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Original Article

PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA (PCNSL), RETROSPECTIVE ANALYSIS OF COMBINED CHEMO-RADIATION USING HIGH DOSE METHOTREXATE, EXPERIENCE FROM A SINGLE INSTITUTE

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ABSTRACT

Introduction: Primary CNS lymphoma (PCNSL) is an aggressive primary brain tumor, cranial irradiation alone rarely result in long term disease control or prolonged survival. We analyzed our data for the impact of adding high dose methotrexate (HDMTX) prior to whole brain irradiation (WBI).
Materials and Methods: All patients with PCNSL diagnosed and managed during 20012004- were identified from Oncology Data Unit. Patient's characteristics, prognostic factors, details of treatment and outcome were reviewed. Twenty-four patients were identified combined modality therapy included 34- cycles of HDMTX (3gm/m2) followed by WBI were given to all patients.
Result: Median age was 39.2 years (range 1860-). Twenty nine percent (n=7) had ECOG performance status of greater than 2. There were 17 (70.8%) males and 7(29.2%) females with a male to female ratio of 2.4 to 1. Overall response rate (CR+PR) was 75%. Complete remission rate was 1145.8%) 24/) while partial response rate was 29.2% (724/). Median follow is 25.7 months (+/-19.1m); the median overall survival (OS) was 45 months (95% CI 14.589- months). Univariate analysis revealed that age and response had impact on OS and EFS, while only age was the only factor to have impact on survival in multivariate analysis.
Conclusion: This retrospective study supports other phase II trials results that high dose methotrexate followed by WBI in PCNSL improves outcome.

Key Words: Primary central, nervous, system lymphoma (PCNSL), retrospective, analysis of combined.

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INTRODUCTION

Primary Central Nervous System Lymphomas (PCNSL) are extra-nodal lymphomas arising from brain parenchyma, meninges, spinal cord or eyes in the absence of any systemic involvement by lymphoma[1]. PCNSL account for 4% of all primary malignant neoplasia of central nervous system and 4-6% of extra-nodal lymphomas[2]. The incidence of PCNSL lymphoma has been steadily rising during the past three decades, increasing from 2.5 per million in 1973 to 30 per million in 1997[1-3]. The risk factors for PCNSL have included acquired hereditary immune deficiency states i.e. infection with human immune deficiency virus, organ transplantation, severe combined immune deficiency, ataxia telengiectasia, Wiskott Aldrich syndrome as well as autoimmune or inflammatory disorders requiring long term immune suppression such as Rheumatoid arthritis, systemic lupus erythematosus, Jorgen's syndrome, Myasthenia Gravis and vasculitides[4-7].

Although pathology of PCNSL is diffuse large B cell in 95% of the cases, other histologies like T-cell lymphomas, anaplastic large cell and even indolent histologies are regularly encountered[8,9]. Unfortunately no prospective randomized controlled data are available to guide the management of PCNSL and most experience comes from small prospective phase II studies and retrospective series[10-17]. Traditionally PCNSL was treated with whole brain radiation therapy with a median overall survival of 16 months[17]. However, a meta-analysis of 1180 patients from 50 series published in 1997 suggested that survival may be better when treated with a combined modality approach including chemotherapy and radiation[18]. Adding to this controversy has been several reports stating that survival may be equivalent or even better with chemotherapy alone thus avoiding the long-term toxicity from whole brain radiotherapy[19]. Important issues that remain unanswered are type of chemotherapy, single agent versus combination chemotherapy, dose and technique of radiation therapy, role if an of monoclonal antibody therapy especially in B cell lymphoma.

At our institution PCNSL was treated with WBRT until 2001 when we changed our guidelines to include chemotherapy and radiation as part of primary management of PCNSL. We therefore decided to review our results of combined modality therapy.

MATERIALS AND METHODS

After obtaining approval from our institutional review board, we identified all patients diagnosed and treated with primary central nervous system lymphoma at our institution from January 2001 to December 2004. For inclusion into this analysis the patients above 18 years of age had to have a confirmed histologic diagnosis of central nervous system lymphoma in the absence of any radiologic evidence of systemic involvement. The patient had to have a follow-up of at least 6 months to be included in this analysis. Patients with any congenital or acquired immune deficiency states including HIV or therapeutic immune-suppression were excluded. Data on age, sex, histology, performance status at diagnosis, location of lesions (deep versus superficial), type of surgery (biopsy versus debulking) and multiplicity of lesions as well as primary treatment and treatment intent were collected. Surgical debulking was performed in 23 patients (95%) while biopsy was only done in one patient (5%).

Treatment:

All patients before start of treatment had gross disease after surgery and before start of chemotherapy. Chemotherapy consisted of high dose methotrexate at a dose of $3gm/m^2$ at two weekly intervals for a total of 4 cycles. Standard precautions with aggressive pre-chemotherapy hydration and alkalization of urine as well as post-chemotherapy rescue with intra-venous and oral folinic acid were instituted until serum methotraxate levels became non-toxic according to our laboratory reference ranges.

Radiation therapy was delivered with curative intent in the total dose exceeded 40 Gy given over at least 4 weeks to the whole brain (180-200 cGy/fraction, 5 fractions per week). The radiation was given in 2 parallel opposed fields using 6-10 MV linear accelerator machine. In combined modality regimen, radiation had to start within 4 weeks of the last cycle of chemotherapy. Boost dose was given in some patients to escalate the total radiation dose to at least 50 Gy aiming to improve the outcome.

Disease Evaluation and Follow-up:

The patients underwent MRI scan of brain at diagnosis as well as computed tomographic scans of chest, abdomen and pelvis and lumbar puncture at diagnosis. A repeat MRI scan to assess response was done after the end of chemotherapy in those who were managed with combined modality therapy. All patients had evaluation of response at the end of all planned treatment with an MRI and were then followed at 3 monthly intervals with a follow-up MRI scan as well as clinical evaluation to assess residual neurologic deficit and/or long-term toxicity from treatment.

Statistical Analysis:

All statistics were performed with SPSS soft ware (Statistical Package for Social Science, Version 11). Description statistics was presented as number and percentage (frequency distribution). Fisher's exact test was used to compare the results for significance with p value of <0.05 was considered as significant results. A complete response (CR) is obtained if there is complete disappearance of all enhancing abnormalities on gadolinium-enhanced MRI and the patient has not received any corticosteroids for at least two weeks. A partial response (PR) is documented for patients who meet all of the following criteria: no new sites of disease, an at least 50 percent decrease in the contrast-enhancing lesion seen on MRI compared to baseline and patients may be receiving corticosteroid treatment. Stable disease (SD) is that which does not meet the criteria for CR, PR, or progressive disease. Progressive disease (PD) is documented if any of the following are noted: There is a more than 25 percent increase in the contrast-enhancing lesion seen on MRI, an increase in the vitreous cell count, new lesions in an old site or involvement of a new site of disease.

Over all survival (OS) was defined as time from date of diagnosis to date of last follow up or death. Event free survival (EFS) was defined as time from date of diagnosis to date of initiation of additional treatment or relapse, where, residual disease after treatment, time to change in treatment or death was considered to be events. Time to progression (TTP) is defined as time from date of achieving CR or PR to date of recurrence or distant metastasis. Cox regression analysis was used for univariate and multivariate analysis of factors affecting survival, with a p-value of < 0.05 was used for significance. The Kaplan-Meire method was used to determine survival curves and the log-rank test was used to compare survival in different populations, P value was used with a significance of <0.05.

RESULTS

We identified a total of 24 patients fulfilling the criteria for inclusion into this study between periods of January 2001 to December 2004. There were 17 (70.8%) males and 7(29.2%) females with a male to female ratio of 2.4 to 1. Mean age was 39.2 (+/-2.739) years (range 18-60). Twenty nine percent (n=7) had ECOG performance status of greater than 2, while 70.8% had performance status of 0-2. Twenty three patients (95%) presented with a solitary lesion and one (5%) had multiple lesions at presentation.

Diffuse large B cell lymphoma (DLBCL) was the predominant histology (n=23, 95%). Other subtypes included peripheral T cell lymphoma in one patient (5%). Surgical debulking was performed in 23 patients (95%) while biopsy was only done in one patient (5%). All patients had gross disease before start of chemotherapy with a median size of disease before start chemotherapy was 3.2 cm (Table 1).

Table 1: Patient Characteristics (24 Patients).

Factor		No	%
Age			
	Mean	39.2 +/-2.739	
	Range	18-60	
Gender			
	Male	17	70.8
	Female	7	29.2
PS			
	0-2	17	70.8
	3-4	7	29.2
Multiplicity			
	Solitary	23	95.8
	Multiple	1	4.2
Surgery			
	Partial	23	95.8
	Biopsy	1	4.2
Pathology			
	DLBCL	23	95.8
	PTCL	1	4.2
Size	Median (cm)	3.2	
Site			
	Cerebral	12	50
	Cerebellar	8	33.3
	NA	4	16.7

Response and Survival:

Overall response rate (CR+PR) after chemotherapy was 62.5%. Complete remission rate was 8/24 (33.3%) while partial response rate was 29.2% (7/24). Three patients had progressive disease, 2 patients showed stable disease while 4/24 were not assessed for response. Overall response rate (CR+PR) after chemo-radiotherapy was 75%. Complete remission rate was 11/24 (45.8%) while partial response rate was 29.2% (7/24). Two patients had progressive disease, no patients showed stable disease while 4/24 were not assessed for response. One patient had progression after chemotherapy showed partial response after radiation therapy. Three patients, who didn't achieved CR after chemotherapy, achieved Cr after radiation therapy. Recurrence rates were 16.7% (4/24). Median time to progression (TTP) was 19.8 months (95% CI 13.6-61.8 m) (Table 2).

Table 2: Response Rates (24 Patients).

Response	Chemotherapy		Chemo-radiotherapy	
	No.	%	No.	%
CR	8	33.3	11	45.8
PR	7	29.2	7	29.2
SD	2	8.3	0	0
PD	3	12.5	2	8.3
NA	4	16.7	4	16.7

CR Complete Response, PR Partial Response, SD, Stable Disease, PD. Progressive Disease. NA Not assessed.

In a median follow-up of 25.7 months (+/-19.1m), the median overall survival (OS) was 45 months (95% CI 14.5-89 months) (Figure 1) (58% and 43% at 3 and 5 years, respectively) and median event free survival was 38.4 months (95% CI 21.8-72.3 months) (Figure 2) (52% and 19% at 3 and 5 years, respectively).

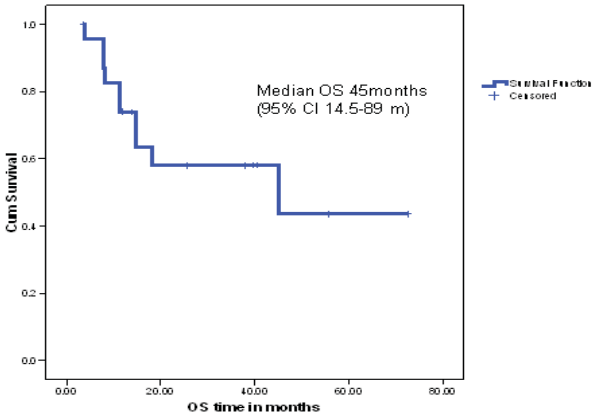

Figure 1: OS whole Group (24 Patients).

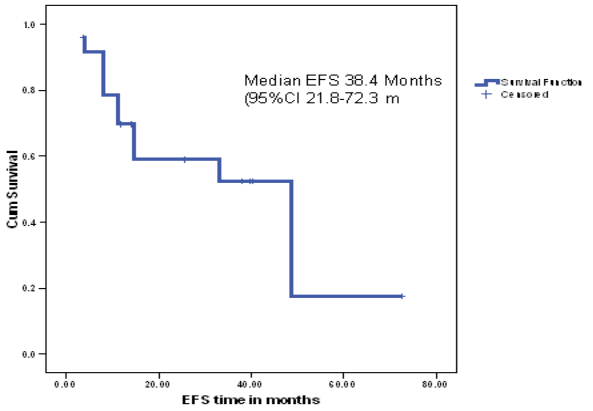

Figure 2: EFS whole Group (24 Patients).

In univariate analysis of prognostic impact of different factors (primary treatment, age, PS, type of surgery, multiplicity of lesions and radiation dose) we found age (<50 or ≥50) (Figures 3 and 4) and response (as a constant factor) to have significant influence on OS and EFS. Age (as a constant factor) was the only significant factor influencing OS and EFS on multivariate analyses (Tables 3 and 4).

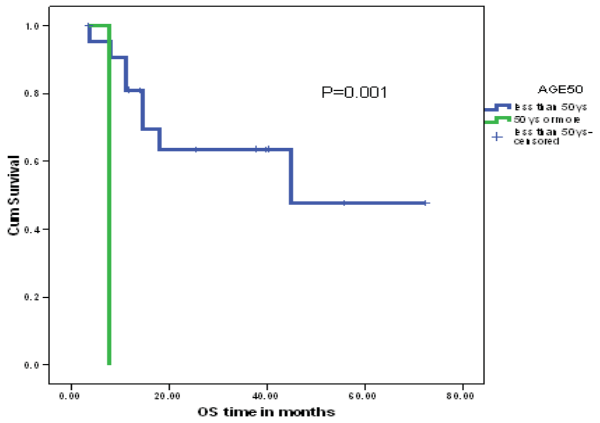

Figure 3: OS According to Age.

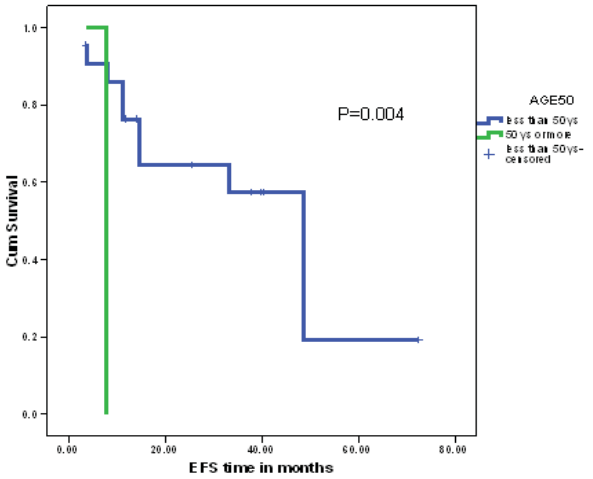

Figure 4: EFS According to Age.

Table 3: Univariate Analysis of Prognostic Factors.

Factor		EFS		OS	
		Median	P	Median	P
Age					
	<50 Y	48.6	0.004	59.2	0.0001
	≥50 Y	12.8		7.9	
Gender					
	Male	48.6	0.65	45	0.41
	Female	33.1		45	
PS					
	0-2	48.6	0.54	45	0.77
	3-4	33.1		45	
Radiation Dose					
	<50Gy	48.6	0.16	NR	0.06
	≥50Gy	14.5		14.56	
Surgery					
	Debulking	54	0.93	55	0.91
	Biopsy	33.1		45	
Response					
	Yes	48.6	0.27	45	o.112
	NO	10.8		17.8	
Response					
	CR	48.6	0.39	45	0.255
	No CR	15.3		18	
Response Constant			0.036		0.004

Table 4: Multivariate Analysis of Prognostic Factors.

Factor	EFS (P Value)	OS (P Value)
PS	0.151	0.097
Radiation Dose	0.476	0.126
Response	0.29	0.147
Surgery	0.316	0.838
Multiplicity	0.98	0.99
Age	0.05	0.042

Toxicity:

There was no reported toxic death in our patient cohort. There was difficult to assess the toxicity because of lack of documentation. The most common reported toxicity was thrombocytopenia in 5 patients (20.9%), followed by leucopenia in 4 patients (16.7%). There was no reported case with febrile neutropenia. One patient had acute transient nephrotoxicity and another one had acute transient elevation of liver enzymes. Encephalopathy was reported in one patient. There was lack of documentation of late toxicity in the files. Cognitive dysfunction was reported in one patient as late toxicity (Table 5).

Table 5: Toxicity to Treatment (24 Patients).

Toxicity	No.	%
Thrombocytopenia	5	20.9
Leucopenia	4	16.7
Febrile Neutropenia	0	0
Mucositis	2	8.3
Diarrhea	2	8.3
Elevated Liver Enzymes	1	4.2
Nephrotoxicity	1	4.2
Encephalopathy	1	4.2
Neuropathy	1	4.2
Cognitive Dysfunction	1	4.2

Relapse and Salvage Treatment:

There was no case with systemic relapse. Recurrence was reported in 4 patients. All the recurrent cases showed CNS recurrence. Out of 6 patients (2 progressed on treatment and 4 with recurrence), 3 patients received salvage treatment in the form of high dose Ara-C. Two patients (66.6%) showed clinical benefit from the salvage treatment.

DISCUSSION

In this population-based study of 24 immunocompetent patients with PCNSL, the median OS was 45 months and the 3-year and 5-year survival rates were 58% and 43%, respectively. The median EFS was 38.4 months and the 3-year and 5-year EFS were 52% and 19%. These survival data is considered higher than reported in similar population-based study cohorts, with median OS range of 17 to 25 months[12,15,20-24]. The reasons for that are our population cohort includes young population with a mean age of 39.2 and only 4 patients were over 50 years old. This makes our patients cohort are of favorable prognosis considering the international extranodal lymphoma study group prognostic score (IELSG)[25] and the Memorial Sloan-Kettering cancer center prognostic model, both of them reported that age is one of the most important prognostic factors[26]. In IELSG score, patients with 60 years old or above showed lower OS than younger patients. In the Memorial Sloan-Kettering cancer center prognostic model, patients with 50 years old or above

showed lower OS than younger patients. Other reasons are that our population cohort showed that most of our cohort was ECOG PS 0-2 (70.8%), most of our population had debulking surgery (95.8%) and 1 patient only had biopsy which may reflect on outcome. The third reason was that 95, 8% of our population had solitary lesion. All these factors make our population cohort of favorable prognosis. In an Australian phase II trial, patients who received 2 cycles of high dose methotrexate (1 gm/m2) followed by 45Gy of whole brain external radiation therapy (WBXRT) had an OS of 33 months which is comparable to our results[23]. In a Radiation therapy Oncology Group (RTOG) study, patients who were given more prolonged methotrexate-based chemotherapy and WBXRT (45GY) followed by high-dose cytarabine had a median OS of 37 months[15]. A retrospective analysis of 357 patients reported in 19 prospective series, reported that patients receiving methotrexate at doses ≥3 g/m2 had a significantly longer median survival compared with those receiving <3 g/m2[27]. There was no difference in overall survival (OS) between mono-CHT and combination CHT (p = 0.38). Of the 119 complete responders, 70 received immediate RT. A RT dose of > or =40 Gy to the whole brain or tumor bed did not improve OS. The 3-year OS was similar between the immediate and delayed RT groups. In multivariate analysis, RT delay had no negative impact on survival[27]. Somewhat similar results were noted in a multicenter study reporting on survival data in 370 patients treated at 23 different centers[19]. Patients treated with radiation therapy alone had the worst two-year overall survival (25 percent), whereas those treated with high doses of MTX and cytarabine had the best 5-year survival (64 percent). These survival data are similar to current trial.

The use of intensified chemotherapy (HDT) and autologous stem cell transplantation (ASCT) demonstrated high efficacy in the treatment of newly diagnosed PCNSL. All these patients are of young age and of good performance to tolerate the high dose chemotherapy and ASCT. For example Illerhaus et al.[28] reported a 5-year OS probability of 69% in 30 patients treated in a phase II trial with HDT and ASCT with consolidating WBXRT. A subsequent pilot trial on HDT and ASCT without WBXRT showed a 5-year OS of 77%[29]. A prospective phase II study (New Approaches for Brain Tumor Therapy NABTT 96-07) evaluated the administration of 8 g/m2 of methotrexate IV, followed by calcium leukovorin rescue, every 14 days until complete response, or to a maximum of 8 cycles[12]. If a partial or complete response was demonstrated on MRI, maintenance chemotherapy with methotrexate (8 g/m2) IV once per month was continued for 11 cycles, or until the occurrence of either unacceptable toxicity or evidence of disease progression. A report of 23 evaluable patients treated on this protocol, demonstrated overall response rate of 74% with 12 complete response and median OS of 23 months. A follow-up report from this study indicated that 5 of the 12 patients (40 percent) who achieved a CR were still alive without disease progression after a median follow-up of 6.8 years[30]. A randomized phase II trial using high dose methotrexate +/- high dose cytarabine reported 3-year EFS of 35% in combined treatment[31]. A cooperative multicenter RTOG/SWOG study enrolled 102 newly-diagnosed patients, using a slightly lower dose of methotrexate (2.5 g/m2); all patients received whole brain XRT[15]. Complete and partial response rates to preirradiation chemotherapy were 58 and 36 percent, respectively, with significantly different overall median survivals of 50 versus 22 months in those <60 and ≥60 years of age, respectively. Severe delayed neurologic toxicity was noted in 12 patients, eight of whom died. The data from these trials support our explanations of high OS in our population cohort.

Our results demonstrated that, age below 50-year and response to treatment had significant impact on survival in univariate analysis. The only factor showed impact on survival in multivariate analysis was age (as a constant factor). Other prognostic important factors didn't have significant impact on survival because of the small number of patients in our trial. We can't compare our results on prognostic factors with that reported by IELSG[25] because of the lack of data collected concerning the LDH, bone marrow aspirate/biopsy results and CSF cytology. Age in our trial showed similar age cut off like the Memorial Sloan Kettering Cancer Center (MSKCC) prognostic score[26]. The MSKCC prognostic score has the advantage of simplicity and widespread applicability. The score take into consideration the age and PS and give 3 different classes, first are patients with age <50-year, second are patients with age >50-year and Karnofsky PS (KPS) >70 and third are patients with age >50-year and KPS <70. These are three classes showed significant impact on survival in favor of first class over the second and in the second class over the third[26]. A prognostic scoring system based on the results of a multicenter study as well as responses to a questionnaire sent to members of the International Extranodal Lymphoma study group reported the following five adverse prognostic factors[19,25], Age >60 years, ECOG performance status >1, Elevated serum level of lactate dehydrogenase, Elevated CSF protein concentration and Involvement of deep regions of the brain (periventricular regions, basal ganglia, brainstem and/or cerebellum). In this proposed system, one point is given for the presence of each of these five adverse factors. For the 105 assessable patients in whom complete information was present, two-year overall survivals for overall scores of zero to one, two to three and four to five were 80, 48 and 15 percent, respectively. For the 75 patients who received high-dose methotrexate-based chemotherapy with or without radiation therapy, two-year overall survivals were 85, 57 and 24 percent, respectively. Age was an important prognostic factor in many small other trials, as an example, in a phase II trial of combined chemo-radiotherapy, In patients >60 years of age, median survival with or without whole brain XRT was 32 and 33

months, respectively; late neurotoxicity was significantly more common in older patients receiving XRT. When whole-brain XRT was deferred in older patients, overall survival was not reduced, but there was less treatment-related toxicity[32]. In a cooperative multicenter RTOG/SWOG study based on the above protocol enrolling 102 newly-diagnosed patients, using a slightly lower dose of methotrexate (2.5 g/m2); all patients received whole brain XRT[15]. Complete and partial response rates to preirradiation chemotherapy were 58 and 36 percent, respectively, with significantly different overall median survivals of 50 versus 22 months in those <60 and ≥60 years of age, respectively. All these data are similar to ours and reflecting the importance of age as a prognostic factor in outcome of PCNSL regardless of treatment given.

CONCLUSION

Current data supports the previously reported phase II and retrospective trials demonstrating the improved outcome of PCNSL treated with high dose methotrexate followed by WBXRT. Age below 50-year showed the favorable prognosis in univariate and multivariate analysis in current trial and in multiple other trials regardless of treatment given.

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