MAK HILL Publications Research Journal of Medical Sciences

Research Article
doi: 10.59218/makrjms.2024.6.6.12

Study of Clinical Features and Outcome in Patients of Primary CNS Lymphoma at a Regional Cancer Hospital

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OPEN ACCESS

Key Words
PCNS lymphoma, ECOG performance status, IELSG score, chemotherapy

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Received: 24 February 2024
Accepted: 2 March 2024
Published: 3 April 2024

Citation: Tushar R. Mule, Pooja S. Mote, Prabhakar S. Jirwankar and Asha A. Anan, 2024. Study of Clinical Features and Outcome in Patients of Primary CNS Lymphoma at a Regional Cancer Hospital. Res. J. Med. Sci., 18: 6-12, doi: 10.59218/makrjms.2024.6.6.12

ABSTRACT

Primary central nervous system lymphoma (PCNSL) is an aggressive lymphoma involving only the CNS (brain parenchyma, spinal cord, eyes, cranial nerves and meninges). Present study was aimed to study clinical features and outcome in patients of primary CNS lymphoma, at a regional cancer hospital. Present study was single-center, prospective, observational study, conducted in patients with pathologically proven Primary central nervous system lymphoma (PCNSL). In present study, out of the 41 patients of PCNS Lymphoma the number of male and females patients were 26 (63.4%) and 15 (36.5%) respectively. Maximum patients were within age group of 51-60 years (29.2 %). Maximum patient in our study were in ECOG PS 3 group i.e. 14 (34.14%) followed by ECOG PS 2 group i.e. 12 (29.26%). Majority patients presented with focal neurological deficit (hemi paresis, cranial nerve palsies, aphasia, cerebellar signs) (58.53%), followed by neuro psychotic symptoms (apathy, depression, confusion or cognitive decline) (53.65%) and features of raised intra cranial tension (headache, vomiting or impaired consciousness) (51.21%). 22 (53.65%) patients with PCNS lymphoma had single brain lesion while 19 (46.34%) patient had multiple brain lesion. Majority patients fall in IELSG score of 3 (29.26%) followed by score 2 (26.82%). Majority patients underwent gross total excision of lesion (51.21%) followed by stereotactic biopsy (24.39%), subtotal excision and open biopsy (9.75% each). Majority received combination chemotherapy plus WBART (39.02%). 37 patients who were available for survival analysis median OS was 14.8 months for maximum follow up of 21.3 months. On univariate survival analysis of possible prognostic factors for survival for the patients with PCNS Lymphoma, factors found to be significant were treatment, ECOG performance status, age and IELSG score.

INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is an aggressive lymphoma involving only the CNS (brain parenchyma, spinal cord, eyes, cranial nerves and meninges). 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)[1,2]. 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 [3,4]. Long term follow up of these patients with special emphasis to radiation induced neurotoxicity is also an important aspect of the management. Various chemotherapeutic regimens, including high dose methotrexate (HD MTX), high dose cytarabine, procarbazine, vincristine and anthracycline based regimens have been tried and studies are on to assess the role of rituximab both systemically and intrathecally[5,6]. Other newer drugs like temozolamide have also been tried in relapsed and progressive disease with limited success. Present study was aimed to study clinical features and outcome in patients of primary CNS lymphoma, at a regional cancer hospital.

MATERIAL AND METHODS

Present study was single-center, prospective, observational study, conducted in department of Department of Medical and Paediatric Oncology, Gujarat Cancer and Research Institute, B.J. Medical College, Ahmedabad, India. Study duration was of 2 years (OCTOBER 2015 TO DECEMBER 2017). Study approval was obtained from institutional ethical committee. In the present study, all patients with pathologically proven Primary central nervous system lymphoma (PCNSL), presented at our hospital during study period, willing to participate in present study were studied. Study was explained to patients in local language and written consent was taken for participation and study. Clinical features (age, sex, presenting symptoms, date of presentation, ECOG-PS) were recorded. Serological tests (HIV by ELISA, CBC, S. RFT, S. LFT and S.LDH) were done in all patients. Radiological test such as Contrast-enhanced MRI brain OR CECT brain, CT or USG of the chest, abdomen and pelvis were done and Imaging features including number, location enhancement characteristics of lesions were recorded. Bone marrow biopsy was done in all the patients to rule out systemic lymphoma. Cerebrospinal fluid (CSF) examination including cytological evaluation for malignant cells was performed in all the patients, except if contraindicated. Histological subtype of the tumor with grading of tumor cells on hematoxylin and eosin-stained slides, and/or immunohistochemical details, including typing for leucocyte common antigen (LCA), CD20 (B cell marker), MUM-1and CD3 (T cell marker) etc. performed on formalin-fixed, paraffin-embedded tissue samples, were recorded.

The time interval from onset of symptoms to establishment of the diagnosis was recorded. Complete ophthalmologic examination was performed in all the patients. The IELSG prognostic score was calculated for each patient. Details of treatment (chemotherapy/radiotherapy) were documented. Follow-up imaging was performed after completion of therapy and then after 3 months. 'Complete response' was defined as the disappearance of all signal enhancement on MRI. Overall survival (OS) was calculated from the date of pathologic diagnosis to death or to the last date of follow-up. Data was collected and compiled using Microsoft Excel, analysed using SPSS 23.0 version. Frequency, percentage, means and standard deviations (SD) was calculated for the continuous variables, while ratios and proportions were calculated for the categorical variables. Difference of proportions between qualitative variables were tested using chi- square test or Fisher exact test as applicable. P value less than 0.5 was considered as statistically significant.

RESULTS AND DISCUSSIONS

In present study, out of the 41 patients of PCNS Lymphoma the number of male and females patients were 26(63.4%) and 15(36.5%) respectively. Male to female ratio was 1.73:1. The mean and median age of distribution were 50.21±17.25 years and 54 years respectively. Including both males and females maximum patients were within age group of 51-60 years i.e. 12 (29.2%). Maximum patient in our study were in ECOG PS 3 group i.e. 14 (34.14%) followed by ECOG PS 2 group i.e. 12 (29.26%). In present study majority of the patient 25 (60.97%) had normal serum LDH levels, had elevated CSF protein level 21 (51.21%) and were negative for CSF cytology 39 (95.12%). Majority patients presented with focal neurological deficit (hemi paresis, cranial nerve palsies, aphasia, cerebellar signs) (58.53%), followed by neuro psychotic symptoms (apathy, depression, confusion or cognitive decline) (53.65%) and features of raised intra cranial tension (headache, vomiting or impaired consciousness) (51.21%). Seizure (19.51%) and visual blurring (2.43%) were least common presentation. In present study 22 (53.65%) patients with PCNS lymphoma had single brain lesion while 19 (46.34%) patient had multiple brain lesion. Maximum patients

had lesion in frontal lobe (41.46%) followed by periventricular (36.58%) whereas corpus callosum (12.19%) and cerebellum (7.31%) were least commonly involved sites. Majority patients fall in IELSG score of 3 (29.26%) followed by score 2 (26.82%). In present study, majority patients underwent gross total excision of lesion (51.21%) followed by stereotactic biopsy (24.39%), subtotal excision and open biopsy (9.75% each). Out of the 24 patient who have received combination chemotherapy plus WBART 16 (39.02%) patients were treated with deangelis protocol, 3 (7.31%) patient were treated with RMVP protocol and 1 (2.43%) patient was treated with SA MTX. 4 (16.66%) out of 24 patients received WBRT first of which 3 patients were treated with RCHOP and 1 with DHAP. In our study out of 41 patients of PCNS lymphoma 4 (09.75%) patients lost to follow up. Five (12.19%) of the 41 patients did not receive any chemo-or radiotherapy. Again 5 (12.19%) of the 41 patients were treated with WBRT only due to poor performance status and advanced age. Three (07.31%) patients have received chemotherapy only. In present study total 16 patients could complete DEANGELIS protocol. One Patient died at week 7 of DEANGILIS protocol due to febrile neutropenia. When these patients were evaluated at completion of therapy 12 (70.58%) patients were in CR, 3 (17.64%) patients were in PR and 1 (5.88%) patient was in SD with ORR of (88.22%). All the 12 patients who were in CR at 3 months were in CR at final visit. Of the 3 patients who were in PR 1 remained in PR and 2 patients were dead at the time of final evaluation. Median OS was not reached and at 30-month follow-up OS was 82%.

All the 3 patients treated with RMVP were in CR at completion of treatment and at the time of final evaluation with ORR of 100%. One patient was treated with WBRT followed by DHAP for 6 # was in CR at completion and at the time of final evaluation with ORR of 100%. Of the 3 patients treated with WBRT+RCHOP 2 (67%) were in CR and 1 (33%) was in PR at completion with ORR Of 100%. Of the 2 patients who were in CR at completion of therapy 1 was in CR at the time of final evaluation and 1 patient died. One patient who was in PR was dead at the time of final evaluation. Comparison between individual protocol was not possible as sample size was too small. (CR-complete radiographic response computed, PD-progressive disease, PR-partial response, SD-Stable disease). Of the 27 patients who received chemotherapy, the treatments had been well tolerated in 20 patients. Five and two patients had grade 3 and above neutropenia in HD MTX based group and Cyclophosphamide based group respectively. One patient in both the group had febrile neutropenia. Mucositis was observed in 4 and 1 patient in MTX based and Cyclophosphamide based group respectively. Vomiting was observed in 2 and 1 patient in MTX based and Cyclophosphamide based group respectively. Anemia and thrombocytopenia were observed in 2 patients in HD MTX based chemotherapy. One patient in HD MTX group had died at week 7 of DEANGILIS protocol due to febrile neutropenia and renal failure. One patient in Cyclophosphamide based group who received one course of CVP died of septic meningitis.

In present study 1 patient was treated with WBRT followed by DHAP and he was presented with complaints of decreased hearing, SNHL was reported in this patient after pure tone audiometry. Overall toxicity was less in our study as patients were positively selected for the treatment. In present study 37 patients who were available for survival analysis median OS was 14.8 months for maximum follow up of 21.3 months. On univariate survival analysis of possible prognostic factors for survival for the patients with PCNS Lymphoma, factors found to be significant were treatment ($p<0.0001$), ECOG performance status ($p<0.0001$), age ($p<0.013$) and IELSG score ($p<0.0001$).

Primary central nervous system lymphoma (PCNSL) is an uncommon variant of extra nodal non-Hodgkin lymphoma (NHL) that involves the brain, leptomeninges, eyes, or spinal cord without evidence of systemic disease. PCNSL represents approximately 4% of newly diagnosed primary central nervous system (CNS) tumors, with an age-adjusted incidence rate of four cases per million persons per year[1,2].

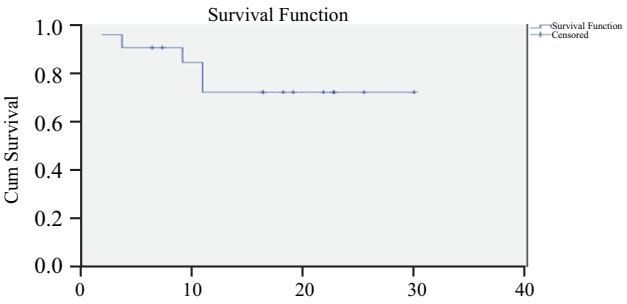

Fig. 1: Cum Survival and Survival Function and Months

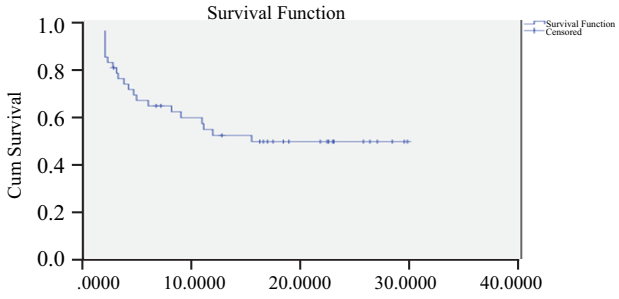

Fig. 2: Cum Survival and Survival Function and Months

Table 1: Age wise distribution

Age (Years)	Male	Female	Total
11-20	0	2 (13.33%)	02 (04.87%)
21-30	3 (11.53%)	3 (20.00%)	06 (14.63%)
31-40	3 (11.53%)	0	03 (07.31%)
41-50	5 (19.23%)	1 (06.66%)	06 (14.63%)
51-60	6 (23.07%)	6 (40.00%)	12 (29.26%)
61-70	5 (19.23%)	2 (13.33%)	07 (17.07%)
71-80	4 (15.38%)	1 (06.66%)	05 (12.19%)
Total	26 (63.4%)	15 (36.6%)	41 (100%)
Mean Age (Years)	50.21 ± 17.25		

Table 2: ECOG PS status

ECOG PS status	No. of patients (n = 41)	Percentage
0	2	4.88
1	9	21.95
2	12	29.27
3	14	34.15
4	4	9.76

Table 3: Biochemical and cytology findings

Parameter	No. of patients (n = 41)	Percentage
LDH Level		
Normal	25	60.98
Elevated	16	39.02
CSF Protein		
Normal	20	48.78
Elevated >45mg/dl	21	51.22
CSF Cytology		
Positive	2	4.88
Negative	39	95.12

Table 4: Clinical presentation

Clinical Presentation	No. of patients (n = 41)	Percentage
Focal Neurological deficit	24	58.54
Neuro psychotic symptoms	22	53.66
Raised intracranial tension	21	51.22
Seizure	8	19.51
Visual	1	2.44

Table 5: Brain lesion

Brain Lesion	No. of patients (n = 41)	Percentage
Numbers		
Single	22	53.66
Multiple	19	46.34
Location		
Frontal	17	41.46
Parietal	9	21.95
Temporal	12	29.27
Cerebellar	3	7.32
Thalamus	7	17.07
CC	5	12.2
PV	15	36.59

Table 6: IELSG score

IELSG Score	No. of patients (n = 41)	Percentage
0	1	2.44
1	11	26.83
2	7	17.07
3	12	29.27
4	6	14.63
5	4	9.76

Table 7: Mode of biopsy

Mode of Biopsy	No. of patients (n = 41)	Percentage
Stereotactic Biopsy	10	24.39
Gross Total Excision	21	51.22
Subtotal excision	4	9.76
Open biopsy	4	9.76
Decompression	2	4.88

Most cases of non-AIDS related PCNSL are diagnosed in patients between 45 and 65 years of age, with a median age at diagnosis is 55-60 years[3,4]. In the study conducted by Pankaj A Agrawal *et al.*[4] males were 61.53%, while Miller *et al.*[3] also had 61.53% male patients. In majority of studies including present study there was male preponderance. PCL accounts for up to 15% of non-Hodgkin lymphomas (NHLs) in human immunodeficiency virus (HIV)-infected patients compared with only 1 percent of NHLs in the general population[5]. The incidence of PCL increases with prolonged survival from human immunodeficiency

Table 8: Treatment wise distribution

Treatment	No. of patients (n = 41)	Percentage
CT+RT	24	58.54
DEANGELIS	16	39.02
RMVP	3	7.32
RCHOP	3	7.32
DHAP	1	2.44
SAMTX	1	2.44
CT	3	7.32
RT	5	12.2
Supportive Rx	5	12.2
No Rx- LFU	4	9.76

Table 9: Response at completion of therapy and at final visit

	DeAngelis + WBRT(n=16+1)		RMVP + WBRT (n=3)		SA MTX+WBRT (n=1)		WBRT +RCHOP (n=3)		WBRT+DHAP (n=1)	
	At completion	At final visit	At completion	At final visit	At completion	At final visit	At completion	At final visit	At completion	At final visit
CR	12	12	3	3	1	1	2	1	1	1
PR	3	1	-	-	-	-	1	-	-	-
SD	1	-	-	-	-	-	-	-	-	-
PD	-		-	-	-	-	-	-	-	-
Relapse Or Death	1	4	-	-	-	-	-	2	-	-

Table 10: Complications associated with treatment

	DeAngelis (N = 17) + RMVP (N = 3) + SA MTX (N = 1)	RCHOP (N = 4) +CVP (N = 1)	DHAP (N = 1)
Anemia	2 (09.04%)	-	-
Neutropenia	5(23.80%)	2 (50%)	-
Thrombocytopenia	2 (09.52%)		-
Febrile neutropenia	1 (04.76%)	1 (25%)	-
Nausea	2 (09.52%)		-
Vomiting	2 (09.52%)	1 (25%)	-
Mucositis	4(19.04%)	1 (25%)	-
Renal failure	1 (04.76%)	-	-
SNHL	-		1
Death	1	1	

Table 11: Univariate analysis

	No of patients	Mean OS (Months)	(Min-Max)	p-value
IELSG Score				
<3	28 (75.67%)	14.71 ± 10.55	(0-31)	0.002
>3	9 (24.32%)	3.10±3.41	(0-10)	
Age (years)				
≤60	27 (72.97%)	14.46±10.63	(0-31)	0.013
>60	10 (27.02%)	5.64±7.60	(0-28)	
ECOG PS				
≤2	22 (59.45%)	16.95±9.15	(0-27)	<0.0001
>2	15 (40.54%)	5.39±8.64	(0-31)	
Treatment				
CT+RT	24 (58.53%)	18.85±8.21	(4-31)	<0.0001
CT	3 (07.31%)	1.51±1.10	(0-3)	
RT	5 (12.19%)	7.37±5.59	(1-7)	
Supportive Rx	5 (12.19%)	1.75±1.07	(0-3)	

Means and Medians for Survival Time for all the patient n = 37

Meana				Median			
Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
		Lower Bound	Upper Bound			Lower Bound	Upper Bound
17.099	2.182	12.823	21.376	14.860	2.182	12.823	21.376

a. Estimation is limited to the largest survival time if it is censored.

virus (HIV)-1 infection and requires a more severe degree of immunosuppression, the CD4 counts in affected patients are generally less than 50 cells/microL[6,7]. Immunocompromised patients have an increased risk for developing PCNSL. In this setting, PCNSL is typically secondary to AIDS, iatrogenic immunosuppression for transplantation or congenital immunodeficiency syndromes[8,9]. The life time risk for developing PCNSL is reported to be 1-5% for transplant patients and 4% for patients with congenital immune deficiency syndrome[9]. In majority of the studies including present study, most common presentation was Focal Neurological deficit followed by Neuro psychotic symptoms and features of Raised intra cranial tension. Seizure and visual symptoms were least common presentation in most of the studies including present study[4,10]. In majority of studies including present study maximum patient were in ECOG PS OF 2-4, Except for the study done by Pankaj A Agarwal *et al.*[4] and Yongchel Ahn *et al*.[10] where maximum patients were in ECOG PS OF 0-1. In study done by Eloranta *et al*.[11] equal no of patients was in ECOG PS of 0-1 and 2-4. In our study most patients were in ECOG PS of 3 and 2. This may be due to the fact that we included all the patients with PCNS Lymphoma presenting to our department.

There is wide variation in PS of the patients with PCNS Lymphoma involved in various studies. This difference may be due to fact that 1) some studies included only intent to treat population. 2) Difference

in nature of studies; prospective v/s retrospective, real life v/s trial. 3) Wide variation in involved population in different studies. 4) Small number of patients studied. In most of the studies[12] including present study majority of the patients with PCNS Lymphoma had single brain lesion except in studies done by Pankaj A Agrawal *et al*.[4] and Lakshmaiah *et al.*[13] where majority of patients had multiple lesion. This difference may due to the fact that small number of patients involved in the study and both these studies have 2 and 1 patient with HIV respectively. 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 cerebellum)[14]. In this proposed system, one point is given for the presence of each of these five adverse factors. In our study, we used International Extranodal Lymphoma Study Group (IELSG the score and a higher score was associated with a poor survival.

In all of the studies including present study maximum patients had IELSG SORE of 2-3 followed by IELSG SCORE 0-1, while least number of patients had IELSG SORE of 4-5. Irrespective of treatment modality, several factors appear to influence patient outcome and survival[14,15]. Of these, the most consistent prognostic factors are age and performance status. In order to adequately assess patients with this disorder, various standardized systems for prognosis have been proposed[14,16].

In studies done by Lakshmaiah *et al.*[13] maximum patient underwent stereotactic biopsy (49%). In present study maximum patient underwent gross total excision of lesion i.e. 51.21%. The diagnosis of PCNSL is established by stereotactic brain biopsy and resection of lymphoma has not been recommended because of increased post-operative neurological deficits without any improvement in the outcome[3]. But the diffuse nature of PCNSL mirrors that of gliomas, where there is evidence suggestive of a therapeutic benefit to debunking[17,18]. Only 30% of PCNSL cases involve basal ganglia, brainstem or corpus callosum, with the remaining being lobar lesions (70%) that may be amenable to surgical resection without increased morbidity[19]. The ORR (overall response rate) and CR (complete response rate in present study were 88% and 71% which were similar to most of the other studies. Median OS in study done by DeAngelis *et al.*[20], YI *et al.*[21] and Abrey *et al*.[22] was 36.9 months, 26 months and 60 months respectively. In present study for maximum follow up of 30 months Median OS was not reached and was 82%.

The prognosis of primary central nervous system lymphoma is considerably worse than for most other lymphomas in spite of advanced therapy. The comparison of the mortality rates in different studies is hampered by selection bias and the fact that only a few studies are population based. In the present population-based study the median survival of the patients who were available for survival analysis n = 37 was 14.8 months. This compares favorably with other population-based studies[23,24]. Although treated patients are positively selected, survival in our study seemed greatly influenced by the treatment. In accordance with other studies, patients receiving radiotherapy or both chemo and radiotherapy had a significantly better survival than patients receiving no therapy at all[25,26]. The heterogeneity of the chemotherapy and the radiation regimens applied and the limited sample size makes it difficult to compare the survival among patients receiving the different regimens. By univariate analysis we have demonstrated that young age, good performance status, radiotherapy either alone or in combination with chemotherapy and lack of malignant cells in CSF are associated with longer survival. These findings correspond with reports by other groups[25,27,28].

CONCLUSION

Primary central nervous system lymphoma (PCNSL) is an aggressive lymphoma involving only the CNS. Maximum patients were within age group of 51-60 years, had focal neurological deficit, neuro psychotic symptoms and features of raised intra cranial tension. Majority patients required gross total excision of lesion or stereotactic biopsy. Post-surgery majority received combination chemotherapy plus WBART. (39.02%). 37 patients who were available for survival analysis median OS was 14.8 months for maximum follow up of 21.3 months. On univariate survival analysis of possible prognostic factors for survival for the patients with PCNS Lymphoma, factors found to be significant were treatment, ECOG performance status, age and IELSG score.

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