation; WBRT, whole brain radiotherapy; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; OS, overall survival; PCNSL, primary central nervous system lymphoma.

5th percentile, range 1–10, standard deviation 1.5]. Most common induction regimens were rituximab methotrexate vincristine (RMV) (47%) followed by rituximab methotrexate procarbazine vincristine (RMPV) (23%).

Patients who received consolidative ASCT had significantly better OS than those receiving other consolidation regimens (mean OS 170 *vs.* 128 months, P=0.01 and median OS not reached compared with 80 months, *Figure 1E*). All patients receiving ASCT were HIV negative. There was no difference between one year OS between ASCT and whole brain radiotherapy (WBRT) (87% *vs.* 76%, P=0.08). Adding procarbazine to induction regimens did not improve OS (median OS 147 *vs.* 122 months, P=0.23). The survival rate in those who underwent ASCT was remarkable, with 87.5% alive at the time of last visit (range time from transplant: 161 to 2 months, median OS after ASCT 30 months). Race/ethnicity, age and SES did not affect access to ASCT or OS. PLWH were significantly less likely to receive not only ASCT (P=0.01) but any induction treatment (60% *vs.* 95%, P=0.01). There is no difference in receiving induction WBRT in two groups (OR =9, P=0.09) than those without HIV. All HIV negative patients received treatment but 20% of PLWH did not receive any treatment. We evaluated why PLWH were not deemed to be suitable candidates for transplant and found that all the patients with uncontrolled HIV (60%, 6/10) (CD4 T cell count <200 cells/microlitre and HIV RNA >500 copies/mL) did not get ASCT due to poor performance status. Four PLWH with Eastern Cooperative Oncology Group (ECOG) performance status 0–1 after induction treatment and controlled HIV did not receive ASCT due to refusal (reasons like religious/personal beliefs in 2/4) and treating provider's recommendation for WBRT given poor compliance to prior oncological treatment (2/4, *Table 1*). PLWH did not have a significantly different ORR

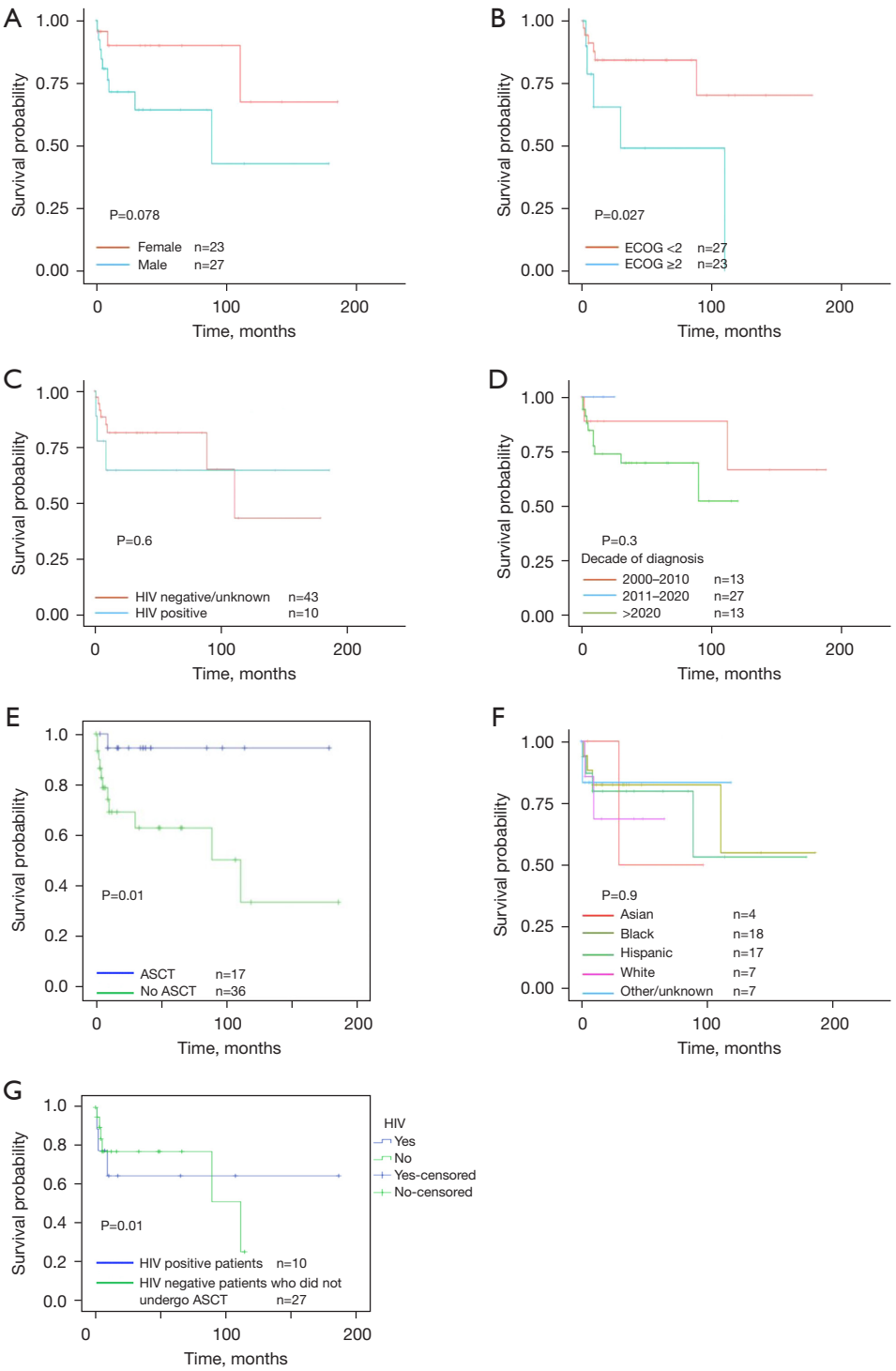

Figure 1 Survival probability curves comparing various clinical and demographic characteristics. (A) Survival probability curve comparing the genders; (B) survival probability curve comparing different ECOG performance statuses at the time of diagnosis; (C) survival probability curves by HIV status; (D) survival probability curve according to the decade of diagnosis; (E) survival probability curve comparing those who received consolidative ASCT after methotrexate-based induction regimen with those who did not; (F) survival probability curve comparing various races; (G) survival probability curve comparing HIV positive patients with HIV negative patients who did not receive ASCT. ECOG, Eastern Cooperative Oncology Group; HIV, human immunodeficiency virus; ASCT, autologous stem cell transplantation.

(70% *vs.* 40%, P=0.5) and 1-year OS (65.5% *vs.* 80%, P=0.5) than their HIV negative counterparts. Comparable survival outcomes in PCNSL patients with and without HIV are described in literature and are likely multifactorial but may be explained by the fact that 90% of PLWH were receiving HAART which has alone shown to lead to long-term remission and improved outcomes (1,11). The benefits of consolidative ASCT for PLWH could not be addressed in this study as no PLWH underwent ASCT [for detailed information, see the Supplementary file (Appendix 1)].

To conclude, ASCT improved survival in PCNSL but HIV positive status limited the utilization of ASCT, mainly due to poor functional status. Despite the cohort being socioeconomically disadvantaged and with potential barriers to treatment, the survival outcomes were pretty impressive with 70% (7/10) of the PLWH and 81.4% (35/43) of the HIV-negative/unknown patients alive at the last follow-up. To the best of our knowledge, this is the first study describing the disparities in utilization of ASCT in PCNSL PLWH. Early treatment with improved HAART and expanding access to multidisciplinary healthcare will enhance functional status and utilization of ASCT in PLWH. Limitations to our study include a retrospective design, small sample size, minority rich cohort which may not be generalizable and a single-center experience.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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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.

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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.

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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.