

Survival and failure outcomes in PCNSL with WBRT followed by CHOP Chemotherapy: An alternative treatment approach in community settings in low resource countries

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ABSTRACT

Introduction: Primary central nervous system lymphoma (PCNSL) is relatively uncommon malignancy with potentially aggressive behavior. The standard management of PCNSL is high-dose methotrexate (HD-MTX) based chemotherapy and whole brain radiotherapy (WBRT). This treatment is associated with toxicity and requires in-patient admission with intensive monitoring. An alternative approach with WBRT followed by systemic chemotherapy with standard cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) regimen can be used in community settings in a cohort of patients who cannot receive the standard treatment due to logistic reasons. **Materials and Methods:** We retrospectively reviewed the patients of PCNSL treated in our institute from January 2004 to May 2010. A total of 39 patients of PCNSL were treated. All patients received WBRT followed by systemic chemotherapy with standard CHOP regimen. Survival analysis was done with Kaplan-Meier method using Statistical Package for Statistical Analysis (SPSS version 15). Prognostic factor influencing survival was evaluated using Cox regression analysis. Toxicity and overall treatment compliance analysis was also evaluated. **Results:** Overall compliance to RT and chemotherapy was excellent, 37 (94.9%) patients completed planned treatment within the stipulated time period. Grades II-III skin toxicity was seen in three patients and Grade II hematological toxicity was seen in two patients. At 1 month after completion of planned treatment, 15 patients had no symptoms and 20 patients had significant improvement while four patients deteriorated clinically while radiological imaging showed complete response, partial response, progression of disease in 22, 12 and 5 patients respectively. Mean overall survival (OS) was 36.34 months and median OS was 20.0 months with 3-year actuarial OS of 38%. Age of 50-year was a significant ($P < 0.05$) prognostic factor for survival. **Conclusions:** The standard of care in management of PCNSL is HD-MTX based chemotherapy. However, considering poor compliance and tolerability to treatment in low resource countries in routine clinical setting, WBRT followed by systemic chemotherapy with standard CHOP regimen for treatment of PCNSL demonstrate reasonably good outcome. This regimen is quite economic as well as simple to implement.

Key words: Chemotherapy, primary central nervous system lymphoma, whole brain radiotherapy

INTRODUCTION

Non-Hodgkin's lymphoma (NHL) arising in and confined to the central nervous system (CNS) is termed as primary CNS

lymphoma (PCNSL).^[1] It accounts for approximately 1-3% of all CNS malignancies.^[2] Most PCNSLs involves brain but eye, leptomeninges and spinal cord are also involved less commonly. Source of PCNSL is unclear because brain lacks lymphatics and lymph node. The possible source is lymphocytes, which travel in and out in CNS.

Previously, treatment consisted of whole brain radiotherapy (WBRT), which frequently produced a complete tumor response and ameliorated symptoms in most patients but resulted in a median survival of only 12-14 months and a 5-year survival rate of <5%.^[3] The combination chemotherapy regimen of cyclophosphamide,

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doxorubicin, vincristine, and prednisone (CHOP) is the best chemotherapy regimen for systemic NHL, but the combination of CHOP with whole brain radiation for PCNSL did not result in improved survival over WBRT alone.^[4-7] Various newer studies have shown that high-dose methotrexate (HD-MTX) based regimens with or without WBRT resulted in improved outcomes in PCNSL but it is associated with significant treatment related toxicities.^[8-14] However in low resource countries in community settings, a large group of the patient population cannot receive this HD-MTX based treatment due to unavailability of advanced facilities and significant treatment related toxicities.

MATERIALS AND METHODS

A total of 39 patients of PCNSL were registered in the Department of Radiotherapy between January 2004 and May 2010. 32 patients had histologically confirmed diagnosis and seven patients were diagnosed radiologically. Baseline investigations (hemogram, liver function test, kidney function test, contrast-enhanced computed tomography base of the skull to whole pelvis, bone marrow biopsy from B/L iliac bone, cerebrospinal fluid cytology for malignant cells) had been performed on all patients to rule out any systemic disease.

After diagnosis, all patients received WBRT, followed by systemic chemotherapy with standard CHOP regimen. RT was given to the whole brain, including the posterior part of the eye and the medulla oblongata, leptomeninges. The first course of chemotherapy was started 3-4 weeks post-completion of RT. All patients received systemic chemotherapy with standard CHOP regimen to total 6 cycles at 3 weekly intervals. Patients were evaluated 1 month after treatment completion both clinically and radiologically.

RESULTS

Patient characteristics are summarized in Table 1. Mean duration of presenting symptoms was 2.7 months (range: 1-10 months) and common presenting symptoms were symptoms of raised intracranial pressure (82%), motor weakness (59%) and seizures (20.5%). All patients received WBRT first followed by systemic chemotherapy with standard CHOP regimen to total 6 cycles at 3 weekly intervals. A total of 21 patients received total RT dose of 36 Gy in 20 fractions at the rate of 1.8 Gy/fraction and 18 patients received total RT dose of 40 Gy in 20 fractions at the rate of 2 Gy/fraction.

Toxicity and response

Overall compliance to RT and chemotherapy was good, 37 (94.9%) patients completed planned treatment within the stipulated time period. Significant RT and chemotherapy

induced acute reactions as per Radiation Therapy Oncology Group (RTOG) grading criteria encountered were skin Grades II-III in three patients, anemia Grade II in two patients, leucopenia Grade II in two patients. On clinical and radiological assessment of patients at 1 month after completion of planned treatment, 15 patients had no symptoms and 20 patients had significant improvement while four patients deteriorated clinically while radiological imaging showed complete response, partial response, progression of disease in 22, 12 and 5 patients respectively. There was no treatment related mortality encountered.

Survival

Survival analysis was performed using Kaplan-Meier (KM) method that demonstrated mean overall survival (OS) 36.34 months (standard deviation [SD]: 5.37; 95% confidence interval [CI]: 25.84-46.90) and median OS 20 months (SD: 9.19; 95% CI: 1.97-38.02) with 3-year actuarial OS of 38% [Figure 1]. Impact of Karnofsky performance status (KPS) of the patient was also included into KM survival individually as well as after stratification of the data on age (categorized into ≤ 50 and > 50) and sex respectively. The result shows that survival seems to be unaffected by KPS status of the patient. Since KPS is a known prognostic factor along with age and therefore Cox regression analysis was performed using KPS, age as continuous in nature along with gender. The result shows that the patient's mean age of 50-year seems to be a significant ($P < 0.05$) prognostic factor for survival [Figure 2].

DISCUSSION

PCNSL is a rare neoplasm of CNS and comprises 1-3% of all CNS malignancies.^[1,2] Overall prognosis is poor.

Table 1: Patient characteristics

Characteristics	Number (%)
Age (years)	
Median	53
Range	30-75
Sex	
Male	20 (51)
Female	19 (49)
KPS	
50	8 (20)
60	15 (38)
70	11 (29)
80	5 (13)
Location	
Frontal	14 (36.0)
Temporal	8 (20.5)
Periventricular	7 (17.9)
Others	10 (23.5)
Surgery	
Complete	9 (23)
Partial	13 (33)
Biopsy	10 (25.6)
No	7 (17.9)

KPS: Karnofsky performance status

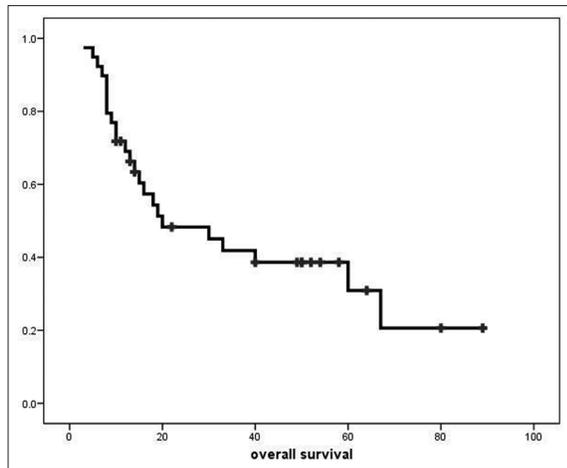


Figure 1: Kaplan-Meier curve showing overall survival

Multimodality management is required including surgery, RT and chemotherapy.

The role of surgery is limited to diagnosis of PCNSL. Debulking surgery is indicated for patients with masses large enough to cause impending herniation. Gross total resection is unnecessary because of the tumor's inherent sensitivity to chemotherapy, steroids and RT and it has no impact on survival. The most important role for surgery is to obtain and sample adequate tissue with stereotactic biopsy.^[15]

Radiation therapy is an integral component of PCNSL treatment. The radiosensitivity of this tumor is not surprising considering the histopathologic similarities to systemic NHL. Patients treated with focal RT had significant rates of infield recurrence as well as outside of the radiation field and magnetic resonance imaging significantly underestimates the extent of involvement. Therefore WBRT is a standard component of treatment, but the dose has been controversial. The ideal dose based on several studies is somewhere in the range of 35-50 Gy. Patients receiving greater than 50 Gy had poorer outcomes in terms of neurotoxicity.^[3,16,17] The addition of a boost to the tumor bed provides no benefit.^[3,18] With WBRT alone, there is significant resolution of the disease radiologically, but the OS is poor and ranges from 12 to 14 months only.^[3] In our series, the median WBRT dose was 36 Gy and it ranged from 36 to 40 Gy. All of our patients completed the planned WBRT and had no signs or symptoms of neurotoxicity.

There is evidence that PCNSL is sensitive to systemic chemotherapy and combined-modality therapy results in superior outcomes. Chemotherapeutic agent should be able to penetrate the blood-brain barrier when given systemically. Methotrexate has been identified in many studies as the single most effective drug. Others are cytarabine, vincristine. The most effective drugs against

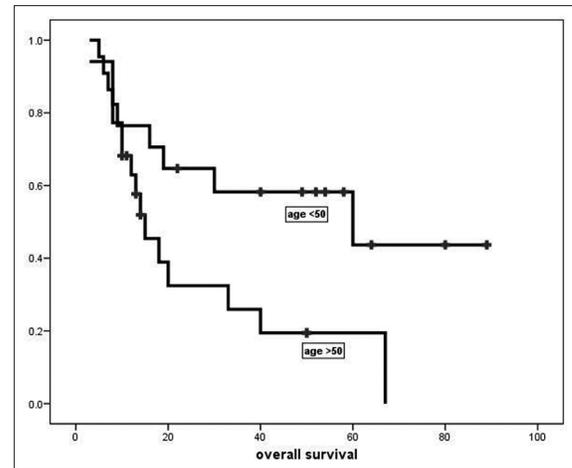


Figure 2: Survival curve showing age as a prognostic factor

NHL, doxorubicin and cyclophosphamide, are associated with unsatisfactory results. Except prednisone, none can adequately penetrate an intact blood-brain barrier. Because of their poor blood-brain barrier penetration, CHOP regimen is not as effective as HD-MTX based regimen in the treatment of PCNSL.^[5-7,19] There have now been two multicenter phase II studies and one prospective randomized phase III trial of CHOP for PCNSL.^[4,5,20] The RTOG conducted a study in which patients received three cycles of CHOP followed by cranial irradiation.^[20] The median survival was only 12.8 months for the 51 patients treated. A separate multi-institutional trial of pre-radiation CHOP had 46 evaluable patients, with estimated median survival of approximately 9.5 months. Only 54% of patients completed two cycles of CHOP to begin RT; the others had disease progression or toxicity, with 15% mortality. There was no difference in survival or failure-free survival in-patients treated with WBRT alone compared with WBRT and CHOP. In our series, the treatment approach was slightly different from the three published results of CHOP chemotherapy in PCNSL. We administered WBRT first which caused the resolution of the tumor and further improvement in symptoms and general condition of the patients. WBRT itself causes the disruption of blood-brain barrier and subsequent chemotherapy with CHOP regimen had better penetration in the brain. Thus, the median survival was 20 months seen in our series was better than the previous published a series of CHOP and WBRT.

HD-MTX is the single most active agent for the treatment of PCNSL. HD-MTX based combination chemotherapy in conjunction with RT and treatment of leptomeningeal disease considerably prolongs survival when compared with RT alone. These combined-modality methotrexate based regimens in combination with WBRT result in median OS ranging from 25 to 60 months.^[9-14,21] However methotrexate based regimens, when combined with WBRT, carry a significant risk of severe, irreversible neurotoxicity

characterized by dementia, ataxia and incontinence.^[17,22,23] In addition, HD-MTX based regimens requires intensive monitoring, poor compliance due to toxicity and have approximately 10% treatment related mortality rates.^[9] Most of the results are from patients in trial settings with proper care and quality control, whereas even now in clinical settings in low resource countries the OS with methotrexate based regimens is around 10-12 months and it is associated with significant treatment related toxicity.^[24]

All of the studies combining CHOP with WBRT have administered CHOP chemotherapy before WBRT. We had administered CHOP chemotherapy after WBRT and it may be hypothesized that pre-chemo WBRT lead to better penetration of the chemotherapeutic agents in the brain. In our study, mean OS was 36.34 months and median OS was 20 months with 3-year actuarial OS of 38%. There was no treatment related mortality.

Corticosteroids are important in PCNSL and can lead to significant tumor regression. Steroids induce apoptosis in lymphoma cells; the mechanism of action is therefore via cytotoxic effects rather than the reduction in cerebral edema.^[25,26] Patients have clinical improvement and imaging sometimes show complete remission of contrast enhancing abnormalities. Although durable remissions have been reported, most responses are short-lived, and almost all patients will develop resistance after prolonged exposure.

Age and performance status have long been recognized as significant prognostic factors for PCNSL.^[27,28] In our series, survival was unaffected by KPS status of the patient, though age less than 50-year was a significant prognostic factor.

CONCLUSIONS

PCNSL is a rare malignant neoplasm of CNS. Currently, HD-MTX based regimens in combination of WBRT is the standard of care but is associated with severe toxicity and requires in-patient admission with intensive monitoring. However, in community settings in low resource countries, administering HD-MTX based regimen is often not practically feasible. Though the survival outcome of WBRT followed by CHOP chemotherapy is inferior to methotrexate based regimens, but still this retrospective analysis suggests a simpler regimen that can be used in-patients in low resource countries in community settings with satisfactory results in terms of compliance and survival.

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