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Real-world outcomes for primary and secondary central nervous system lymphoma

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ABSTRACT

Aims: Central nervous system lymphoma (CNSL) is a rare and aggressive subtype of extranodal non-Hodgkin lymphoma, including primary and secondary forms. Despite advances in treatment, outcomes remain suboptimal. In this study, real-world treatment outcomes and prognostic factors in CNSL patients were evaluated.

Methods: We retrospectively analyzed 40 patients diagnosed with CNSL at Gazi University Hospital between 2003 and 2022. Clinical characteristics, treatment modalities, response rates, transplantation and survival outcomes were evaluated.

Results: The median age was 53 years, and 62.5% of patients had primary CNSL. High-dose methotrexate-based regimens yielded high response rates, with overall response rates (ORR) of 92.3% for the MATRix regimen and 86.7% for the modified Bonn protocol. Autologous stem cell transplantation (ASCT) was associated with an improvement in complete/unconfirmed complete response rates (67.8% pre-ASCT vs. 83.8% post-ASCT). At a median follow-up of 1124 days, the overall survival (OS) and progression-free survival rates were 52.5% and 35%, respectively. Relapse occurred in 50% of patients. Prognostic scoring systems demonstrated limited applicability due to missing data and the small sample size.

Conclusion: High-dose methotrexate-based regimens followed by ASCT remain effective in CNSL; however, relapse rates remain high. Improved prognostic models and novel therapies are needed.

Keywords: Central nervous system lymphoma, primary central nervous system lymphoma, methotrexate, autologous stem cell transplantation

INTRODUCTION

Central nervous system lymphoma (CNSL) is a rare, aggressive form of extranodal non-Hodgkin lymphoma that can develop as primary or secondary due to systemic disease.[1] Primary central nervous system lymphoma (PCNSL) is defined as the presence of disease in the brain, spinal cord, cranial nerves, leptomeninges or eyes without systemic lymphoma. Secondary central nervous system lymphoma (SCNSL) initially presents systemically and then relapses with central nervous system (CNS) involvement, or systemic and CNS involvement are seen simultaneously at diagnosis.[2,3] Although they are biologically different diseases, treatment approaches are similar in PCNSL and SCNSL. High-dose methotrexate-based multiagent chemotherapy protocols form the basis of induction therapy in CNSL. Autologous stem cell transplantation (ASCT) or radiotherapy is used in consolidation treatment.[4-6] Different prognostic scores are available for PCNSL, such as the International Extranodal Lymphoma Study Group (IELSG), Nottingham/Barcelona, Memorial Sloan Kettering Cancer Center and Taipei Score. Although the IELSG model was created based on a relatively large patient sample from multiple centers, it is not easy to use in daily practice, as information on cerebrospinal fluid protein is not available in many patients.[7]

In this retrospective study, we evaluated the treatment outcomes and prognostic factors in patients diagnosed with CNSL.

METHODS

Ethics

This study was approved by the Clinical Researches Ethics Committee of Gazi University (Date: 10.10.2022, Decision No: 730). All procedures were conducted in accordance with ethical guidelines and the principles of the Declaration of Helsinki.

Patients

A total of 40 patients diagnosed with CNSL at Gazi University Hospital between October 1, 2003 and September 27, 2022 were retrospectively reviewed. The pathology of all patients diagnosed with PCNSL and SCNSL in this study was diffuse large B-cell lymphoma.

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Response Assessment

Response assessment was performed using [18F] FDG-PET/CT and contrast-enhanced MRI according to the criteria of the International Primary CNS Lymphoma Collaborative Group.[8] Lugano response assessment criteria were also used for patients with concomitant systemic and CNS involvement.[9]

Chemotherapy Protocols

Treatment was administered according to time period-based standard treatment protocols recommended in the literature. Patients who received 3–4 cycles of the MATRix regimen were treated with a combination immunochemotherapy consisting of rituximab, high-dose methotrexate, cytarabine, and thiotepa, including leucovorin rescue therapy. In patients treated with the modified Bonn regimen, Bonn A consisted of high-dose methotrexate–based chemotherapy including vincristine, dexamethasone, and ifosfamide with mesna support; Bonn B consisted of high-dose methotrexate–based chemotherapy including vincristine, dexamethasone, and cyclophosphamide with mesna support, with leucovorin rescue administered in both; and Bonn C consisted of high-dose cytarabine with vincristine and dexamethasone.

Transplant Protocol

In patients undergoing ASCT for consolidation, the conditioning regimen consisted of thiotepa, cyclophosphamide, and busulfan. Hematopoietic stem cells were cryopreserved. Median infused CD34+ cell count was 5(2.92–9.07)×106/kg. All patients received 30 MIU filgrastim until neutrophil engraftment occurred on day +4th after transplantation.

Statistical Analysis

The primary endpoints of the study were overall response rate (ORR), progression free survival (PFS) rate and overall survival (OS) rate. Secondary endpoints were assessment of prognostic factors and autologous stem cell transplantation outcomes. Continuous variables were expressed as median/range and categorical variables as frequency/percentages using descriptive statistics. The Kaplan Meier test was used for survival analysis. SPSS 26.0 (IBM Corp, Armonk, NY, USA) program was used for statistical analysis.

RESULTS

A total of 40 patients were included in the study [median age: 53(27-77) years, male/female: 23(57.5%)/17(42.5%)]. Twenty-five patients (62.5%) had PCNSL, 8 patients (20%) had relapses with SCNSL, 7 patients (17.5%) had concomitant SCNSL. Of the 29 patients who underwent subtyping, 18 patients (62.1%) had a non-germinal center phenotype, 11 patients (37.9%) had a germinal center phenotype. No patient was found to be HIV positive; 2 patients (5%) had a history of renal transplantation. Hypogammaglobulinemia was observed in five of the 35 patients (14.3%). Seven patients (17.5%) had B-symptoms. The median IELSG score among patients with PCNSL was 2 (range: 0–5), and cerebrospinal fluid protein levels were available for inclusion in the IELSG score calculation in only 7 patients (28%). Of the 8 patients who did not have CNS involvement at diagnosis, 6 patients had a high CNS-IPI risk score and 2 patients had an intermediate CNS-IPI risk score. In these patients, relapses with CNS occurred after a median of 318 (180-887) days and 6 patients had not received prophylaxis against CNS relapse. The median number of chemotherapy lines was 2 (0-5) including ASCT. Seventeen patients (42.5%) received radiotherapy, of whom two were treated in the first-line setting. One patient underwent craniospinal irradiation, while the remaining patients received cranial radiotherapy (94.1%). Among the 13 patients evaluable for radiotherapy response, 5 (38.5%) achieved a partial response (PR), whereas 8 (61.5%) achieved a complete response or unconfirmed complete response (CR/CRu). The characteristics of the study population are summarized in **Table 1**, and the characteristics of patients with SCNSL are summarized in **Table 2**.

Table 1. Patient characteristics

Age, years, median (range)	53 (27-77)
Gender (male/female) [n (%)]	23 (57.5)/17 (42.5)
Disease [n (%)]	
Primary CNSL	25 (62.5)
Relapses with secondary CNSL	8 (20)
Concomitant secondary CNSL	7 (17.5)
ECOG status [n (%)]	
≤1	25 (62.5)
2	11 (27.5)
3	4 (10)
Serum LDH [n (%)]	
Normal	11 (28.9)
High	27 (71.1)
Involvement area [n (%)]	
Parenchymal	32 (80)
Leptomeningeal	1 (2.5)
Parenchymal & leptomeningeal	7 (17.5)
Deep brain involvement [n (%)]	
Yes	29 (72.5)
No	11 (27.5)
Follow up period, day, median (range)	1124 (18-7765)
Relapse pattern [n (%)]	
CNS only	18 (45)
CNS+systemic	2 (5)
Relapse time [n (%)]	
<1 year	12 (30)
1-2 years	5 (12.5)
>2 years	3 (7.5)
Mortality rate [n (%)]	19 (47.5)
Disease-related	14 (35)
Transplantation-related	3 (7.5)
Non-relapse	2 (5)
Progression-free survival rate [n (%)]	14 (35)
Overall survival rate [n (%)]	21 (52.5)

CNS: Central nervous system, CNSL: Central nervous system lymphoma, ECOG: Eastern Cooperative Oncology Group, LDH: lactate dehydrogenase, n: number

In the first-line treatment, 13 patients received the MATRix protocol, and 15 patients received the Modified Bonn protocol. The ORR was 92.3% in patients receiving MATRix therapy, whereas it was 86.7% in those receiving Modified Bonn chemotherapy (p=0.63). For patients receiving the Modified Bonn and MATRix protocols, the 2-year OS rates were 86% and 61% (log-rank p=0.33), while the 2-year PFS rates were 58% and 52% (log-rank p=0.82), respectively (**Figure 1A, 1B**).

ASCT was performed in 31 patients (77.5%). Among patients who underwent ASCT, response rates before transplantation were 67.8% for CR/CRu, 22.6% for PR, and 9.7% for PD. Following ASCT, the CR/CRu rate increased to 83.8%,

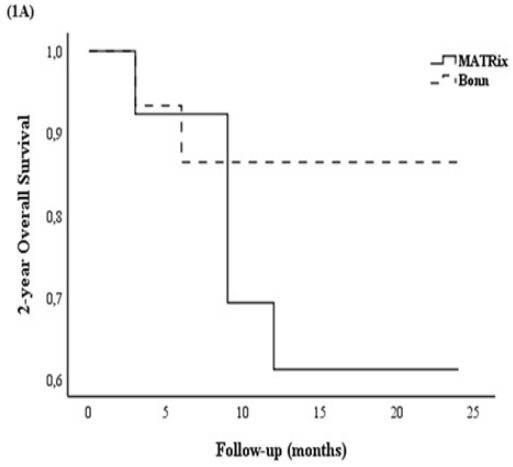
while the rates of PR and PD decreased to 6.5% and 3.2%, respectively. The characteristics of patients who underwent ASCT are presented in **Table 3**.

Table 2. Characteristics of patients with secondary central nervous system lymphoma

Ann Arbor stage at diagnosis [n (%)]	
Stage 2	1 (6.7)
Stage 3	2 (13.3)
Stage 4	12 (80)
Bulky mass [n (%)]	
Yes	3 (20)
No	12 (80)
Splenic involvement [n (%)]	
Yes	3 (20)
No	12 (80)
Bone marrow involvement [n (%)]	
Yes	1 (6.7)
No	14 (93.3)
Extranodal involvement [n (%)]	
0	3 (20)
1	2 (13.3)
≥2	10 (66.7)
International Prognostic Index [n (%)]	
2	5 (35.7)
3	4 (28.6)
4-5	5 (35.7)
Missing	1(6.7)

n: number

(A) Overall survival rate.



(B) Progression-free survival rate.

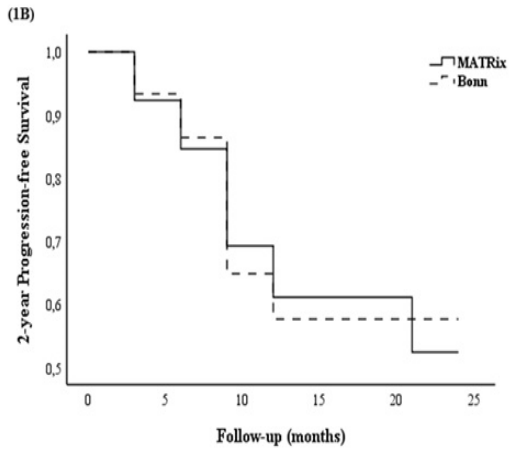


Figure 1. Estimated 2-year survival analysis comparing MATRix and modified Bonn protocols

Table 3. Transplantation characteristics

ASCT performed [n (%)]	
Yes	31 (77.5)
No	9 (22.5)
Pre-transplantation HCT-CI, median (range)	0 (0-7)
CD34+ cell count (×10⁶/kg), median (range)	5 (2.92–9.07)
Pre-transplantation disease status [n (%)]	
Complete response	11 (35.5)
Unconfirmed complete response	10 (32.3)
Partial response	7 (22.6)
Progressive disease	3 (9.7)
Post-transplantation disease status [n (%)]	
Complete response	25 (80.6)
Unconfirmed complete response	1 (3.2)
Partial response	2 (6.5)
Progressive disease	1 (3.2)
Death before response assessment	2 (6.5)

ASCT: Autologous stem cell transplantation, HCT-CI: Hematopoietic Cell Transplantation-specific Comorbidity Index, n: number

When patients with PCNSL were evaluated according to the Taipei score, 6 patients (24%) had a score of 0 and were classified as low risk, 11 patients (44%) had a score of 1 and were classified as intermediate risk, and 8 patients (32%) had a score of 2 and were classified as high risk. Due to the small sample size, survival analysis was performed by grouping patients into two categories: low risk and intermediate–high risk. OS was 66.7% in the low-risk group and 47.4% in the intermediate–high-risk group; however, this difference was not statistically significant (p=0.34). PFS was 66.7% in the low-risk group and 42.1% in the intermediate–high-risk group, and this difference was also not statistically significant (p=0.27). The laboratory findings at diagnosis are presented in **Table 4**.

Table 4. Laboratory findings of patients

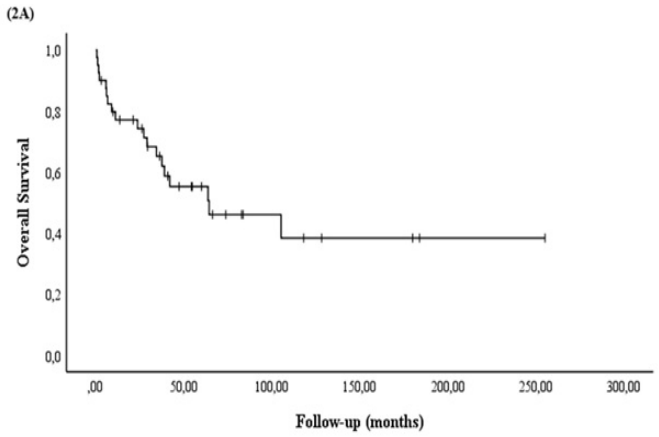
Hemoglobin (g/dl), median (range)	13.2 (8.1-17.1)
Leukocyte count (/μL), median (range)	9250 (3720-18180)
Lymphocyte count (/μL), median (range)	1400 (130-4980)
Lactate dehydrogenase level (U/L), median (range)	315 (168-1916)
Albumin (g/dl), median (range)	3.9 (2.2-5.1)

At a median follow-up of 1124 days (18–7765), the OS rate was 52.5% and the PFS rate was 35% (**Figure 2A, 2B**). Twenty patients (50%) experienced relapse, with a median of 1 relapse (1–4). The median PFS was 363.5 days (18–5476), and the median OS after CNS involvement was 1117 days (18–7378).

DISCUSSION

High-dose methotrexate-based multiagent chemotherapy constitutes the backbone of induction therapy in CNSL; however, no universally accepted standard regimen exists. In this context, we aimed to evaluate treatment outcomes across different therapeutic approaches. Additionally, both ASCT and radiotherapy are utilized in consolidation, ASCT has increasingly become the preferred strategy, and we therefore specifically analyzed transplantation outcomes in our study. Given the limited availability of cerebrospinal fluid protein measurements, which are required for the IELSG score, we employed the Taipei score as a more feasible tool for prognostic assessment in patients with PCNSL in this retrospective single-center study.

(A) Overall survival rate.



(B) Progression-free survival rate

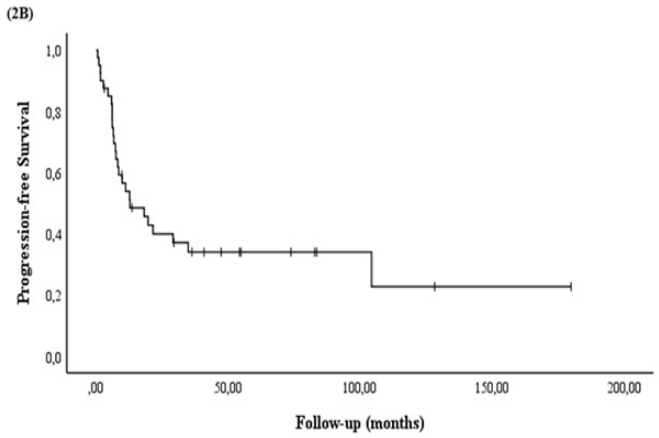


Figure 2. Survival analysis

Although ORR was high in both the MATRix and modified Bonn regimen groups, no statistically significant difference was observed between the two regimens (92.3% vs. 86.7%, p=0.63). Among patients treated with the MATRix and Modified Bonn regimen protocols, the 2-year OS rates were 61% and 86% (log-rank p=0.33), respectively, while the corresponding 2-year PFS rates were 52% and 58% (log-rank p=0.82). This lack of statistical significance in OS may be related to the limited sample size. However, despite the favorable ORR, survival outcomes remained comparatively modest. In the IELSG32 study,[10] among patients treated with the MATRix regimen and consolidated with radiotherapy or ASCT, the 4-year OS rates were 85% and 83%, respectively (p=0.39). Zeyen et al.[11] reported 2-year PFS and 5-year OS rates of 56% and 76%, respectively, in patients receiving the modified Bonn regimen. The poorer survival outcomes in the MATRix group may be explained by the inclusion of patients with SCNSL and the limited sample size in our study. [10,11]

In our study, CR/CRu rates increased from 67.8% prior to ASCT to 83.8% after transplantation. This finding is consistent with existing evidence supporting ASCT as a consolidation strategy in patients with CNSL. Recent studies have demonstrated that ASCT following thiotepa-based conditioning regimens is associated with improved PFS and OS, particularly in patients who achieve a response to induction chemotherapy.[12,13]

The role of radiotherapy in CNSL continues to evolve. In our study, radiotherapy proved effective as a salvage or consolidation modality, achieving high complete response rates among evaluable patients. However, concerns regarding neurotoxicity and quality of life are increasing. Recent studies have increasingly shifted radiotherapy to a less prominent role, particularly in younger and transplant-eligible patients.[14]

Despite these encouraging response rates, disease relapse remains a major clinical challenge. In line with previous reports, relapse was observed in 50% of patients in our cohort, even with intensive induction and consolidation approaches.[15,16] Despite the use of high-dose methotrexate-based induction regimens followed by consolidation with ASCT, relapse rates remain substantial, thereby necessitating the development of novel therapeutic approaches. Phase I/II trials evaluating targeted agents such as ibrutinib and lenalidomide in induction therapy are ongoing, with long-term outcomes awaited.[6,17] Immune checkpoint inhibitors and CAR-T cell therapies represent emerging options, particularly in heavily pretreated patients. PD-1/PD-L1 blockade has shown potential clinical benefit in CNS lymphomas, suggesting a role in overcoming immune evasion.[18,19] Additionally, tirabrutinib monotherapy has demonstrated encouraging activity in relapsed disease in phase I/II studies.[20, 21]

Limitations

Our analysis of prognostic scoring systems underscores notable limitations in their applicability to routine clinical practice. Despite its extensive validation, the IELSG score could not be fully calculated in the majority of our cohort due to the unavailability of cerebrospinal fluid protein data. This previously acknowledged constraint highlights the necessity for more pragmatic and readily implementable prognostic models. Although the Taipei score, proposed as a simplified alternative, demonstrated a capacity to stratify patients into distinct risk groups within our cohort, this differentiation did not achieve statistical significance, likely attributable to the limited sample size.[7]

The limitations of this study include its retrospective design, the small sample size, and the heterogeneous patient population. Further prospective randomized controlled trials with larger, more homogeneous cohorts are warranted.

CONCLUSION

Our findings support the continued use of high-dose methotrexate-based induction regimens followed by ASCT consolidation in eligible patients with CNSL. While high response rates can be achieved, relapses remain a major obstacle, highlighting the need for improved risk stratification and incorporation of novel therapeutic strategies.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Clinical Researches Ethics Committee of Gazi University (Date: 10.10.2022, Decision No: 730).

Informed Consent
This retrospective study used pre-existing anonymized patient data. No additional intervention was performed, and there was no direct patient contact. The study was approved by the Ethics Committee, and the requirement for written informed consent was waived by the ethics committee.

Peer Review Process
This manuscript was subject to external peer review.

Conflict of Interest
The authors declare no conflicts of interest related to this study.

Financial Disclosure
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Author Contributions
Concept: BBD, MY; Design: BBD, ZNÖ, ZAY, MY; Control: BBD, MY; Materials: BBD, ZNÖ, ZAY, MY; Data Collection and/or Processing: BBD, ZNÖ, ZAY, MY; Analysis and/or Interpretation: BBD; Literature Review: BBD, MY; Writing the Article: BBD; Critical Review: BBD, ZNÖ, ZAY, MY.

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