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Role of Whole Brain Radiotherapy in Patients of Primary Central Nervous Lymphoma in the Era of High Dose Methotrexate-Based Chemotherapy – A Single Institution Retrospective Audit

Research Article

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Abstract

Introduction: Primary central nervous system lymphoma (PCNSL) is an aggressive form of non-Hodgkin lymphoma that primarily affects the brain and its surrounding structures. The introduction of high-dose methotrexate-based chemotherapy (HD-MTX) has led to more individualized treatment approaches based on patient and disease characteristics.

Materials and Methods: This retrospective audit was conducted at a tertiary care center in Northern India for PCNSL patients treated between 2015 to 2024. Patient records were anonymized and variables such as age, sex, performance status, comorbidities, and disease characteristics were recorded. Treatment details included chemotherapy regimens and radiotherapy techniques. Survival outcomes were analyzed using Kaplan-Meier methods and univariate and multivariate analyses were performed to identify prognostic factors.

Results: The study cohort comprised 63 patients, 34 patients treated with curative intent and 29 with palliative intent. The mean age of the patients was 54.2 years. Histology was diffuse large B-cell lymphoma in all patients exceptin one with plasmablastic lymphoma. Among the patients treated with curative intent, 55.8% received HD-MTX-based chemotherapy and WBRT, while 32.3% received HD-MTX chemotherapy alone. Median overall survival (OS) and progression-free survival (PFS) in patients treated with curative intent and palliative intent was 39 months vs. 5 months ($p<0.0001$), and 37 months vs. 5 months ($p<0.0001$), respectively. On univariate analysis poor performance status at diagnosis was a significant predictor of worse survival outcomes ($p<0.00001$). In patients receiving WBRT, neurological function scale (NFS) improved in 8.5%, remained stable in 82.5%, and worsened in 21.3%. Importantly, no correlation was found between the delivery of radiotherapy and changes in NFS ($p=0.08$).

Conclusion: This audit demonstrates that WBRT remains an important component of PCNSL management along with HD-MTX regimen. Despite advancements in chemotherapy, WBRT continues to play a crucial role in consolidating treatment outcomes for PCNSL patients.

Keywords: Primary Central Nervous System; Lymphoma; Chemotherapy; Radiotherapy

Introduction

Primary central nervous system lymphoma (PCNSL) is a rare, aggressive non-Hodgkin lymphoma that primarily affects the brain, eyes, spinal cord, and meninges. It accounts for up to 4% of intracranial tumors in immunocompetent individuals, with a higher incidence in elderly men and White populations [1]. Incidence has risen since the 1960s with increased prevalence among immunocompromised individuals, particularly those with HIV, organ transplants, or autoimmune diseases requiring immunosuppression [2]. Diffuse large B-cell lymphoma is the most common subtype, although T-cell variants are also observed [3]. It commonly occurs in the periventricular white matter, basal ganglia and corpus callosum and can infrequently involve the cerebellum and brainstem [4].

Before the introduction of high-dose chemotherapeutic regimens, whole-brain radiotherapy (WBRT) was the standard treatment. Currently, treatment decisions are individualised based on patient-related factors such as age, performance status and comorbidities and disease-related factors like neurological function, size and extent of the disease. Patients eligible for curative treatment receive chemotherapy with high-dose methotrexate (HD-MTX)-based regimens, followed by an assessment for consolidation with WBRT. Other options for consolidation include cytosine arabinoside and autologous stem cell transplant. Unfit patients are usually treated with WBRT alone [5–7]. In this article, we present a single institutional experience of PCNSL patients diagnosed and treated over the last decade.

Materials and Methods

This is a retrospective single institutional audit conducted in a large tertiary care centre in Northern India. Departmental ethical clearance was obtained. Records of patients with PCNSL registered in the Department of Radiotherapy and Oncology from 2015-2024 were retrieved. Patient identifiers such as name and address were masked for the purpose of the study. Patient related variables entered in to the data included age, sex, performance status and comorbidities. Disease related variables included site, size, number of lesions, histology and molecular subtype. Treatment related variables included baseline investigations, surgery, radiotherapy and chemotherapy. Radiotherapy details included the dose fractionation regimen and the technique of radiotherapy. Chemotherapy details included the regimen and number of cycles .Various prognostic indices such as Charlson's Comorbidity index, IELSG score, MSKCC RPA score and the 3F score were calculated [8, 9].

Study related variables were entered into SPSS v25 (Statistical package for social sciences – IBM). Patients treated with curative and palliative intent were analysed separately. Descriptive data was generated for variables in the study. Independent samples T-test was used to analyse normally distributed continuous data and Mann Whitney U test was used to analyse non-normal continuous data. Chisquare and Fischer's exact test were used to compare categorical variables in both the groups. Overall survival (OS) was calculated from the date of diagnosis to the date of death due to any cause or the time of last follow up. Progression free survival (PFS) was calculated from the date of diagnosis to the date of progression or death. Survival analysis was done by Kaplan-Meir method. Univariate analysis of the factors affecting survival was performed with the log rank test and multivariate analysis was done with the Cox regression analysis.

Results

Baseline characteristics

A total of 63 patients were included in the analysis. Thirty-four patients were treated with curative intent and 29 patients were treated with palliative intent (Table 1). The mean age of the patients was 54.2 ± 13.8 years. The gender distribution was similar across both the groups. All patients had a negative serology for HIV and Hepatitis B, whereas one patient was positive for Hepatitis C virus. Among 20 patients with poor performance status (ECOG 3-4), two received treatments with curative intent, while 18 received palliative treatment. Total 46(73%) of the patients had a single lesion and 52(82.5%) of patients had lesions in the supratentorial location. On histology 62 patients had diffuse large B-cell lymphoma and one patient had plasmablastic lymphoma. Molecular subtyping was not available for 29 patients. Three patients belonged to the GCB subtype and 31 patients belonged to non-GCB subtype. On risk stratification, 18(28.6%), 28(44%) and 30(47.5%) of patients belonged to the high-risk group as per the IELSG, MSKCC RPA and 3F scoring systems, respectively.

Treatment detail

In patients treated with curative intent, 17(50%) received chemotherapy followed by WBRT, 11(32.3%) received chemotherapy alone and 4(11.7%) received chemotherapy followed by WBRT and cytosine arabinoside consolidation (Table 2). Two patients with performance status of ECOG 3 were treated with WBRT followed by HD-MTX-based chemotherapy in view of marked improvement in their performance status. These patients were considered as being treated with curative intent. In patients treated with curative intent, 14(41.1%) of patients received HD-MTX-based chemotherapy with R-MVP DeAngelis regimen and 20(58.8%) received R-MVP Morris regimen. In those treated with palliative intent, 5(17.3%) received best supportive care, 15(51.7%) received WBRT alone, 3(10.3%) received chemotherapy followed by WBRT and 6(20.6%) received WBRT followed by chemotherapy. The chemotherapeutic regimens used included R-CHOP 2(6.8%), CHOP 2(10.3%) and R-Temozolomide-Dexa 4(13.7%).

For WBRT, radiotherapy technique was fluoroscopy guided 2 dimensional (2D)and 3D conformal radiotherapy (3D-CRT) in 36(57%) and 12(19%) patients, respectively. In patients who received HD-MTX-based chemotherapy, 7(20.5%) patients received reduced dose WBRT (23.4 Gy in 13 fractions or 24 Gy in 12 fractions) after having achieved complete response. Nine (26.5%) patients with a partial response received WBRT with definitive intent (36-45 Gy at 1.8 Gy/#). Seven (20.5%) patients received 30 Gy in 10 fractions – 5(14.7%) of them had stable or progressive disease after high-dose chemotherapy and 2(5.8%) received WBRT upfront. After WBRT, 14 (41%) of patients achieved complete remission. Among those treated with palliative intent, WBRT was delivered in doses ranging from 30 Gy in 10 fractions to 45 Gy in 25 fractions. In these patients, neurological function scale (NFS) improved in 2 patients (8.3%), and remained stable in 22 patients (91.6%). In forty-seven patients who

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Table 1: Baseline characteristics of the study cohort.

Characteristics	Total (n=63)	Treatment intent		p
		Curative (n= 34)	Palliative (n= 29)	
Mean Age ± SD (years)	54.25 ± 13.8	51.56 ± 14.03	57.41 ± 13.11	0.09
Sex – Male Female	35 (55.6%) 28 (44.4%)	18 (52.9 %) 16 (47.1%)	17 (58.6%) 12 (41.4%)	0.651
ECOG at diagnosis 1 2 3 4	 23 (36.5%) 20 (31.7%) 19 (30.2%) 1 (1.6%)	 19 (55.9%) 12 (35.3%) 2 (5.9%) 0 (0%)	 4 (13.8%) 8 (27.6%) 17 (58.6%) 1 (2.9%)	0.0001
Number of lesions – Single Multiple	 46 (73%) 17 (27%)	 22 (64.7%) 12 (35.2%)	 24 (82.7%) 5 (17.2%)	0.427
Location of lesions Supratentorial Infratentorial Both	 52 (82.5%) 6 (9.5%) 5 (7.9%)	 30 (88.2%) 2 (5.9%) 2 (5.9%)	 22 (75.9%) 4 (13.8%) 3 (10.3%)	0.425
Deep regions involved	48 (76.2%)	29 (85.3%)	19 (65.5%)	0.06
Eloquent areas involved	39 (61.9%)	21 (61.8%)	18 (62.1%)	0.980
IELSG risk group Low Intermediate High	 11 (17.5%) 34 (54%) 18 (28.6%)	 8 (23.5%) 19 (55.9%) 7 (20.6%)	 3 (10.3%) 15 (51.7%) 11 (37.9%)	0.196
MSKCC RPA group Low Intermediate High	 24 (38.1%) 11 (17.5%) 28 (44.4%)	 19 (55.9%) 6 (17.6%) 9 (26.5%)	 5 (17.2%) 5 (17.2%) 19 (65.5%)	0.003
3F Risk group Low Intermediate High	 13 (20.6%) 20 (31.7%) 30 (47.6%)	 11 (32.4%) 13 (38.2%) 10 (29.4%)	 2 (6.9%) 7 (24.1%) 20 (69%)	0.004

Table 2: Treatment details of the study cohort.

Treatment	Overall (n=63)	Treatment intent		p
		Curative (n= 34)	Palliative (n= 29)	
Type of surgery - Stereotactic biopsy Gross total excision Subtotal excision	 34 (53.9%) 15 (23.8%) 14 (22.2%)	 18 (52.9%) 7 (20.5%) 9 (26.4%)	 16 (55.1%) 8 (27.5%) 5 (17.2%)	0.603
Treatment sequence- Best supportive care WBRT alone Chemotherapy alone Chemotherapy followed by WBRT Chemotherapy followed by WBRT followed by Ara-C WBRT followed by Chemotherapy	 5 (7.9%) 15 (23.8%) 11 (17.4%) 20 (31.7%) 4 (6.3%) 8 (12.6%)	 0 (0%) 0 (0%) 11 (32.3%) 17 (50%) 4 (11.7%) 2 (5.8%)	 5 (17.2%) 15 (51.7%) 0 (0%) 3 (10.3%) 0 (0%) 6 (20.6%)	0.0001
Chemotherapy regimen CHOP R-CHOP R-MVP DeAngelis R-MVP Morris R-Temozolomide-Dexamethasone	 3 (4.7%) 2 (3.1%) 14 (22.2%) 20 (31.7%) 4 (6.3%)	 0 (0%) 0 (0%) 14 (41.1%) 20 (58.8%) 0 (0%)	 3 (10.3%) 2 (6.8%) 0 (0%) 0 (0%) 4 (13.7%)	0.0002
WBRT dose fractionation 23.4 Gy/13 fractions 24 Gy/12 fractions 30 Gy/10 fractions 30 Gy/15 fractions 36 Gy/20 fractions 45 Gy/25 fractions (36 Gy/20 fractions Followed by 9 Gy/5 fractions boost)	 2 (3.1%) 5 (7.9%) 17 (26.9%) 1 (1.5%) 5 (7.9%) 18 (28.5%)	 2 (5.8%) 5 (14.7%) 7 (20.5%) 0 (0%) 1 (2.9%) 8 (23.6%)	 0 (0%) 0 (0%) 10 (34.5%) 1 (1.5%) 4 (13.7%) 10 (34.5%)	0.237
WBRT technique 2D Conventional 3D-CRT	 36 (57.1%) 12 (19%)	 16 (47%) 8 (23.5%)	 20 (68.9%) 4 (13.7%)	

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received radiotherapy, NFS was improved in 4 (8.5%), was stable in 33 (82.5%) and worsened in 10 (21.3%) of patients. Among 16 patients who did not receive radiotherapy, NFS improved in 1 (6.3%), remained stable in 7(43.8%) and worsened in 8 (50%) patients. There was no correlation between the delivery of radiotherapy and change in NFS (p=0.08).

Survival outcomes

The median follow-up duration was 23 months (1-84 months). The median PFS was 37 months (95% CI - 9.2-54.7 months) in those patients treated with curative intent and 5 months (95% CI - 2.7-7.2 months) in those treated with palliative intent (p<0.0001) (Figure 1) (Table 3). The median OS was 39 months (95% CI - 18.3-59.6 months) in those patients treated with curative intent (Figure 2) and 5 months (95% CI - 2.7-7.2 months) in those treated with palliative intent (p<0.0001). Univariate analysis revealed that a poor performance status at diagnosis was a significant predictor of worse survival (p<0.00001). Charlson comorbidity index, IELSG, MSKCC RPA and 3F scores and classification did not significantly affect survival in this cohort in either univariate or multivariate analysis (Tables 4) (Table 5).

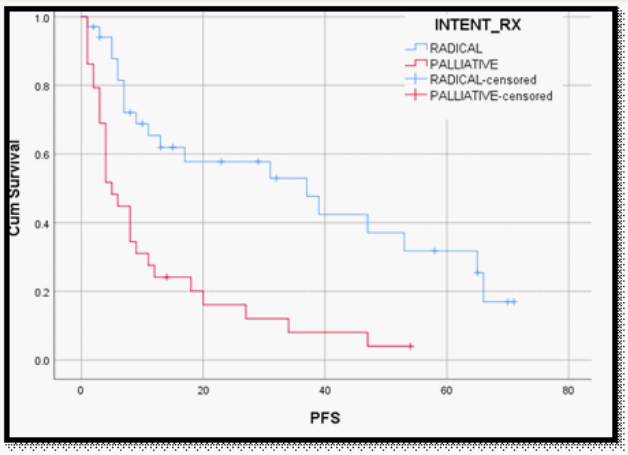

Figure 1: Progression free survival based on treatment intent.

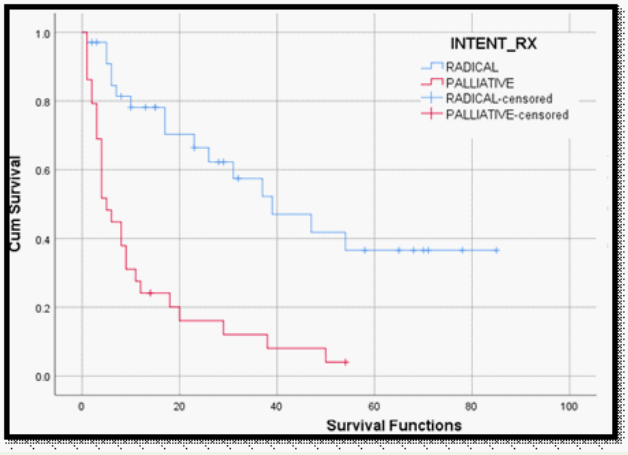

Figure 2: Overall survival based on treatment intent.

Discussion

In this single institutional retrospective study of 63 patients with PCNSL, 34 patients were treated with radical intent and 29 with palliative intent. Median OS was 39 months in those treated with curative intent and 5 months in those treated with palliative intent. Poor performance status at baseline the significant factor affecting OS in these patients.

PCNSL treatment has advanced significantly over the past decade. Initially, WBRT was the mainstay of treatment, achieving high response rates of up to 90%, but limited OS of 12-18 months and substantial rates of intracranial recurrences [10 -12]. The addition of conventional chemotherapy regimens like CHOP and R-CHOP did not improve survival due to inadequate intracranial penetration of these drugs [13]. The addition of HD-MTX, marked a major breakthrough, significantly improving median OS to 30-60 months [13, 14]. Combination regimens with HD-MTX, cytarabine, rituximab, and other agents like procarbazine and vincristine further enhanced efficacy [15, 16]. In the present study we could achieve a median survival of 39 months as compared to 14 months in a previous

Table 3: Survival outcomes of the study cohort based on treatment intent.

Outcome	Treatment intent		p
	Curative (n=34)	Palliative (n=29)	
Median OS (95% CI)	39 months (18.3-59.6 months)	5 months (2.7-7.2 months)	<0.0001
1 year OS	78%	28%	
2-year OS	66%	16%	
Median PFS	37 months (9.2-54.7 months)	5 months (2.7-7.2 months)	<0.0001
1-year PFS	65%	28%	
2-year PFS	58%	16%	

Table 4: Univariate analysis of factors affecting the overall survival.

Factors	Overall survival (median)	p
ECOG 0-2 vs. 3-4	31 months vs. 4 months	< 0.00001
Age < 65 years vs. ≥ 65 years	18 months vs. 8 months	0.177
Largest lesion size < 5 cm vs. ≥5 cm	18 months vs. 17 months	0.182
IELSG – Low vs. Intermediate vs. High	18 months vs. 23 months vs. 6 months	0.158
MSKCC RPA – Low vs. Intermediate vs. High	23 months vs. 31 months vs. 8 months	0.281
3F SCALE – Low vs. Intermediate vs. High	47 months vs. 10 months vs. 8 months	0.111

Table 5: Multivariate analysis of factors affecting the overall survival.

Factor	Hazard ratio (95% CI)	p
ECOG	1.68 (1.13 – 2.49)	0.01
Age	0.995 (0.945 – 1.047)	0.841
Largest tumour dimension	1.26 (0.95-1.67)	0.107
Charlson Comorbidity index	0.950 (0.865-1.04)	0.284
IELSG Score	1.00(0.64 – 1.56)	0.980
MSKCC RPA score	0.647 (0.20-2.05)	0.459
3F score	1.23 (0.54 – 2.80)	0.613

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study from our institute, which is a remarkable achievement for these patients 13. Intensified chemotherapy regimens such as MATRIX have shown promising results, especially in younger, fit patients with complete remission rates as high as 49% [17]. In our study complete remission was observed in 41% patients.

Decisions regarding the intent of treatment in PCNSL are made after a multidisciplinary discussion and considering factors such as age, performance status, comorbidities, disease burden, neurological function status and social support. Those patients who are unfit for curative treatment are treated with palliative intent. Options for palliation include best supportive care (BSC), WBRT alone and single agent chemotherapy [18–20]. In the current study, 34 patients were treated with curative intent and 29 patients were treated with palliative intent. Among those patients treated with palliative intent withWBRT, NFS improved in 2 (8.3%) of patients and remained stable in 22 (91.6%) of patients.

In patients treated with curative intent, WBRT was delivered up to a dose of 45 Gy. In 18 (28.5%) of patients this was achieved in two phases,in the first phase 36 Gy was delivered to the whole brain and a 9 Gy boost to the gross disease in patients where lesions were well localised and could be delineated. Currently, patients who receive radiotherapy alone and those with residual disease after high-dose chemotherapy are treated with this dose fractionation. A study by Thiel et al., have shown that patients treated with WBRT had significantly better PFS compared to those who were kept on observation after induction therapy[21].Off late, concerns regarding neurocognitive decline have prompted the adoption of a risk stratified approach for radiotherapy. Patients who achieve a complete remission after chemotherapy are often given a reduced dose WBRT of 23.4-30 Gy [16, 17, 22]. We treated 8(22%) patients with this schedule. Alternative strategies being studied in this group to avoid WBRT include consolidation withautologous stem cell transplantation or cytosine arabinoside [23, 24]. In the current study, those patients who received HD-MTX-based chemotherapy, 7(11%) patients received reduced dose WBRT after complete response and 17(26.5%) received WBRT with definitive intent (36-45 Gy). Four (6%) patients received consolidation therapy with cytosine arabinoside in addition to WBRT.

The PRECIS study compared the neurocognitive outcomes of patients who were randomised to receive consolidation with either ASCT or WBRT with a dose of 40 Gy. The authors reported that compared with the ASCT group, more patients in the WBRT group had significant deteriorations in balance and neurocognition during follow-up. However, all patients in the WBRT arm received a dose of 40 Gy despite 46% of them achieving a complete response after induction therapy [23]. A myriad of factors plays a role in neurocognitive function in PCNSL. Apart from radiotherapy, the intensity of chemotherapy, location, size and number of lesions may also influence cognition [25]. In the current study, where radiotherapy dose was adapted based on intent of treatment and response to induction therapy, no correlation between radiotherapy and worsening NFS was found. In 47 patients who received radiotherapy, NFS improved in 4 (8.5%), remained stable in 33 (82.5%) and worsened in 10 (21.3%) patients. Among sixteen patients who did not receive radiotherapy, NFS improved in 1 (6.3%), remained stable in 7 (43.8%) and worsened in 8 (50%) of patients (p=0.08). However, it should be noted that detailed MMSE and neurocognitive assessment was not done in the present study.

According to the SEER database, OS significantly increased from 12.5 months in the 1970s to 26 months in the 2010s [26]. In the current study, median PFS was 37 months in those treated with curative intent and 5 months in those treated with palliative intent (Figure 1). Median OS was 39 months in patients treated with curative intent and 5 months in those treated with palliative intent (Figure 2). Studies that incorporated high-dose chemotherapy along with WBRT reported a median OS ranging from 30-60 months[13, 16, 27]which is in line with the present study of 39 months. On univariate analysis, a poor performance status at diagnosis was a significant predictor of worse survival. Many studies have reported other factors which adversely affect prognosis such asadvanced age, poor performance status, multifocal lesions, male gender, frontal lobe location and high CSF protein concentrations [29-35].

Limitations of the study are single institutional, retrospective and lack of neurocognitive assessment of the patients.

Conclusion

In this single institution retrospective audit of patients with PCNSL, median OS was 39 months in those treated with curative intent and 5 months in those treated with palliative intent. Radiotherapy dose was adapted based on intent of treatment and response to induction therapy.There was no correlation between the radiotherapy and worsening NFS. WBRT plays an important role in the management of PCNSL in the era of high-dose chemotherapy.

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