

Improved survival with combined chemo-radiotherapy in primary central nervous system lymphoma

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BACKGROUND: Primary CNS lymphoma (PCNSL) is an aggressive primary brain tumor. Cranial irradiation alone rarely results in long term disease control or prolonged survival. We retrospectively analyzed data on the effect of adding high-dose methotrexate (HDMTX) prior to whole brain irradiation (WBI).

METHODS: All patients with PCNSL diagnosed and managed during 1991-2004 were identified and demographic characteristics, prognostic factors, treatment and outcome were reviewed. Of 62 patients, 10 were excluded (4 had WBI <40 Gy and 6 had no treatment). Radiation alone was considered curative with a dose >40 Gy. Combined modality therapy included 3-4 cycles of HDMTX (3 g/m²) followed by WBI.

RESULT: Of 52 patients analyzed for outcome, 36 had WBI (dose >40 Gy), 16 received 3-4 cycles of HDMTX followed by WBI (combined modality therapy [CMT]). Median age was 48.2 years; 42 years in the CMT group, 51 years in WBI. Patient characteristics were comparable between two groups except for higher multifocal tumor in the CMT group (92% vs. 22%, $P=0.029$). Median follow up was 12.83±6.4 months. The hazard ratio for an event was 0.64 (95% CI, 0.52-0.98) and for death 0.58 (95% CI, 0.48-0.92), both in favor of CMT. Univariate regression analysis using one-way analyses of variance (ANOVA) and multivariate Cox regression analysis for prognostic factors including age (<60 vs. >60), ECOG PS (0-2 vs. 3-4), extent of surgery (biopsy vs. debulking), solitary vs multifocal tumor and dose of radiation therapy (<50Gy vs. >50Gy) failed to identify any prognostic factor.

CONCLUSION: This retrospective comparison supports phase II trial results that indicate that high-dose methotrexate followed by WBI in PCNSL improves outcome.

Primary central nervous system lymphomas (PCNSL) are extra-nodal lymphomas arising from brain parenchyma, meninges, the spinal cord or eyes in the absence of any systemic involvement by lymphoma.¹ PCNSL accounts for 4% of all primary malignant neoplasia of the central nervous system and 4% to 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 or hereditary immune deficiency states i.e. infection with human immune deficiency virus, organ transplantation, severe combined im-

mune deficiency, ataxia telangiectasia, Wiskott-Aldrich syndrome as well as autoimmune or inflammatory disorders requiring long term immune suppression such as rheumatoid arthritis, systemic lupus erythematosus, Sjogren syndrome, myasthenia gravis and vasculitides.⁴⁻⁷

Although the 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 (WBRT) 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, and the role if any 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 with combined modality therapy.

METHODS

After obtaining approval from our institutional review board, we identified all patients diagnosed and treated with primary central nervous system lymphoma from the Oncology Data Unit at our institution from 1994 to 2004. For inclusion into this analysis, patients older than 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 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.

Chemotherapy consisted of high-dose methotrexate at a dose of 3 g/m² 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 intravenous and oral folinic acid were instituted until serum methotrexate levels became nontoxic according to our laboratory reference ranges.

Radiation therapy was considered to have been delivered with curative intent if the total dose exceeded 4000 Gy given over at least 4 weeks to the whole brain (180-200 cGy/fraction, 5 fractions per week). The radiation was given in two parallel opposed fields using 6-10 MV linear accelerator machine. Radiation given

Table 1. Patient characteristics (n=62).

Factor	Number	%
Age		
Median	48.2	
Range	29-76	
Gender		
Male	34	54.8
Female	28	45.2
Performance status		
0-2	21	33.9
3-4	41	66.1
Lesions		
Solitary	46	74.2
Multiple	16	25.8
Surgical		
Debulking	22	35.5
Biopsy	40	64.5
Pathology		
DLBCL	57	91.9
PTCL	3	4.8
Follicular	1	1.6
Immunological	1	1.6
Primary treatment		
CRT	16	25.8
XRT	36	58.1
Palliative treatment	10	16.1

DLBCL: diffuse large B cell lymphoma, CRT: chemo + radiation therapy, XRT: external radiation therapy

at a total dose lower than 4000 cGy was considered to have been delivered with palliative intent. In combined modality group radiation had to start within 4 weeks of the last cycle of chemotherapy.

The patients underwent MRI scan of the brain at diagnosis as well as CT scans of the 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.

Table 2. Patient characteristics by group.

Factor	Combined therapy (n=16)		Radiation therapy (n=36)		P
	No.	%	No.	%	
Age					
Median	42		51.9		.56
Gender					
Male	11	68.8	19	52.8	.2
Female	5	31.3	17	47.2	
Performance status					
0-1	7	43.75	3	8.3	.05
2-4	9	56.25	33	91.7	
Multiple lesions					
Yes	15	93.8	22	61.1	.029
No	1	6.2	14	38.9	
Surgery					
Debulking	5	31.3	15	41.7	.38
Biopsy	11	68.8	21	58.3	
Pathology					
DLBCL	16	100	36	100	.18

DLBCL: Diffuse large B cell lymphoma

Table 3. Response rates by group.

Response	Combined therapy (n=16)		Radiation therapy (n=36)		P
	No	%	No	%	
Complete response	7	43.8	13	36.1	.50
Partial response	5	31.3	7	19.5	
Stable disease	3	18.8	12	33.3	
Progressive disease	1	6.3	4	11.1	

Table 4. Recurrence rates by group.

Recurrence	Combined therapy (n=16)		Radiation therapy (n=36)		P
	No.	%	No.	%	
Yes	3	18.8	18	50	.01
No	11	68.8	9	25	
NA	2	12.5	9	25	
Time-to-progression	11.8 months		4.8 months		.06

All statistics were performed with SPSS software (version 11). Description statistics are presented as number and percentage (frequency distribution). The Fisher exact test was used to compare the results for significance with a *P* value of $<.05$ considered a significant result. A complete response (CR) was defined as disappearance of all evidence of tumor, and with the patient free of all disease-related symptoms. A partial response (PR) was defined as a $>50\%$ reduction in the sum of the products of the diameters of all measurable lesions, without an increase in size or new lesions appearing. Stable disease (SD) was defined as no change or $<25\%$ in the sum of the products of the diameters of any measurable lesions. Progressive disease (PD) was defined as an increase of $>25\%$ in the sum of the products of the diameters of any measurable disease or unequivocal appearance of new lesions. Overall 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 were considered to be events. Time-to-progression (TTP) was 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 $<.05$ indicating significance. The Kaplan-Meier method was used to determine survival curves, and the log-rank test was used to compare survival in different populations, with a *P* value of $<.05$ indicating significance.

RESULTS

We identified 62 patients treated from 1994 to 2004 who fulfilled the criteria for inclusion. There were 34 males and 28 females with an almost equal male-to-female ratio. Median age was 48.2 years (range 29-76). Sixty-six percent (n=41) had an ECOG performance status of greater than 2, while 34% had a performance status of 0-2. Forty-six patients (74%) presented with a solitary lesion and 16 (26%) had multiple lesions at presentation.

Diffuse large B cell lymphoma (DLBCL) was the predominant histology (n=57, 92%). Other subtypes included peripheral T cell lymphoma in 3 patients (4.8%), follicular lymphoma and immunoblastic lymphoma in one patient each (Table 1).

Treatment consisted of combined modality therapy (CMT) in 16 (26%), radiation therapy with curative intent in 36 patients (58%) and radiation therapy with palliative intent in 10 (16%). To eliminate bias towards CMT we excluded 10 patients treated with palliative intent from further analyses and present the response

and survival data on patients treated with CMT and radiation therapy with curative intent (n=52). In this group all histology was DLBCL. Median age was 52 years in the radiation alone group while it was 42 in the CMT group (Table 2). The male-to-female ratio was 2:1 in the CMT group while it was equal in the RT group. Nine of 16 patients (56%) in the CMT group presented with PS of <2 while 33 of 36 (92%) has PS >2 in RT group ($P=.05$). Multiple parenchymal lesions were present in only one patient in the CMT group while 14 of 36 in the RT group had multiple lesions ($P=.029$). Surgical debulking was performed in 5/16 (31%) patients in CMT group and 15/36 (41%) patients in RT group. Surgical intervention consisted of biopsy alone in the rest of the patients.

Response and Survival

Overall response rate (CR+PR) was 74% in the CMT group and 55% in the RT group. The complete remission rate was 7/16 (44%) and 13/36 (36%) while the partial response rate was 31% (5/16) and 19% (7/36) in the CMT and RT groups, respectively ($P=.50$ for PR). One patient in the CMT and 4 in the RT group had progressive disease while 3 and 12 had stable disease in their respective groups (Table 3). The recurrence rate was significantly lower in the CMT group compared to the RT group, 19% (3/16) and 50% (18/36), respectively ($P=.01$). Two patients and one patient in each group, respectively, were not assessed for recurrence. Median TTP was 11.8 months in the CMT group and 4.8 months in the RT group (Table 4).

For the entire group, at a median follow-up of 25.7 months (SD=19.1 months), the median EFS was 8 months (22.5% and 16.8% at 3 and 5 years, respectively) (Figure 1). Median OS was 11 months (36% and 22% at 3 and 5 years, respectively) (Figure 2). Median EFS was 33.1 months and 7.1 months for CMT and RT, respectively (at 3 years 48.8% and 22.1% and at 5 years 24.4% and 17.7%, respectively; $P=.035$; HR=0.58 with 95% confidence interval of 0.48-0.93) (Figure 3). Median OS was 45 months and 10.5 months for CMT and RT, respectively (at 3 years 57% and 31.6% and at 5 years 38% and 20.3%, respectively; $P=.033$; HR=0.64 with 95% confidence interval of 0.52-0.98) (Figure 4).

In the univariate analysis of the prognostic impact of different factors (primary treatment, age, PS, type of surgery, multiplicity of lesions and radiation dose) we found primary treatment (CMT vs. RT) and age (<50 or >50 years) (Figures 5, 6) to have a significant influence on survival (Table 5). Age (as a constant factor) was the only significant factor influencing survival on multivariate analyses (Tables 6).

DISCUSSION

In this retrospective series, the median OS and EFS for the entire group was 11 and 8 months, respectively. OS was significantly longer (45 months) for the CMT group compared to the radiation therapy group (10.5 months) ($P=.033$). EFS was similarly prolonged in the CMT group (33.1 months vs. 7.1 months; $P=.035$). Patients who received RT were older, with poorer performance and with a higher frequency of multifocal disease. These findings were likely responsible for the lower EFS and OS and the loss of significance in the multivariate analysis. Our data for CMT is similar to previous results from both retrospective analyses and prospective trials.^{12,15,20-}

²⁴ In an Australian phase II trial, patients who received two cycles of high-dose methotrexate (1 g/m²) followed by 45 Gy of whole brain external radiation therapy (WBXRT) had an OS of 33 months.²³ Similarly in a Radiation Therapy Oncology Group (RTOG) study, patients who were given more prolonged methotrexate-based chemotherapy and WBXRT (45 Gy) 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 ($P=.04$).²⁵ There was no difference in overall survival (OS) among those receiving single agent chemotherapy and combination chemotherapy ($P=.38$). Of the 119 complete responders, 70 received immediate RT. A RT dose of ≥ 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 a multivariate analysis, RT delay had no negative impact on survival.²⁵ 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 OS (25 percent), whereas those treated with high doses of methotrexate and cytarabine had the best survival (64 percent).

The overall survival with combined modality therapy appears to be superior to that in previous reports. This may be because our patient cohort belonged to a more favorable prognostic group based on the International Extranodal Lymphoma Study Group (IESLG) and Memorial Sloan Kettering Cancer Center (MSKCC) prognostic criteria.^{26,27} Our patient population consisted predominantly of young patients, with good performance status. Most of them had undergone debulking surgery and 98.5% of them had solitary lesions. All of these are favorable prognostic features in IESLG and MSKCC prognostic scores for PCNSL.

Unfortunately, no randomized data exist to prove su-

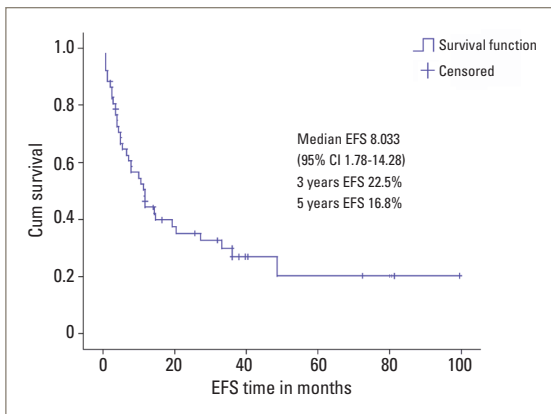


Figure 1. Event free survival whole group.

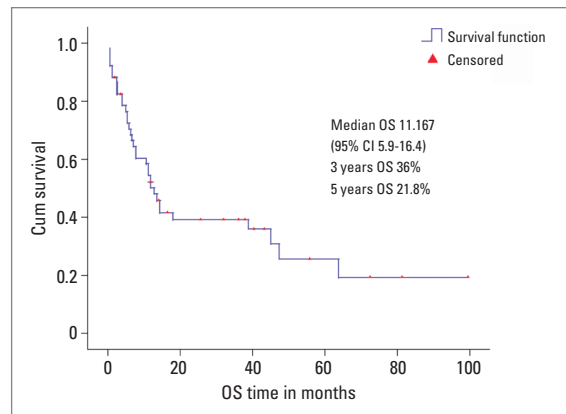


Figure 2. Overall survival whole group.

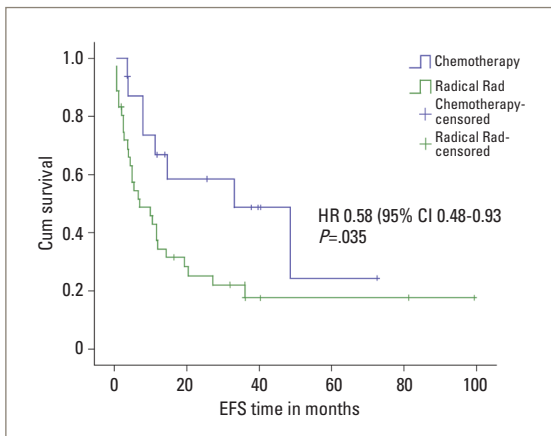


Figure 3. Event free survival according to treatment (CRT vs. RT).

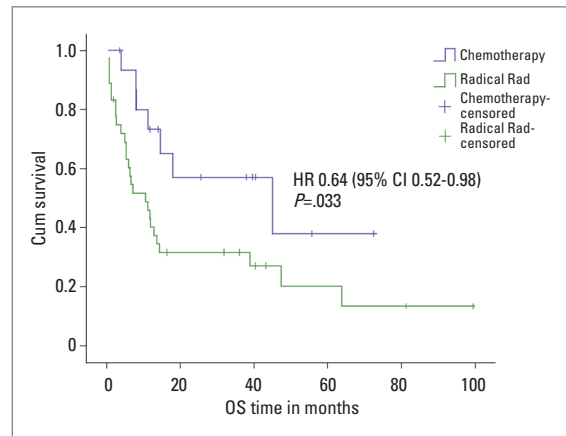


Figure 4. Overall survival according to treatment (CRT vs. RT).

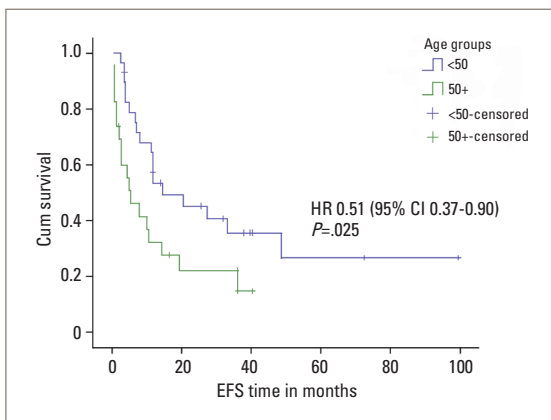


Figure 5. Event free survival according to age (<50 vs. >50).

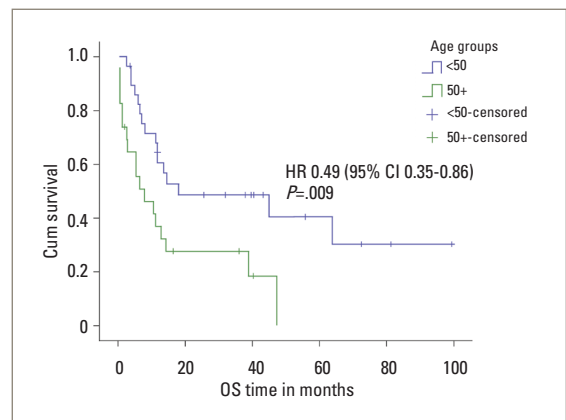


Figure 6. Overall survival according to age (<50 vs. >50).

priority of one regimen over the other. Chemotherapy alone with radiation has also been reported in prospective phase II trials. Use of high-dose methotrexate (8 g/m²) with leucovorin rescue followed by maintenance methotrexate without radiation therapy, reported a median OS of 23% in 23 evaluable patients.¹² Similarly a 3 year EFS of 35% has been reported in a randomized phase II trial of high dose methotrexate ± high dose cytosine arabinoside.²⁸ A SWOG/RTOG trial of 102 patients with a lower dose of methotrexate followed by WBRT reported a median OS of 36.9 months (60 and 21.8 months, respectively, for those younger and older than 60 years of age).¹⁵ A 5-year OS of 77% has been reported with use of high-dose chemotherapy and stem cell transplantation without RT in a single arm phase II trial.²⁹

Our analysis failed to show a prognostic impact for any factors except age and primary therapy (CMT vs. RT alone) in univariate analysis while on multivariate analysis, age alone appeared to be the prognostic factor. We did not have enough data to analyze the impact of other prognostic factors reported by IESLG (LD, bone marrow involvement and CSF cytology).

In conclusion, our data support the previously reported retrospective data and prospective phase II data of superiority of combined modality therapy with chemotherapy and radiation compared to either one alone with age alone being the significant factor impacting prognosis in our study. Combined chemoradiotherapy should therefore be the treatment of choice for newly diagnosed primary CNS lymphoma until randomized trials provide data to the contrary.

Author Contributions

Abdelsalam raised the research idea, wrote the proposal, collected the data, analysed the data and wrote the manuscript. El Husseini reviewed most of the radiation therapy data, collected the data and reviewed the manuscript. Akhtar supervised the whole procedure, collected the data and reviewed the manuscript. Khafaga collected and reviewed the radiation therapy data. Alshabana collected and reviewed the radiation therapy data. Albussaini collected the data. Elweshi, collected and analyzed the data. Rabal collected the data. Maghfoor supervised the whole procedure, collected the data, and reviewed and corrected the manuscript.

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Table 5. Univariate analysis of prognostic factors.

Factor	Event-free survival		Overall survival	
	Median	P	Median	P
Primary treatment				
CRT	33.1	.035	45	.033
XRT	7.1		10.5	
Age				
<50 y	14.56	.0001 (CV) ^a	14.6	.0001 (CV) ^a
>50 y	5.43		18.03	
Performance status				
0-1	14.3	.168	18.03	.16
2-4	10.5		11.3	
Multiplicity				
Yes	14.3	.16	14.5	.21
No	4.9		6.6	
Surgical				
Debulking	11.8	.75	14.3	.74
Biopsy	10.5		11.9	
Radiation dose				
>50 Gy	14.3	.26	14.3	.32
<50 Gy	5.4		7.1	

^aCV: Continuous variable

CRT: chemo + radiation therapy, XRT: external radiation therapy

Table 6. Multivariate analysis of prognostic factors.

Factor	EFS	OS
	P	P
Constant	.011	.043
Primary treatment	.51	.49
Age (cont. variable)	.007	.003
Performance status	.2	.34
Multiplicity	.79	.87
Surgery	.71	.66
Radiation dose	.28	.51

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