

Primary central nervous system lymphoma: An Indian Perspective

K. C. Lakshmaiah, Vishwanath Sathyanarayanan, K. Govind Babu, D. Lokanatha, K. N. Lokesh, M. C. Suresh Babu, Clementina Rama Rao¹, C. S. Premalatha¹, T. M. Suresh, Vineetha Unnikrishnan, Linu Jacob Abraham

Departments of Medical Oncology and ¹Pathology, Kidwai Memorial Institute of Oncology, Bengaluru, Karnataka, India

ABSTRACT

Context: Primary central nervous system lymphoma (PCNSL) is an unusual entity comprising around 5% of extra nodal lymphomas with a dismal prognosis in spite of a multi-modality treatment protocol involving chemotherapy and radiotherapy. There is sporadic data from this part of the world and hence we took up this study to analyze the outcome with various modalities of treatment. **Materials and Methods:** We undertook this study between January 2007 and January 2013 on 33 consecutive patients diagnosed with PCNSL to analyze the clinical profile and treatment outcomes of PCNSL at a tertiary care oncology center in South India. Twelve patients received the DeAngelis protocol and the remaining 21 patients received either radiotherapy or a combination of radiotherapy and anthracycline based therapy or steroids. This study also compared the outcomes with protocols of DeAngelis *et al.* and cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) regimen with/out radiotherapy. **Results:** A total of 33 patients with PCNSL were studied. Median age was 40 years (range 22-75 years). Male: Female ratio was 3.1:1. All 33 were histologically diffuse large B-cell lymphoma (DLBCL). HIV was positive in 1. The most common presenting symptom was focal neurological deficits in 19 (58%). Cerebrospinal fluid was positive in 2 (6%). The area of involvement was mainly cerebral hemispheres 20 (61%). The treatment protocols followed were DeAngelis in 12, cyclophosphamide, doxorubicin, vincristine and prednisolone with radiotherapy (CHOP + radiation therapy [RT]) in 12, RT alone in 6, CHOP in 2 and 1 received no therapy. On a median follow-up of 17 months, the median overall survival was 15 months (range 1-60 months) with DeAngelis protocol and 12 months (range 8-24 months) with CHOP + RT. **Conclusions:** DeAngelis protocol has improved the prognosis in patients with PCNSL compared with other protocols as shown in our study. Newer chemotherapy regimens or targeted therapies need to be evaluated to further improve the survival.

Key words: DeAngelis protocol, cyclophosphamide, doxorubicin, vincristine, and prednisone, India, primary central nervous system lymphoma

INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is an aggressive lymphoma involving only the (CNS-brain parenchyma, spinal cord, eyes, cranial nerves, and/or meninges.^[1] It is an unusual entity comprising around 5% of extra nodal lymphomas with a dismal prognosis in spite of a multi-modality treatment protocol. Most of the PCNSL are histologically diffuse large B-cell lymphoma (DLBCL). The prognosis of patients with PCNSL is dismal and inferior

compared with DLBCL occurring in other sites. PCNSL exhibits unique biologic features and only certain drugs penetrate the blood brain barrier and give a therapeutic benefit. Moreover, the patients with PCNSL generally have a poor Eastern Cooperative Oncology Group (ECOG) performance status at presentation and delivering the right chemotherapeutic drug with minimal toxicity and achieving the maximum benefit becomes a challenge. Long-term follow-up of these patients with special emphasis to radiation induced neurotoxicity is also an important aspect of the management.^[2] Various chemotherapeutic regimens, including high-dose methotrexate (HD-MTX), high-dose cytarabine, procarbazine and vincristine have been tried. Anthracycline based regimens have also been tried and studies are on to assess the role of rituximab both systemically and intrathecally. Other newer drugs like temozolamide have also been tried in relapsed and progressive disease with limited success. We undertook this study at our center to analyze the profile and outcome in

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Address for correspondence: Dr. Vishwanath Sathyanarayanan, Department of Medical Oncology, OPD-5, Kidwai Memorial Institute of Oncology, Dr. MH Marigowda Road, Bengaluru - 560 029, Karnataka, India. E-mail: vishsathya@gmail.com

our patients with PCNSL treated with DeAngelis Protocol or radiotherapy alone or a combination of radiotherapy and anthracycline based therapy (cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP]). The DeAngelis protocol^[3] consists of 19 weeks of therapy, which involves chemotherapy and radiotherapy. It involves a combination of MTX, intrathecal MTX, vincristine, procarbazine, dexamethasone, high-dose cytarabine, and whole brain radiotherapy (WBRT). CHOP was given q3 weekly in this study.

MATERIALS AND METHODS

This was a retrospective study, undertaken at Kidwai Memorial Institute of Oncology, Bangalore, Karnataka, India between January 2007 and January 2013 on 33 consecutive patients diagnosed with PCNSL. Twelve patients received the DeAngelis protocol and the remaining 21 patients received either radiotherapy or a combination of radiotherapy and anthracycline based therapy.

The DeAngelis protocol^[4] is summarized below:

- MTX intravenous (iv) 2.5 g/m² on weeks 1, 3, 5, 7 and 9
- Vincristine iv 1.4 mg/m² on weeks 1, 3, 5, 7, 9
- Procarbazine per oral 100 mg/m²/day for 7 days on weeks 1, 5, 9
- Intrathecal MTX 12 mg on weeks 2, 4, 6, 8, 10
- Leucovorin per oral 20 mg every 6 h for 12 doses on weeks 1, 3, 5, 7, and 9 following MTX
- Dexamethasone per oral tapering dose for 7 days (16, 12, 8, 6, 4, 2 mg on weeks 1-6)
- WBRT was planned for a total dose of 45 Gy in 1.80 Gy fractions (weeks 11-15)
- Cytarabine 3 g/m²/day for 2 days on weeks 16 and 19.

The CHOP regimen included: Cyclophosphamide 750 mg/m² iv d1, Vincristine 1.4 mg/m² iv d1, adriamycin 50 mg/m² iv d1, prednisolone PO 100 mg/day × 5 days. This regimen was given q3 weekly for 6 cycles.

All the patients underwent a detailed history and physical examination including a neurological assessment. Investigations directed to the diagnosis - contrast-enhanced computed tomography (CT) of the brain or magnetic resonance imaging, positron emission tomography (if affordable), cerebrospinal fluid (CSF) analysis for cytology, histopathological diagnosis (following stereotactic or open biopsy), CT of the thorax and abdomen and bone marrow biopsy were done. Investigations to assess the general status, including hemogram, comprehensive metabolic profile, chest X-ray, and two-dimensional-echocardiography were also done. Memorial-Sloan Kettering Cancer Center (MSKCC) prognostic score was calculated. Class 1 - patients < 50 years. Class 2 - patients ≥ 50 years; Karnofsky performance

status (KPS) ≥ 70. Class 3 - patients ≥ 50 years; KPS < 70. A diagnosis of PCNSL was made only if the primary site of involvement was brain, spinal cord, meninges or eyes. Involvement of other sites other than the above were included under secondary lymphoma with CNS involvement and hence excluded from the study. Median overall survival (OS) was calculated from the date of diagnosis to the date of death.

RESULTS

Of the 33 patients who were studied, median age was 40 years (range 22-75 years). Male: Female ratio was 3.1:1. All were histologically DLBCL. Of 33 patients of PCNSL, one patient had HIV positivity. B symptoms are very uncommon in patients with PCNSL and 7 out of 33 patients (21.21%) had B symptoms in our study. The most common presenting symptoms were focal neurological deficits (hemi paresis, cranial nerve palsies, aphasia, cerebellar signs), followed by raised intracranial tension features, neuropsychiatric features, seizures and ocular symptoms. This has been summarized in Table 1. CSF cytology was positive in two patients (6%). The median serum lactate dehydrogenase (LDH) was 234 U/L and was elevated in nine patients (27%). The area of involvement was mainly cerebral hemispheres 20 (61%), periventricular regions 8 (24%), thalamus in 9 (27%), leptomeninges in 3 (9%), corpus callosum in 5 (15%) and cerebellum in 4 (12%). It has been summarized in Table 2. The risk stratification according to MSKCC risk score was Class 1 in 61%, class 2 in 12% and Class 3 in 27%. The diagnostic

Table 1: Summarizing clinical presentation of the 33 patients in our study

Symptoms and signs	Number (N=33)	%
Focal neurological deficits (hemiparesis, cranial nerve palsies, aphasia, cerebellar signs)	19	58
Raised intracranial tension (headache, vomiting, papilledema)	10	30
Neuropsychiatric features (behavioural abnormalities, somnolence, memory disturbances)	7	21
Ocular symptoms (blurring of vision, floaters, blindness)	3	9
Seizures	5	15

Table 2: Summarizing different areas of involvement in our study

Area of involvement	No (N=33)	%
Multifocal	23	70
Solitary	10	30
Hemispheres	20	61
Periventricular regions	8	24
Thalamus/basal ganglia	9	27
Leptomeningeal enhancement	3	9
Corpus callosum	5	15
Cerebellum	4	12

procedures employed were stereotactic biopsy in 49%, surgical decompression in 24%, excisional biopsy in 18% and open biopsy in 9%. The treatment protocols followed were DeAngelis in 12, CHOP + radiation therapy (RT) in 12, RT alone in 6, CHOP in 2 and 1 received no therapy. The median OS was 15 months (range 1-60 months) with DeAngelis protocol and 12 months (range 8-24 months) with CHOP + RT [Table 3].

DISCUSSION

Primary central nervous system lymphoma is an unusual entity comprising approximately 3-4% of all intracranial neoplasms and 5% of extra nodal lymphomas. It is a tumor confined to the CNS involving the brain parenchyma, leptomeninges, spinal cord and also the eyes.^[5,6] Involvement of these sites in the context of systemic manifestations is secondary CNS lymphoma. It presents most commonly with focal neurological deficits and has a dismal prognosis in spite of various chemotherapeutic and radiation oncological interventions.

The only documented and established role as a risk factor is congenital or acquired immune deficiency. Though HIV was a major cause of PCNSL in the 1980s and 1990s, the trend has changed with the introduction of antiretroviral therapy (ART). With the advent of ART, the incidence in HIV positive individuals was reduced and on the contrary, the incidence in immune competent individuals is increasing manifold.^[7]

This pattern is also seen in our series from a regional cancer center, where we analyzed 33 consecutive patients with PCNSL over the last 6 years, there was only one patient with HIV positivity. Histologically, more than 90% of PCNSLs are DLBCL with expression of B-cell markers - CD19, CD20, CD22, CD79a and BCL-6 and presence of immunoblasts and centroblasts with an affinity for blood vessels. Burkitt's and T-cell lymphomas account for the remaining 10% of the cases encountered.^[8,9]

Primary central nervous system lymphoma arises from late germinal center lymphoid cells and confined to the CNS. Gene expression studies have revealed germinal center type, activated B-cell type and large B-cell variants

of DLBCL.^[9] Though there are no B lymphocytes in the CNS, activated B lymphocytes from elsewhere in the body, which have acquired unique surface markers enter the CNS and multiply in an environment where there is no immunological surveillance.^[10]

Various pathogenesis mechanisms have been suggested for the development of PCNSL including interaction of extracellular matrix proteins confined to the CNS and tumor cells, the NF-kB activation, inactivation of p14ARF and p16INK4a and the upregulation of IL-4 pathway with its major mediator, the activated form of STAT6. High STAT6 has also got prognostic significance with patients poorly responding to MTX based chemotherapy. Up regulation of osteopontin (SPP1) is also observed in PCNSL, which is involved in CNS tropism and B-cell migration.^[11] Other mechanisms for the development of PCNSL include mutations in the PRDM1 gene, missense polymorphism D919G in methionine synthase, CpG island promoter hypermethylation, vascular endothelial growth factor (VEGF) up regulation and altered homocysteine and folate metabolism.^[12-14] The median age of diagnosis for PCNSL is around 60 years in immunocompetent individuals with a male preponderance. In our study, the median age was 40 years (range 22-75 years) with a male preponderance (1.3:1). In immunocompromised patients, PCNSL incidence is two decades earlier.^[15]

However, in our study, there was one patient with HIV positivity who received DeAngelis protocol. B symptoms are very uncommon in patients with PCNSL and a similar observation was made in our study with only 21.21% having B symptoms.^[6] Patients present with focal neurological deficits, organic brain syndromes, and personality changes.^[16] Patients can also present with increased intracranial tension features presenting with headaches, nausea and vomiting. In our study, focal neurological deficits were seen in 19 (58%) - the most common symptom followed by raised intracranial features in 10 (30%). Seven presented with memory disturbances and five presented with seizures. Seizures are not quite common as the tumor mainly involve the sub cortical white matter rather than the epileptogenic grey matter.^[16] Five of our patients who had seizures had involvement of frontal cortex. Ocular symptoms are seen in around 10% of patients. Three of our patients (9%) had visual blurring.^[17] Making a diagnosis of PCNSL should be made with caution and exclusion of systemic lymphoma with CNS involvement is a prerequisite. Evaluation should include examination of enlarged and testicular examination as primary testicular lymphoma has a predilection for the CNS. The International PCNSL collaborative group guidelines were used to diagnose PCNSL and also excludes systemic lymphoma.^[18] The guidelines include a detailed history

Table 3: Summarizing the treatment details in our study

Treatment	No. of patients	CR	PR	PD
DeAngelis protocol	12	9	1	1
CHOP+RT	12	7	3	2
RT alone	6	3	2	1
CHOP	2	1	1	0
No treatment	1	0	0	0

CHOP: Cyclophosphamide, doxorubicin, vincristine, prednisolone, RT: Radiotherapy, CR: Complete response, PR: Partial response, PD: Progressive disease

and physical examination, ophthalmological evaluation, HIV serology, LDH, CSF cytology, flow cytometry and immunoglobulin heavy chain polymerase chain reaction. Imaging includes CT brain, thorax, abdomen and pelvis, MRI brain and testicular ultrasonography in elderly men. Concurrent meningeal involvement is detected by CSF cytology examination in 16% of patients and in our study, CSF cytology was positive in two patients (6%).^[19] We did all the above investigations except CSF flow cytometry and immunoglobulin heavy chain assessment in CSF due to financial constraints.^[17] MRI brain, contrast-enhanced CT brain and PET scan are used to diagnose PCNSL. They present as solitary or multifocal lesions which are isointense or hypointense on T2-weighted MRI, with perilesional edema and homogeneous contrast-enhancement.^[20] Where MRI is not possible, contrast-enhanced CT scan of the brain is done. The lesions are usually found in hemispheres, basal ganglia, corpus callosum, and periventricular regions. Various oncological and non oncological conditions-gliomas, metastases, tuberculosis, toxoplasmosis, sarcoidosis, and progressive multifocal leukoencephalopathy are to be considered in the list of differential diagnosis.^[20] In our study, multifocal involvement was more common - seen in 70% of the patients, which is in contrary to other studies where solitary lesions are common.

Most PCNSL involve deeper structures of the brain in contrary to inflammatory conditions. Nevertheless, it is not possible to diagnose this entity radiologically with 100% accuracy. 18F-fluorodeoxyglucose PET-CT scanning can be done to differentiate from PCNSL from systemic lymphoma involving CNS. Use of PET-CT scanning has also been used in other studies to exclude an occult systemic lymphoma.^[21] In our study, we used 18F-fluorodeoxyglucose PET-CT scanning for one of our patient (61 year/female) who had progressive disease following DeAngelis protocol. International Extranodal Lymphoma Study Group (IELSG) scoring system and the MSKCC prognostic score based on age, performance status (PS), and extent of disease are used to assess the prognosis of patients with PCNSL. The IELSG prognostic score includes age more than 60 years, ECOG score more than 1 (KPS < 70%), elevated serum LDH level, high CSF protein concentration, and involvement of the deep regions of the brain (periventricular regions, basal ganglia, brainstem, and/or cerebellum).^[22,23] In our study, we used the MSKCC score and a higher score was associated with a poor survival. Treatment involves a multi-modality approach of chemotherapy and RT. Surgery is not shown to be advantageous and studies have not shown a difference in OS. Craniotomy for decompression of the mass (no change in outcome)/stereotactic/open biopsy is required for a histopathological diagnosis.^[3] The treatment of this entity has evolved over the years with radiotherapy in the form of WBRT being the most important treatment until the early

2000s. WBRT is associated with a higher complete response rate (CRR), but also high recurrence rate. Hence, it has been more or less replaced by combining chemotherapy to the WBRT. These chemotherapeutic agents should have the capability to cross the blood brain barrier. HD-MTX is widely recognized as the single most effective chemotherapeutic agent for PCNSL. In a large study by DeAngelis *et al.* in 2002,^[4] involving 102 newly diagnosed immunocompetent patients with PCNSL, patients first received five cycles of HD-MTX, vincristine, procarbazine and intraventricular MTX (12 mg). WBRT was administered to a total dose of 45 Gy and all patients received high-dose cytarabine after WBRT. Fifty-eight percent of patients with measurable disease had a CR to preirradiation chemotherapy and 36% had a partial response, with a 94% response rate. Median progression-free survival (PFS) was 24.0 months and OS was 36.9 months. Yi *et al.* in 2006 reported his data of 18 patients with DeAngelis protocol with a median OS of 26 months.^[24] In an Indian study by Agarwal *et al.*, 22 patients were studied with DeAngelis protocol. They reported a median OS of 10 months.^[25] Shah *et al.* demonstrated a CRR of 78% with DeAngelis protocol and an estimated 2 years PFS and OS was 57% and 67% after a median follow-up of 37 months.^[26] Rubenstein *et al.* studied 44 patients with immunochemotherapeutic regimen in a multicenter cooperative group trial without WBRT. In this trial, patients were treated with induction chemotherapy consisting of HD MTX at 8 g/m² (day 1, q 2 weekly for the first 7 doses with leucovorin rescue 100 mg/m² q 6 hourly until MTX level < 0.05 nM, rituximab at 375 mg/m² (day 3 once per week × 6 doses), and temozolomide at 150 mg/m² (days 7-11 of first 5 months)- MTR induction. MTR induction was followed by consolidation chemotherapy that included intravenous etoposide 5 mg/kg as a continuous infusion over 96 h (total 40 mg/kg) and cytarabine at 2 g/m² every 12 h for 8 doses. The CRR on induction chemotherapy was 66%. With a median follow up of 4.9 years, the 2 years PFS was 57% and the median OS was not reached.^[27]

In our study, we used DeAngelis protocol or RT + CHOP or only RT. On a median follow-up of 17 months, the OS was 15 months (range 1-60 months) with DeAngelis protocol and 12 months with CHOP + RT. The comparison of other studies where DeAngelis protocol was used with our study has been summarized in Table 4. The clinical characteristics of our patients where DeAngelis protocol was used is also mentioned in Table 5. Anthracycline based chemotherapy - CHOP has been used in patients with PCNSL. In various case series, the addition of CHOP to HD-MTX resulted in increased toxicity with no improvement in survival. There is a rapid response with CHOP regimen, but also early relapse and progressive disease. Anthracyclines act mainly in the area where blood brain barrier is disrupted and hence the rapid response. With the attainment of response, the BBB is normalized and hence

Table 4: Comparison of various studies using DeAngelis protocol and the current study with outcome

Study	No. of patients	Protocol	HIV	WBRT	Relapse	Response (%)	PFS	OS
DeAngelis (2002) ^[4]	98	De angelis	-	+ (45-55Gy)/36 Gy hyper fractionated regimen	33 patients (34%)	ORR-94 CR-58 PR-36 to chemo CR-61.1	24 months	36.9 m
Yl <i>et al.</i> (2006) ^[24]	18	De Angelis	-	Yes	-	ORR-72.7	-	26 m
Agarwal <i>et al.</i> (2009) ^[25]	22	De Angelis	+ in (2 patients)	Yes	-	ORR-72.7	-	10 m
Present study (2013)	12	De Angelis	-	Yes	-	ORR-90 CR-75	OS 15m	

CR: Complete response, HIV: Human immunodeficiency virus, m: Months, ORR: Overall response rate, OS: Overall survival, PR: Partial response, PFS: Progression free survival, WBRT: Whole brain radiotherapy

Table 5: Patient characteristics in the present study (where DeAngelis protocol was used)

Age/sex	Symptoms	ECOG PS	Diagnosis	LDH	CSF	CT/MRI	Biopsy for diagnosis	WBRT	Response	EFS	Outcome
58/M	Behavioural abnormalities, Decreased memory	2	DLBCL	283	+	Corpus callosum involvement	stereotactic biopsy	Yes	CR	26 m	Alive NED
48/F	R hemiparesis, urinary incontinence, dysphagia, irrelevant talk, visual blurring	4	DLBCL	400	-	R Cerebellopontine angle, L diencephalon, L supracellar, medial temporal lesions	stereotactic biopsy	Yes	CR	20 m	LTFU
52/F	Headache, visual blurring, memory disturbance	2	DLBCL	354	-	L frontal lesion	L frontoparietal craniotomy and gross excision	Yes	CR	60 m	Alive NED
44/F	Involuntary movements left side of body	1	DLBCL	173	-	Enhancing lesion extra axial mass in R parafalcine aspect	simpson grade 2 excision	Yes	CR	10 m	Alive with NED
22/M	Headache	2	DLBCL	214	-	Multiple lesions in R and L frontal, basifrontal and periventricular region	R frontal craniotomy	Yes	PR	10 m	LTFU
27/M	Difficulty in walking, seizures	3	DLBCL	256	-	Mediolateral parenchymal, supratentorial and infratentorial enhancing nodular lesions with leptomeningeal cistern, hydrocephalus	Paramedian sub occipital craniotomy+ decompression	Yes	CR	7 m	LTFU
40/M	Headache	1	DLBCL	320	-	Suprasellar mass lesion in third ventricle	Biopsy	Yes	CR	9 m	LTFU
26/F	L focal seizures, blurring of vision	1	DLBCL	164	-	Multiple enhancing lesions R frontal and inferior temporal with mass effect	stereotactic biopsy	Yes	CR	16 m	Alive NED
18/M	Headache, seizures	2	DLBCL	220	-	Bilateral frontal lesions	stereotactic biopsy	Yes	-	2 m	LTFU
32/M	Headache, R sided weakness, convulsions	4	DLBCL	234	-	L high medial frontal lesion	L frontal craniotomy	Yes	-	1 m	LTFU
61/F	Headache, R sided weakness	4	DLBCL	345	-	Ill defined lesion in L temporo-parietal region and basal ganglia	L fronto temporal craniotomy	No	Progressive disease	6 m	Alive with disease
52/M	Headache, visual blurring, memory disturbances, ataxia	2	DLBCL	302	-	CE mass in L fronto-parietal area mass effect R frontal mass	L frontal craniotomy	Yes	CR	60 m	LTFU

CE: Contrast enhanced, DLBCL: Diffuse large B cell lymphoma, R: Right, L: Left, EFS: Event free survival, NED: No evidence of disease, LTFU: Lost to follow up, CR: Complete response, PR: Partial response, L: Left, M: Male, F: Female, ECOG PS: Eastern cooperative group performance status, LDH: Lactate dehydrogenase, CT: Computed tomography, MRI: Magnetic resonance imaging, M: Months, WBRT: Whole brain radiotherapy

anthracyclines no longer act on the microscopic disease and hence the response is short lived.^[28] In the CSF, rituximab reaches 0.1% of the serum concentration.^[29] Therefore, its role is not clear in the management of PCNSL. Schultz *et al.* in 1996 reported 52 patients of PCNSL treated with CHOP with RT having median survival of 16.1 months.^[30]

CONCLUSION

To conclude, the treatment of PCNSL with a HD-MTX combined with cranial irradiation is an effective therapeutic approach to PCNSL. Despite treatment, the outcome is dismal. It needs the development of new protocols involving

high-dose or intraventricular polychemotherapy, rituximab, consolidating radiotherapy, high-dose chemotherapy followed by stem cell rescue. It is of utmost importance to search for new effective and tolerable treatment strategies in case of recurrence. Therapeutic options for PCNSLs in immunocompromised patients should be more thoroughly investigated. Integration of fluoro-deoxyglucose positron emission tomography into prospective trials is warranted to investigate prognostic and therapeutic implications. The strength of the current study includes the large number of patients from a single institution and limitations include the inadequate follow-up. There is limited data on this entity from the sub-continent and hence adds to the current literature. However, further studies are required incorporating newer regimens like the methotrexate, temozolamide and rituximab (MTR regimen) and also on the role of autologous stem cell transplantation.

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