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Primary central nervous system lymphoma: a real-world comparison of therapy access and outcomes by hospital setting

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Abstract

Background. This study analyzes sociodemographic barriers for primary CNS lymphoma (PCNSL) treatment and outcomes at a public safety-net hospital versus a private tertiary academic institution. We hypothesized that these barriers would lead to access disparities and poorer outcomes in the safety-net population.

Methods. We reviewed records of PCNSL patients from 2007–2020 ($n = 95$) at a public safety-net hospital ($n = 33$) and a private academic center ($n = 62$) staffed by the same university. Demographics, treatment patterns, and outcomes were analyzed.

Results. Patients at the safety-net hospital were significantly younger, more commonly Black or Hispanic, and had a higher prevalence of HIV/AIDS. They were significantly less likely to receive induction chemotherapy (67% vs 86%, $P = .003$) or consolidation autologous stem cell transplantation (0% vs. 47%, $P = .001$), but received more whole-brain radiation therapy (35% vs 16%, $P = .001$). Younger age and receiving any consolidation therapy were associated with improved progression-free (PFS, $P = .001$) and overall survival (OS, $P = .001$). Hospital location had no statistical impact on PFS ($P = .725$) or OS ($P = .226$) on an age-adjusted analysis.

Conclusions. Our study shows significant differences in treatment patterns for PCNSL between a public safety-net hospital and an academic cancer center. A significant survival difference was not demonstrated, which is likely multifactorial, but likely was positively impacted by the shared multidisciplinary care delivery between the institutions. As personalized therapies for PCNSL are being developed, equitable access including clinical trials should be advocated for resource-limited settings.

Keywords

health services accessibility | healthcare disparities | outcomes | practice patterns | primary CNS lymphoma (PCNSL)

Primary central nervous system lymphoma (PCNSL) is an aggressive, extranodal non-Hodgkin lymphoma, usually of diffuse large B-cell (DLBCL) histology, that is confined to the neuraxis and typically has a poor prognosis. PCNSLs are relatively rare tumors, accounting for 1–2% of all non-Hodgkin lymphomas.[1] PCNSL can occur in the setting of

immunosuppression, such as patients with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) [PLWH], patients undergoing organ transplant, or on chronic immunosuppressive drugs; however, the incidence has been rising among immunocompetent adults over 60 years of age.[2]

The treatment of PCNSL typically consists of induction chemotherapy and subsequent consolidation therapies.[3,4] Despite general acceptance of induction regimens centered around high-dose methotrexate (HD-MTX) as cornerstones of treatment, consolidation strategies have not been optimized given the paucity of PCNSL.[3–6] Therefore, treatment practices across institutions vary regionally and globally. Additionally, optimal treatment of PCNSL may be subject to resource barriers; data show an increased rate of omitting chemotherapy in patients with markers of low socioeconomic status, specifically, lack of insurance and median income.[7] Further, autologous stem cell transplantation (ASCT), a current consolidation option, is subject to cost barriers.[8,9] At safety-net hospitals, there are often access issues, delays in seeking medical care, and limited treatment options due to insurance barriers and other prohibitive costs. Additionally, the association of patients living with HIV (PLWH) with lower socioeconomic status (SES)[10] reflects a particularly vulnerable population that are subject to both poor PCNSL prognosis and potential access issues.

This study compares the demographics, treatment patterns, and survival outcomes among PCNSL patients treated at a safety-net hospital versus a private academic hospital both treated by the same multidisciplinary team. We hypothesized that patients at our safety-net center would have different patterns of treatment compared to those at our tertiary academic institution and that the higher prevalence of HIV in our publicly funded center would confer inferior outcomes to the safety-net cohort.

Materials and Methods

Patients

University of Texas Southwestern Medical Center is an academic tertiary care center and National Cancer Institute (NCI)-designated comprehensive cancer center, whose patient population is mainly privately insured and Medicare patients. Parkland Hospital serves as a safety-net hospital mainly for uninsured residents of Dallas County. A multidisciplinary team of neuroradiologists, pathologists, neurosurgeons, neuro-, medical-, and radiation oncologists, serve at both clinical locations.

After receiving institutional IRB approval, a retrospective electronic chart review was conducted on medical records of patients treated for PCNSL from 2007 to 2020, at either a public safety-net hospital or an academic tertiary care center, both serving the same metroplex. Informed consent was waived due to the retrospective nature of our analysis. Patients were excluded if they were diagnosed with systemic DLBCL with secondary CNS involvement. Patient demographics and disease characteristics were collected at the time of diagnosis. These include patient age, sex, race, Memorial Sloan Kettering Cancer Center (MSKCC) prognostic class, and International Extranodal Study Group (IELSG) score. We additionally collected data on the induction and consolidation treatment modalities used.

Treatment Characteristics

HD-MTX protocols were utilized in treating PCNSL at both institutions. HD-MTX was typically given at 1–8 grams/m^2/cycle depending on the specific protocol, patient's baseline renal and hepatic function, and patient tolerance. Standard hydration and urinary alkalinization with target urine pH of 7.5 was utilized in all HD-MTX cases. Folinic acid rescue was provided 24 hours after each methotrexate dose and continued until serum methotrexate level was ≤ 0.10 uM/L. Following a positive response to induction HD-MTX, patients could be offered consolidation autologous stem cell transplantation (ASCT), whole-brain radiation therapy (WBRT), or further chemotherapy.

Outcomes

The primary outcomes analyzed were overall (OS) and progression-free survival (PFS). OS was defined as the time from initial treatment to death resulting from any cause or last follow-up. PFS was defined as the time from initial treatment to MRI-confirmed disease progression, relapse, death, or last follow-up. Response was assessed by brain magnetic resonance imaging (MRI) per the International Primary CNS Lymphoma Collaborative Group (IPCG) criteria.[11] Patients were retrospectively evaluated for the incidence of neurological toxicity as documented by the treating provider. Neurotoxicity was defined as neurologic deficits attributable to and following PCNSL treatment that was not caused by tumor recurrence, residual disease, or another identifiable cause. As our current standard of care, formal neurocognitive and neuropsychological testing is done at baseline and sequentially during and after treatment for PCNSL; however, in this retrospective analysis, this data was largely incomplete and based upon provider documentation of adverse effects of PCNSL treatment.

Statistical Analysis

Categorical variables and response rates were compared using Fisher's exact test. Continuous variables were compared using Mann-Whitney U test. Survival functions for overall- and progression-free survival (OS and PFS) were estimated by the Kaplan-Meier method and compared using a log-rank test. Cox proportional hazards regression was used for multivariable analysis to assess for confounding variables.

Results

Patient and Disease Characteristics

Median follow-up was 39 months for surviving patients and 11 months for all patients. Baseline characteristics of the study population are shown in Table 1. Compared to the tertiary academic center, patients at the safety-net hospital

Table 1. Baseline Characteristics of Patients at Diagnosis

Characteristic		Public safety-net hospital ($n = 33$)		Private academic center ($n = 62$)		Total ($n = 95$)		*P*-value
		N, % or Median, IQR		*N*, % or Median, IQR		*N*, % or Median, IQR		
Age		48	38–59	61	47–68	56	44–65	.002
Age groups	<60	26	79%	30	48%	56	59%	.008
	60–70	6	18%	19	31%	25	26%	
	70+	1	3%	13	21%	14	15%	
KPS		70	50–90	70	60–90	70	58–90	.394
Race	Asian	4	12%	5	8%	9	10%	<.001
	Black	8	24%	4	7%	12	13%	
	Caucasian	4	12%	41	66%	45	47%	
	Hispanic	17	52%	12	19%	29	31%	
Gender	Female	10	30%	33	53%	43	45%	.051
	Male	23	70%	29	47%	52	55%	
HIV status	PLWH	15	46%	3	5%	18	19%	<.001
MSKCC PC	Class I	18	55%	18	31%	36	40%	.091
	Class II	8	24%	24	41%	32	35%	
	Class III	7	21%	16	28%	23	25%	
ECOG PS	0	4	12%	7	12%	11	12%	.898
	1	10	30%	22	39%	32	36%	
	2	10	30%	17	30%	27	30%	
	3	5	15%	7	12%	12	13%	
	4	4	12%	4	7%	8	9%	
IESLG PS	low	7	21%	18	33%	25	28%	.358
	intermediate	22	67%	28	51%	50	57%	
	high	4	12%	9	16%	13	15%	
Deep structure involvement		23	70%	31	50%	54	57%	.083
Elevated serum LDH		11	33%	19	31%	30	32%	.820

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; IELSG PS, International Extranodal Lymphoma Study Group Prognostic Score; KPS, Karnofsky performance status; LDH, lactate dehydrogenase; MSKCC PC, Memorial Sloan Kettering Cancer Center Prognostic Class; PLWH, patients living with HIV.

were significantly younger, had better MSKCC prognostic class, more commonly Black or Hispanic, and had a higher proportion of PLWH.

Induction Modalities and Response

Figure 1 depicts the course of treatment and responses for our cohort by hospital setting.

Induction regimens used were either HD-MTX-based systemic chemotherapy ($n = 75$, median age 57 years) or WBRT ($n = 16$, median age 46 years). Four patients received only steroids and/or palliative care due to advanced disease/poor performance status at presentation (all treated at tertiary academic center, median age 65.5 years). The median number of cycles administered was 4 (range 1–9). Safety-net patients were significantly less likely to receive induction chemotherapy (22/33 [66.7%] vs 53/62 [85.5%], $P = 0.003$). Of patients who received induction HD-MTX, overall response rate (PR or CR) was 68.9%. There was no significant difference in response rate to chemo-based induction between safety-net and academic center patients (77.3% vs 60.4%, respectively, $P = 0.414$).

Within the total cohort, 27 (36%) had complete response (CR) and 22 (30%) had partial response (PR), while 23 (31%) had either progressive disease (PD) or no response to therapy. There was no difference in distribution of PRs and CRs by hospital setting ($P = 0.269$).

Consolidation Modalities

Patients who had a positive response to induction chemotherapy ($n = 49$) received either consolidative WBRT

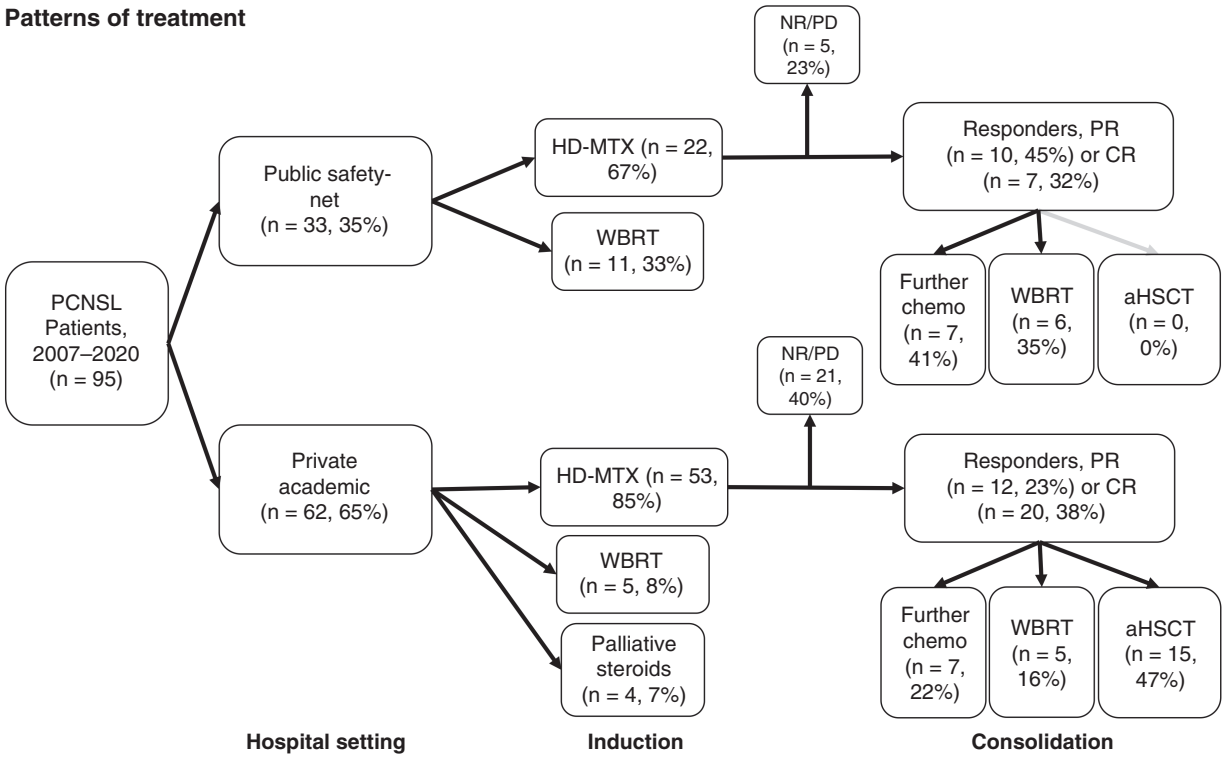

Figure 1. Treatment course of patients. Abbreviations: aHSCT: autologous hematopoietic stem cell transplant; CR: complete response; HD-MTX: high-dose methotrexate; NR/PD: no response/progressive disease; PCNSL: primary CNS lymphoma; PR: partial response; WBRT: whole-brainradiation therapy.

(*n* = 11), ASCT (*n* = 15), nonmyeloablative chemotherapy (*n* = 14), or no further treatment (*n* = 9) due to rapid disease relapse or poor performance status. When comparing safety-net and academic center patients, hospital location did not significantly affect whether patients received consolidation therapy following a response to induction (82.4% vs. 76.5%, respectively, *P* = 0.731). Patients over the age of 60 were significantly less likely to receive consolidation (9/16 [56.3%]) when compared to younger patients (31/35 [88.6%], *P* = 0.023).

Safety-net hospital patients were significantly less likely to receive ASCT (0% vs. 44.1%, *P* = 0.001) and had higher rates of consolidative WBRT (35.3% vs 14.7%, *P* = 0.001).

Second-Line and Salvage Treatments

Fifteen patients received second-line treatment for relapsed or refractory disease (chemotherapy, *n* = 9 [60%], a combination of chemotherapy and radiation (*n* = 3, [20%]), or WBRT, *n* = 3 [20%]). Only patients at the academic center received combined modality regimens.

Survival

The median PFS for our entire cohort was estimated to be 25 months. PFS rates at two years following diagnosis were 56% vs 43% at the safety-net and academic center hospitals, respectively, and were not significantly different (*P* = 0.294, Figure 2A). Younger age significantly increased PFS (*P* = 0.0017, Figure 2B). When adjusted for the differences in age distributions in the two patient populations, hospital setting again was not associated with PFS (*P* = 0.725, Odds Ratio [OR]: 1.12, 95% Confidence Interval [CI]: 0.60–2.09).

Median OS was not reached in our overall cohort. There was no significant difference in OS between patients treated at the safety-net compared to the academic center on univariate comparison (2-year OS: 77% vs 55%, *P* = 0.061, Figure 2E) or when adjusted for age (*P* = 0.226, OR: 1.66, 95% CI: 0.73–3.77). Younger age was independently associated with higher OS (*P* = 0.0012, Figure 2F). We also repeated our survival statistics after excluding PLWH and found similar results across hospital settings in both PFS and OS.

When comparing by induction treatment strategy, neither PFS nor OS were significantly different between patients receiving HD-MTX or upfront WBRT (2-year PFS: 56% vs 35%, *P* = 0.28, Figure 2C; 2-year OS: 67% vs 55%, *P* = 0.6, Figure 2G). In patients who had a response to induction HD-MTX (*n* = 49), receiving any form of consolidation following a response to induction chemotherapy was significantly associated with improved PFS and OS (*P* < 0.001 for both). Comparing survival outcomes between consolidation strategies in patients who received them (*n* = 40), there were no significant differences in PFS (*P* = 0.843, Figure 2D) or OS (*P* = 0.32, Figure 2H) between WBRT (2-year PFS: 91%,

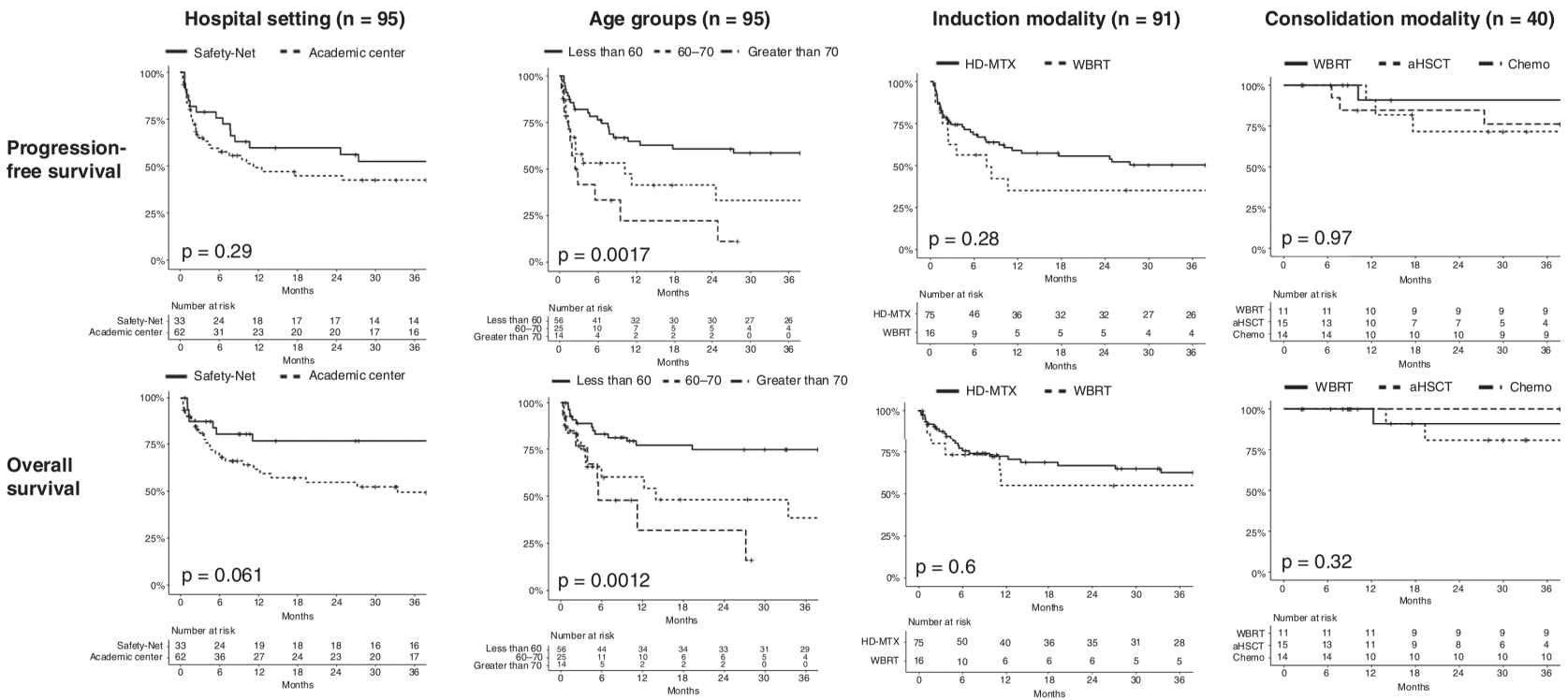

Figure 2. Survival curves by demographic and treatment factors. Abbreviations: aHSCT, autologous hematopoietic stem cell transplant; HD-MTX, high-dose methotrexate; OS, overall survival; PFS, progression-free survival; WBRT, whole-brain radiation therapy.

Table 2. Baseline Characteristics of Patients Living With HIV (PLWH)

Characteristic		PLWH (n = 18) N, % or Median, IQR	
Age		40	31–48
Age groups (Years)	<60	17	94%
	60–70	1	6%
	70+	0	0%
KPS		60	55–90
Race	Asian	3	17%
	Black	5	28%
	Caucasian	2	11%
	Hispanic	8	44%
Gender	Female	1	6%
	Male	17	94%
MSKCC PC	Class I	14	82%
	Class II	1	6%
	Class III	2	12%
ECOG PS	0	3	18%
	1	3	18%
	2	7	41%
	3	2	12%
	4	2	12%
IESLG PS	low	5	29%
	intermediate	11	65%
	high	1	6%

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; IELSG PS, International Extranodal Lymphoma Study Group Prognostic Score; KPS, Karnofsky performance status; MSKCC PC, Memorial Sloan Kettering Cancer Center Prognostic Class.

2-year OS: 91%), ASCT (2-year PFS: 72%, 2-year OS: 81%), or chemotherapy (2-year PFS: 85%, 2-year OS: 100%).

PLWH Subset Analysis

Our cohort included 18 confirmed PLWH, 15 of which were treated at the safety-net hospital. PLWH were overall younger (median age 40 vs 60, $P < 0.001$) and had a higher proportion of MSKCC prognostic score 1 (82.4% vs. 29.7%, $P = 0.001$) [Table 2]. Eleven (61%) received WBRT (10 at the safety-net hospital and 1 at the academic center) and 7 (39%) received upfront MTX-based chemotherapy (5 at safety-net hospital and 2 at academic center) as initial induction treatment. PLWH were less likely to receive chemotherapy (38.9% vs 88.9%, $P < 0.001$) and more likely to receive WBRT as initial treatment (61.1% vs. 6.9%, $P < 0.001$) when compared to the rest of the cohort. All 7 PLWH who received induction chemotherapy had a treatment response (PR or CR). There was no statistically significant effect of HIV status on response rates to induction (78% vs 58% for rest of cohort, $P = 0.177$) or on progression rates (17% vs 39%, $P = 0.100$). Our PLWH trended towards higher OS (81% 1-year OS, $P = 0.055$) and had significantly better PFS (1-year PFS 79%, $P = 0.039$) [Supplementary Figure 1]. When adjusted for age, these associations lost statistical significance (PFS $P = 0.154$, OS $P = 0.469$). Age remained a significant predictor of OS ($P = 0.012$, HR: 1.04 [1.01–1.07] for each year of age) on this analysis. When adjusted for age and HIV status, hospital setting remained a nonsignificant predictor of PFS ($P = 0.547$) and OS ($P = 0.371$).

Neurotoxicity

Three cases of neurotoxicity were documented in our cohort. All responded to initial MTX-based chemotherapy and proceeded to consolidation: 1 with WBRT, 1 with ASCT, and 1 with further chemotherapy. These patients' PCNSL was in CR to treatment at time of documented neurotoxicity. Neurotoxicity rates did not differ between hospital settings (3.0% at the safety-net hospital vs 3.2% at academic center, $P = 0.99$) and no neurotoxicity cases were documented in PLWH. Median time to neurotoxicity was 18.6 months. Of note, data from formal neurocognitive scales and scores sequentially were not available for most patients included in this analysis.

Discussion

This study retrospectively compared PCNSL patients treated at two hospital settings by the same team of

providers: a public safety-net hospital and a tertiary academic center, serving the same geographic region. We describe the differences in demographic characteristics and treatment patterns of patients at these institutions. Patients at the safety-net hospital were younger and trended towards a better baseline MSKCC prognostic class compared to those at the academic center. They also were more likely to be from a racial minority (Hispanic or Black) and be PLWH. The safety-net hospital patients less often received induction chemotherapy and did not receive a consolidative ASCT, with comparatively higher use of consolidative WBRT. Despite these treatment differences, there were no significant statistical differences in survival outcomes between the two cohorts.

Treatment patterns differed in both induction and consolidation between the two hospital settings despite being treated by the same multidisciplinary team. However, the divergence in induction patterns seem to be tied to demographic differences of the populations treated. Our finding of lower usage of induction HD-MTX in the safety-net setting in comparison to patients treated at the tertiary academic center can be strongly attributed to the high prevalence of PLWH (45.5%) in our safety-net cohort. HIV affects people with lower socioeconomic status (SES) at disproportionately high rates,[10] which is reflected in our higher rates in the resource-limited population traditionally treated at the safety-net hospital. Patients' HIV status is an important factor in the treatment modality and survival of patients with PCNSL. In general, HIV-associated lymphomas may present with more advanced disease and have decreased overall survival compared to HIV-negative patients.[2,12] Historically, HIV-associated PCNSL patients have been shown to have received a lower percentage of chemotherapy.[7] This was reflected in our PLWH cohort, which was significantly less likely to receive induction HD-MTX. This difference may be due to clinician decision to initially defer chemotherapy in PLWH who may have compromised immune status, concomitant opportunistic infections, and/or decreased functional reserve that resulted in pursuing nonchemotherapy treatment modalities such as WBRT.

All PLWH in our cohort that received HD-MTX had a PR or CR to induction (7/7). However, most PLWH (11/18) received WBRT as initial treatment, which led to our finding of higher upfront WBRT in our overall safety-net cohort.

Despite this treatment difference in induction therapy, OS and PFS were not statistically different in the safety-net cohort when compared to the tertiary hospital cohort, which more frequently received HD-MTX, and in fact trended towards better OS for safety-net patients (76.7% vs 54.7%, $P = 0.061$) on univariate but not age-adjusted analysis. This is contrary to many reports which have definitively demonstrated better outcomes with chemotherapy in PCNSL over WBRT alone.[13–19] However, our patients receiving WBRT alone had a median age of 46 years and were predominantly PLWH. We expected HIV to confer a poor outcome; however, our PLWH had improved survival outcomes when compared to the rest of our cohort on initial analysis despite their poorer prognosis and higher likelihood of chemotherapy omission. When adjusted for age, this comparison lost its significance; however, survival outcomes were still comparable to our cohort. Though our favorable survival in PLWH is contrary to the expected poor prognosis of this PCNSL subset, other more recent reports have also documented good outcomes in HIV-associated PCNSL. Research utilizing the National Cancer Database (NCDB), as well as single-center studies, have demonstrated increases in chemotherapy application in PLWH over time, correlating with improved survival in this population, though studies hypothesize that this also corresponds to improving antiretroviral therapy.[7,12,20] A retrospective Japanese series of 23 PCNSL patients who were treated with WBRT (along with antiretroviral therapy), found similar good outcomes.[21] Further, two recent series analyzing HIV-associated PCNSL treated with HD-MTX (again, along with antiretroviral therapy) found similar survival rates to immunocompetent PCNSL patients.[22,23] These studies postulated that advances in antiretroviral therapy had dramatically improved outcomes for this traditionally vulnerable patient population. Though we were unable to accurately obtain the details of the antiretroviral regimens employed in our patients, many of our patients were followed at a dedicated HIV clinic at our institution, so perhaps aggressive HIV/AIDS control was achieved. However, the main limitation of our analysis is the small total number of PLWH in our cohort (18 patients). Further, our data does not capture patients without a biopsy, and so may have excluded patients whose disease was too advanced to be a candidate for biopsy. This may disproportionately exclude PCNSL in PLWH, which as noted, have had historically poorer prognosis. Our study is underpowered and perhaps nonrepresentative, precluding us from making any definitive statements about the treatment of this vulnerable demographic. Prospective trials should be conducted to optimize clinical decision-making for this population specifically, who are subject not only to a more advanced disease course, but also concomitant access issues due to deeply rooted ties between lower SES and HIV.

Our study also showed significant differences in patterns of consolidation treatment following a positive response to HD-MTX-based induction chemotherapy. Safety-net patients were more likely to receive WBRT or nonmyeloablative chemotherapy as consolidation as they were unable to receive ASCT. In contrast with differences in induction, which we largely attribute to HIV status, this disparity in consolidation options is most certainly due to access and cost issues, as only patients at the private academic center were able to receive ASCT. In a prior claims database analysis, the median 100-day total costs for ASCT were estimated at $99 899 (interquartile range (IQR), $73 914–140 555).[9,24] Reports have described the barriers to access in stem cell transplantation, with age, sex, race, and insurance status all having been shown to affect likelihood of receiving transplantation.[8,24] With regards to insurance status, which we postulate as the primary reason our safety-net patients could not receive ASCT, the specific barriers could be related to delays in approvals or lack of coverage for this costly medical procedure.

Regardless of modality of consolidative therapy, receiving any form of consolidation therapy after a positive response to induction chemotherapy was a significant predictor of improved survival in our study

when compared to patients who had a positive response and did not proceed to consolidation, though we were unable to identify any statistical differences between the various consolidation regimens employed. When comparing the effect of various modalities of consolidation on survival, prospective studies have shown similar efficacy between WBRT and ASCT.[6,25] Further, high-dose consolidation chemotherapy without WBRT has been shown to have comparable PFS and OS rates to WBRT consolidation.[17] ASCT has been favored over WBRT for consolidation due to risks of radiation-induced neurotoxicity, especially in patients older than 60 years old,[11] while ASCT incurs more hematologic toxicity and associated severe infection risk.

In our study, there was no statistical difference in the rate of neurotoxicity between the two hospital systems. However, our neurotoxicity data is severely limited. The retrospective nature of our study and the lack of standardized neurotoxicity testing precludes us from comparing our data to larger, prospective trials, and inconsistencies in documentation may obfuscate true neurotoxicity rates. Further, there are significant clinical challenges when differentiating neurologic toxicities of PCNSL-directed treatment from deficits that are directly related to patients' disease. Our PLWH cohort presents another confounding variable due to the known association of HIV with neurocognitive impairment. Additionally, our inability to find documented toxicities attributable to PCNSL treatment in PLWH may be due to losing patients to follow-up, as neurotoxicity is known to take months to years to develop.[26] Given that safety-net patients were younger and had a higher percentage of receiving WBRT as a population, further studies in a larger population with standardized, validated assessment tools to assess the risk and severity of neurotoxicity are crucial to improve risk assessment and ensure optimal long-term outcomes for patients with PCNSL in resource-limited settings where WBRT may be the only economically feasible option and there may comparatively higher rates of HIV-associated PCNSL.

Despite these considerations, the optimal consolidation modality remains unknown, with institutional preferences and patient characteristics often playing the deciding role. Our study found no differences in OS or PFS between our hospital settings or the various consolidation strategies employed in our patients after HD-MTX induction. However, our negative findings could reflect differences in patient baseline characteristics due to a younger population at the safety-net hospital, where ASCT was not performed. A previous study by Chertack et. al has shown that integrated care across hospital settings by a single multidisciplinary team yields similar patient outcomes for testicular cancer patients despite variations in patient sociodemographic factors.[27] They hypothesized their outcomes were due to standardized care between hospital settings. Our similar outcomes could also have been impacted by expert management from a unified team overcoming the lack of access to ASCT. Either way, consolidation therapy of any type seems preferred in responders with good performance status over no consolidation, leaving flexibility according to resource availability. Future, prospective studies will be needed to optimize consolidation regimes in PCNSL. Beyond the current options (WBRT, ASCT, chemotherapy), novel targeted agents and immunotherapies are showing promise in relapsed/refractory PCNSL.[28–30]

This study is limited by its retrospective design, the small sample size within each treatment group, and heterogeneity in induction chemotherapy protocols between the hospital systems. Our finding of improved survival in eligible patients receiving consolidation is also underpowered and further, may reflect selection bias as patients who did not proceed to consolidation despite having a positive response may have had a poor baseline performance status that precluded them from receiving any further aggressive therapies. Hospital setting had significant collinearity with PLWH, younger age, and omission of chemotherapy in the safety-net cohort, making it difficult to ascertain each component's true effect on our survival outcomes. Inconsistencies in documentation between different hospital settings could potentially have masked any subtle differences between our cohorts. As previously mentioned, neurotoxicity data was not collected in a standardized fashion and was based on different treating provider documentation, making comparisons between our cohorts difficult.

However, we believe the true strength of the study is the uniqueness of a *"real-world"* comparison of outcomes by hospital setting which has not been undertaken in the PCNSL setting before. Though this is not a randomized study design, our patients were naturally separated by sociodemographic factors in two hospital settings under the same university umbrella. Thus, our findings yield real-world findings of disparities in treatment access in PCNSL that can be prospectively studied, and interventions evaluated across institutions nationally and globally.

Conclusion

PCNSL is an extranodal lymphoma with varying risk factors, diverse clinical presentations, and a heterogeneous approach to management. Our study shows that there are significant treatment differences between a public safety-net hospital and an academic cancer center reflecting socioeconomic and healthcare access disparities despite being cared for by the same oncology providers. Though survival outcomes were not different despite varying treatment patterns, the true effect may have been masked by a markedly younger population in our safety-net cohort. As there is still no "gold-standard" and treatment strategies are evolving in PCNSL, further research will be critical to determine how different risk groups (PLWH, other immunocompromised conditions, socioeconomic backgrounds, age, etc.) may be optimally managed using HD-MTX, WBRT, ASCT, alternative nonmyeloablative therapies, and targeted therapies. As these are investigated further, great care should be made to not only disseminate this knowledge beyond the academic community, but also ensure publicly funded hospitals are equipped to deliver consolidation modalities regardless of cost barriers that may exist (particularly in ASCT). It is essential to advocate for equitable access to the whole gamut of treatment strategies in resource-limited settings, to ensure that optimal care will be catered to vulnerable patient populations.

Supplementary Material

Supplementary material is available at *Neuro-Oncology Practice* online.

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Conflicts of interest statement. FTA has provided consultancy to: Genentech, Astrazeneca, Abbvie, Janssen, Pharmacyclics, Gilead sciences, Kite pharma, Celgene, Karyopharm, MEI Pharma, Verastem, Incyte, Beigene, Johnson and Johnson, Dava Oncology, BMS, Merck, Cardinal Health, ADCT therapeutics, Epizyme. PRG has provided consultancy to: Pharmacyclics, Kite pharma and Raphael Pharma. NBD has provided consultancy to Boston Scientific.

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