Clinicopathological Features and Outcomes in Primary Central Nervous System Lymphoma: A 10-year Experience

Abstract

Context: Primary central nervous system lymphoma (PCNSL) is a variant of extranodal lymphoma, accounting for 4% of primary central nervous system tumors. PCNSL was more common in immunocompetent individuals. International Extranodal Lymphoma Study Group (IELSG) scoring was used for prognostication. High-dose methotrexate regimens along with radiotherapy improved outcomes in PCNSL. **Aims:** The aim of this study is to analyze the clinical and pathological features, progression-free survival (PFS), and overall survival (OS) in patients with PCNSL. **Materials and Methods:** Data of patients with PCNSL between 2005 and 2016 were retrospectively analyzed. Outcome was analyzed in patients who received chemotherapy. GraphPad Prism software for Windows Version 6 was used to plot the Kaplan–Meier curves for PFS and OS. Log-rank test was used to calculate P values. $P < 0.05$ was considered as statistically significant. **Results:** A total of 42 patients were available for analysis. Of these, 34 patients who received chemotherapy were evaluable for outcome parameters. The median age at presentation was 46 years (range, 10–75) with male-to-female ratio of 2.2:1. Only 2 (4.7%) patients were HIV positive. Diffuse large B-cell lymphoma (DLBCL) was the most common histology seen in 41 (97.6%) patients. Using IELSG risk scoring, scores of 8 (19%), 19 (45.2%), and 15 (35.8%) were stratified into low, intermediate, and high risk. The median PFS and OS were 11 months (range, 2–72) and 15.9 months (2.4–80.4), respectively. The median OS was 36.2 months (range, 8.8–72), 15.6 months (2–36), and 6.1 months (2.6–12.7) in low-, intermediate-, and high-risk groups, respectively, which was statistically significant (P = 0.0002). **Conclusions:** Immunocompetent patients with PCNSL outnumber immunocompromised patients. DLBCL was the most common histology, and IELSG risk stratification significantly predicts the outcome in PCNSL.

Keywords: *International Extranodal Lymphoma Study Group, primary central nervous system lymphoma, survival*

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Introduction

Primary central nervous system lymphoma (PCNSL) is an uncommon variant of extranodal non-Hodgkin's lymphoma (NHL) involving brain, leptomeninges, eyes, or spinal cord without evidence of systemic disease. PCNSL represents approximately 4% of primary central nervous system tumors and 1% of all intracranial neoplasms.[1-3] Histologically, most of the PCNSLs were diffuse large B-cell lymphoma (DLBCL). Other histologies were seen in very few cases.[4-7] Most were immunocompetent individuals.[7,8] Usage of high-dose methotrexate-based chemotherapeutic regimens with or without whole-brain radiotherapy had improved survivals in PCNSL.[9-11] Addition of rituximab had further improved survivals in PCNSL, and

the International Extranodal Lymphoma Study Group (IELSG) prognostic score has shown to be a useful predictor of survival in PCNSL patients.[12,13] The primary objectives of this analysis were to study the clinicopathological and outcomes in PCNSL patients.

Materials and Methods

A contrast enhanced magnetic resonance imaging (MRI) of brain, Ophthalmological examination with slit lamp and fundoscopy were performed in all patients. Contrast-enhanced computed tomography (CECT) scan of the neck, chest, abdomen, and pelvis or positron emission tomography (PET)-CT scan, bone marrow aspiration and biopsy, testicular ultrasound examination, and cerebrospinal fluid analysis were performed to exclude

systemic lymphoma. The diagnosis was confirmed by stereotactic biopsy or excision of brain lesion.

Blood investigations included a complete hemogram, serum lactate dehydrogenase (LDH), liver function tests, and renal function tests. The IELSG prognostic score[14] was calculated for each patient based on five characteristics, i.e., age, Eastern Cooperative Oncology Group Performance Status, deep brain structure involvement, cerebrospinal fluid (CSF) protein elevation, and serum LDH levels. Each variable was assigned a value of 0 if favorable or of 1 if unfavorable, and the values of the five variables were added for final score calculation. Patients were grouped into risk groups based on final score as low risk (score 0–1), intermediate risk (score 2–3), and high risk (score 4–5).

Progression-free survival (PFS) was defined as the time from start of chemotherapy to the time that PD was documented, death, or lost to follow-up. Overall survival (OS) was defined as the time from start of chemotherapy to death due to any cause or lost to follow-up.

GraphPad Prism software for Windows Version 6 was used to plot the Kaplan–Meier curves for PFS and OS (GraphPad Software, La Jolla, California, USA, www.graphpad.com). Log-rank test was used to calculate *P* values. *P* < 0.05 was considered as statistically significant.

Results

Forty-two patients who were diagnosed with PCNSL between 2006 and 2016 were retrospectively analyzed. The median age at presentation was 46 years (range, 10–75) with male-to-female ratio of 2.2:1. The baseline characteristics of all patients were shown in Table 1. Only 2 patients were HIV positive and rest all were HIV negative.

Clinicopathological features

The most common symptom at presentation was headache (64.2%), followed by neurological deficits (54.7%), vomiting (47.6%), and neuropsychiatric features (19%), respectively. Diagnosis of PCNSL was based on stereotactic biopsy and excisional biopsy in 18 (42.8%) and 24 (57.1%), respectively. DLBCL was the most common histology seen in 41 (97.6%) patients, and Burkitt lymphoma was the histology in 1 (2.4%) patient. All patients were Leukocyte Common Antigen (LCA) and CD20 positive and CD3 negative. The clinicopathological features of all patients are depicted in Table 2.

The site and focality of the lesions in MRI scan were shown in Table 3. PET-CT scan was done in 10 (23.8%) patients, and CECT of the neck, chest, abdomen, and pelvis was done in 32 (76.2%) patients to exclude systemic lymphoma. CSF cytology was done in 38 patients, and out of which, 6 (15.8%) patients had positive CSF cytology and 32 (84.2%) patients had negative CSF cytology. CSF cytology was not done in 4 patients.

Table 1: Demographic features

Parameter	*n* (%)
Median age (range)	46 years (10-75)
Sex distribution	2.2:1
Males	29 (69)
Females	13 (31)
Immune status	
Immunocompetent	40 (95.2)
Immunocompromised	2 (4.8)
ECOG PS	
PS <2	8 (19.1)
PS ≥2	34 (80.9)

PS – Performance status, ECOG – Eastern Cooperative Oncology Group

Table 2: Clinicopathological features (*n*=42)

	n (%)
Symptoms at presentation	
Headache	27 (64.3)
Neurological deficits	23 (54.8)
Vomiting	20 (47.6)
Neuropsychiatric features	8 (19.1)
Seizures	7 (16.7)
Visual disturbances	7 (16.7)
Ataxia	6 (14.3)
Histology	
DLBCL	41 (97.6)
Burkitt lymphoma	1 (2.4)
CSF cytology (*n*=38)	
Positive	6 (15.8)
Negative	32 (84.2)
Serum protein (mg/dl) (range)	46 (20-86)
Serum LDH (IU/L) (range)	520 (220-850)

DLBCL – Diffuse large B-cell lymphoma; LDH – Lactate dehydrogenase; CSF – Cerebrospinal fluid

Table 3: Site and focality of the lesion (*n*=42)

Site of the lesion	*N* (%)
Cerebrum	22 (52.3)
Deep brain structures	20 (47.7)
Focality of the lesion	*N* (%)
Solitary lesion	32 (76.2)
Multifocal	10 (23.8)

Risk stratification

According to IELSG risk stratification, 8 (19%), 19 (45.2%), and 15 (35.8%) patients were stratified into low, intermediate, and high risk, respectively. Risk stratification according to IELSG risk score was shown in Table 4.

Treatment outcomes for all patients

A total of 34 (80.9%) received chemotherapy with or without radiotherapy. Eight (19.1%) patients defaulted and not received any treatment.

The treatment regimens used were shown in Table 5. DeAngelis protocol was the most common treatment regimen used (27/34, 79.4%). Rituximab was added to DeAngelis in 29.4% of patients. The other regimens used were steroid with radiotherapy and Berlin–Frankfurt–Munster-NHL protocol in 6 (17.7%) and 1 (2.9%) patients, respectively.

With a median follow-up period was 18 months, the median PFS and OS were 11 months (range, 2–72) and 15.9 months (range, 2.4–80.4), respectively. The 1-year, 2-year, and 3-year survivals were 61.7%, 32.3%, and 17.6%, respectively. The median PFS and OS were shown in Figures 1 and 2. The median PFS and OS for patients taking DeAngelis protocol were 12.7 months (range, 2–72) and 18.6 months (range, 2.4–80.4), respectively.

The median PFS in low, intermediate, and high risk was 30.5 months (range, 8.8–72), 12 months (range, 2–36), and 4.5 months (range, 2.6–12.7), respectively ($P \leq 0.0001$). The median OS was 36.2 months (range, 14.7–80.4),

15.6 months (range, 4.8–39), and 6.1 months (range, 2.4–15.1) in low-, intermediate-, and high-risk patients, respectively ($P = 0.0002$). The median PFS and OS according to IELSG risk scoring was shown in Figures 3 and 4, respectively.

Discussion

This is a retrospective analysis of patients with PCNSL. In our study, we had evaluated all patients who were diagnosed as primary central nervous lymphoma and those who received chemotherapy and radiotherapy were evaluated for outcome parameters.

Of the 42 patients, 34 were evaluable for outcome parameters. Eight patients were lost to follow-up after diagnosis. They were excluded from the analysis of outcome parameters.

The median age at presentation of 46 years was similar to other studies by Lakshmaiah *et al.*,[15] Paul *et al.*,[16] and Pasricha *et al.*[17] but lower than compared to studies by Haldorsen *et al.*,[18] Agarwal *et al.*,[19] and Gupta *et al.*[20] The gender ratio of 2.2:1 was higher compared to other Indian studies. The comparison of demographic and pathological features with other studies was tabulated in Table 6.

DLBCL was the most common histology accounting for 97.6% of cases similar to the studies by Lakshmaiah *et al.*, Paul *et al.*, Pasricha *et al.*, and Agarwal *et al.*, where 95%–100% of cases were DLBCL. On imaging, solitary lesions are generally considered more common than multiple lesions. In this analysis, solitary lesions were higher than multiple lesions, similar to studies by Gupta *et al.*, Pasricha *et al.*, and Paul *et al.* but in contrast to studies by Agarwal *et al.* and Herrlinger *et al.*[21] which showed multiple lesions are more common than solitary lesions.

The incidence of CSF cytology positivity in immunocompetent patients is reported be 26%–31%.[22] However, in the present study, only 14% had

Table 4: International Extranodal Lymphoma Study Group risk stratification

Risk group	Total number (*n*=42), *n* (%)	Treatment received (*n*=34), *n* (%)
Low risk	8 (19)	8 (23.5)
Intermediate risk	19 (45.2)	17 (50)
High risk	15 (35.8)	9 (26.5)

Table 5: Treatment received (*n*=34)

Treatment received	*n* (%)
Modified DeAngelis	17 (50)
Modified DeAngelis + rituximab	10 (29.4)
Steroid + radiotherapy	6 (17.7)
BFM-NHL protocol	1 (3)

NHL – Non-Hodgkin's lymphoma; BFM – Berlin–Frankfurt–Munster
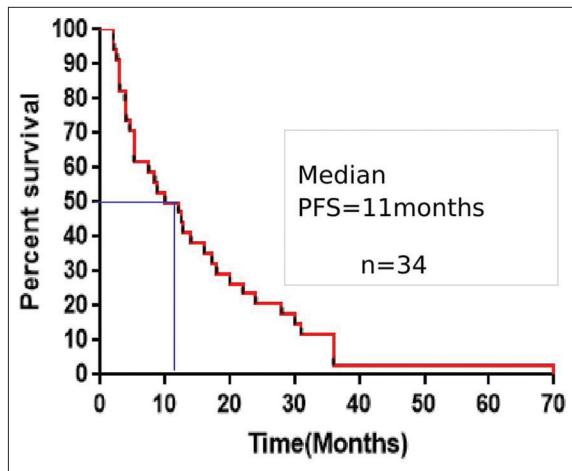

Figure 1: Kaplan–Meier estimates of progression-free survival for all patients (PFS – Progression-free survival)
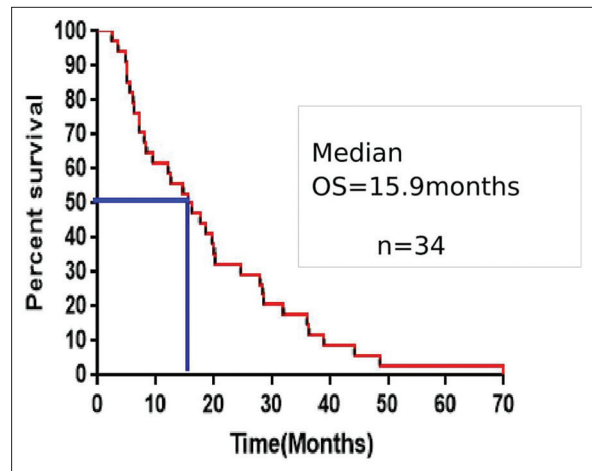

Figure 2: Kaplan–Meier estimates of overall survival for all patients (OS – Overall survival)

Table 6: Comparison of demographic and clinicopathological features with other studies

Parameter	Lakshmaiah *et al.* (*n*=33)	Haldorsen *et al.* (*n*=58)	Paul *et al.* (*n*=56)	Parischa *et al.* (*n*=66)	Agarwal *et al.* (*n*=26)	Present study (*n*=42)
Median age (years)	40	68.3	42	46	59	46
Gender ratio	3.1:1	1:1	1.5:1	1:1	2:1	2.2:1
Immunocompromised	1 (3)	3 (5.1)	1 (1.8)	0	2 (3)	2 (4.8)
Histology						
DLBCL (%)	100	-	100	100	96.2	97.6
Others	-				3.8	3.4
CSF cytology						
Positive	2	3	-	1	0	6 (14.3)
Negative	31	55	-	65		36 (85.7)

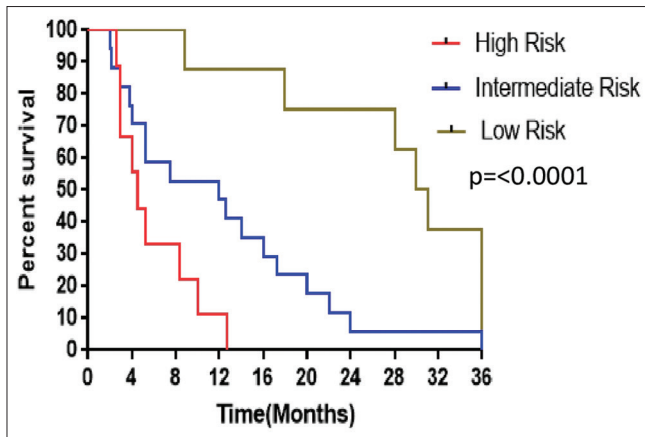DLBCL – Diffuse large B-cell lymphoma; CSF – Cerebrospinal fluid

Figure 3: Kaplan–Meier estimates of progression-free survival of patients based on International Extranodal Lymphoma Study Group risk scoring

Figure 4: Kaplan–Meier estimates of overall survival of patients based on International Extranodal Lymphoma Study Group risk scoring

cytology positivity. This was higher than the reports by Agarwal *et al.* and Lakshmaiah *et al.* and similar to that reported by Haldorsen *et al.*

Various malignant and nonmalignant conditions such as gliomas, metastases, toxoplasmosis, tuberculosis, and progressive multifocal leukoencephalopathy are differential diagnosis for PCNSL, and it is not possible to diagnose PCNSL radiologically in all cases; hence, histopathological examination is mandatory for confirmation of diagnosis. In the present study, 42.8% and 57.2% had diagnosis based on stereotactic biopsy and surgical excision, respectively. CECT of the neck, chest, abdomen, and pelvis or PET-CT scan should be used to exclude disease outside the central nervous system in all cases of PCNSL. In the present study, majority of the patients had CECT scan and only 19% had PET-CT scan as a part of routine staging workup.

IELSG and MSKCC scoring systems[23] are used to prognosticate patients in PCNSL. In the present study, IELSG scoring system was used to risk stratify patients into low, intermediate, and high risk. Treatment of PCNSL involves a multimodality approach with chemotherapy and radiotherapy. With the advent of high-dose methotrexate-based regimens, survivals in PCNSL were improved dramatically and now they became the standard
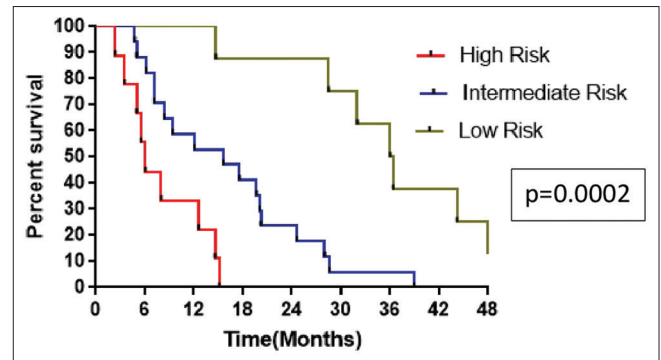
of care. The addition of rituximab to high-dose methotrexate further improved the survivals in PCNSL. In the present study, 50% and 33.3% of patients received high-dose methotrexate chemotherapy with and without rituximab, respectively. Eight patients were lost to follow-up due to various reasons and had not received any further therapy.

In a large study by DeAngelis *et al.*[24] with 102 patients, the use of high-dose methotrexate, high-dose cytarabine, and whole-brain radiotherapy resulted in median PFS of 24 months and OS of 36 months. Abrey *et al.*[25] in their study on long-term survival in PCNSL patients had shown a median cause-specific survival of 42 months, and Yi *et al.*[26] in their study showed median OS of 26 months with DeAngelis protocol. The median OS of 15.6 months in the present study was similar to study by Lakshmaiah *et al.* but higher than the study by Agarwal *et al.*

Risk stratification according to IELSG risk scoring done in the present study showed the median OS of 36.2 months, 15.6 months, and 6.1 months in low-, intermediate-, and high-risk groups, respectively, showing that IELSG risk scoring had a significant impact on outcome. The comparison of survivals with other studies is tabulated in Table 7.

The drawbacks of the present study are that it is retrospective, with limited data on adverse effects of chemotherapy. There is an incomplete documentation of hematological and nonhematological toxicity.

Table 7: Comparison of survival with other studies

	DeAngelis *et al.*	Yi *et al.*	Lakshmaiah *et al.*	Agarwal *et al.*	Present study
Median PFS (months)	24	-	-	-	12
Median OS (months)	36	26	15	10	15.6

PFS – Progression-free survival; OS – Overall survival

Conclusions

The findings of this study have significant implications for clinical practice. Immunocompetent patients with PCNSL outnumber immunocompromised patients. DLBCL is the most common histology of PCNSL. Even though survivals had improved with high-dose methotrexate regimens, they are still low compared to lymphomas of other sites. There is a need to develop more effective regimens. IELSG risk scoring system had a significant impact on survival.

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Conflicts of interest

There are no conflicts of interest.

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