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Outcome of Primary Central Nervous System Lymphoma Treated with Combined Surgical Resection and High-Dose Methotrexate Chemotherapy: A Single-Institution Retrospective Study

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ABSTRACT

AIM: To evaluate the feasibility and long-term clinical results of combined surgical resection and high-dose methotrexate (HD-MTX) chemotherapy for primary central nervous system lymphoma (PCNSL) of the brain.

MATERIAL and METHODS: Fifty-eight patients were diagnosed with PCNSL by histopathological examination of brain biopsy specimens at the Second Affiliated Hospital of Bengbu Medical College from March 2013 to December 2017. All patients received MTX at adose of 3.5 g/m^2 every 2 weeks for 6 cycles. Clinical information, including ages, number of lesions, and tumor locations, were retrospectively collected from the medical records.

RESULTS: The complete remission rates in patients treated with MTX plus craniotomy for surgical resection and those treated with MTX alone were 70.0% and 32.1%, respectively (p=0.021). Adding craniotomy to MTX chemotherapy did not increase the complication rate. The most common adverse events were hematological toxicity, liver toxicity, and gastrointestinal reaction were similar between groups. Multivariate analysis showed that surgical resection was associated with longer progression-free survival (PFS) (OR: p=0.002).

CONCLUSION: Combining craniotomy for surgical resection and MTX-based chemotherapy may be safe and effective for treating PCNSL.

KEYWORDS: Central nervous system, Lymphoma, Methotrexate, Outcome, Surgery

ABBREVIATIONS: CI: Confidence interval, **CR:** Complete remission, **CSF:** Cerebrospinal fluid, **HD-MTX:** High-dose methotrexate, **OS:** Overall survival, **PCNSL:** Primary central nervous system lymphoma, **PD:** Progressive disease, **PR:** Partial remission, **SD:** Stable disease.

INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is a relatively rare and aggressive tumor composed of diffuse, large, neoplastic B cells, and accounts for 1%–2% of primary CNS tumors (13). Survival times in patients with PCNSL range from 12 to 32 months according to recent studies (2,13,15). While previous studies have proposed effective treatments, the standard of care for this disease is still under discussion. High-dose methotrexate (HD-MTX), a first-line therapy for PCNSL, is considered the gold standard. Surgical resection of PCNSL has not been considered an appropriate treatment because of unfavorable complication rates and poor outcomes (5,7), so it is generally not recommended by neurosurgeons or other clinicians.

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However, recent investigations have demonstrated that surgical resection can result in long-term remission and improved survival in patients with PCNSL (4). With the development of magnetic resonance imaging (MRI) and frameless stereotaxy for tumor localization, surgical resection's role in PCNSL is gradually becoming more accepted (2,7,15). Currently, PCNSL treatment remains challenging. In this study, we aim to determine the effectiveness of craniotomy for surgical resection in combination with MTX chemotherapy for treating PCNSL.

MATERIAL and METHODS

Patients

We retrospectively studied 58 patients diagnosed with PCNSL by histopathological examination of a brain biopsy specimen at the Second Affiliated Hospital of Bengbu Medical College between March 2013 and December 2017. Institutional review board approval was obtained, and all patients provided informed consent. Clinical information, including ages, number of lesions, and tumor locations, were collected from the medical records. All patients received MTX at a dose of 3.5 g/m^2 every 2 weeks for 6 cycles (3,6,8,9). Additionally, 30 patients underwent craniotomy for surgical resection of the PCNSL (MTX plus craniotomy group); 28 patients received chemotherapy alone (MTX alone group).

Assessment

MRI with axial and coronal T1-, T2-, and contrast-enhanced T1-weighted sequences were used to evaluate the sizes and locations of the tumors at diagnosis and throughout the follow-up period. Tumor response to treatment was classified as complete remission (CR), partial remission (PR), stable disease (SD), or progressive disease (PD), as described previously (11). Overall survival (OS) was calculated from the date of diagnosis to the time of death from any cause. Progression-free survival (PFS) was calculated from the start of treatment to the time of disease progression or death due to PCNSL. Treatment toxicity was graded using the National Cancer Institute Common Toxicity Criteria version 3.0 (14).

Statistical Analysis

Patient characteristics were compared using the chi-square test. Relationships between the treatment groups and clinicopathological variables were evaluated by Fisher's exact test and chi-square test. Multivariate analyses for OS and PFS were conducted using the Cox proportional hazards regression model. $p<0.05$ was considered as statistically significant.

RESULTS

The patients' clinical characteristics are shown in Table I. Age, sex, number of lesions, and involvement of deep structures did not differ between the two treatment groups; however, the CR rate was significantly higher in the MTX plus craniotomy group than the MTX alone group (70.0% vs.32.1%, p=0.021).

Response rates for the MTX plus craniotomy and MTX alone groups are shown in Table II. Thirty patients (51.7%) achieved CR after treatment, and 15 (25.9%) achieved PR. Eight patients (13.8%) had SD and 5 (8.6%) developed PD. The 30 patients in the MTX plus craniotomy group had the following outcomes: 21 CR (70.0%), 5 PR (16.7%), 3 SD (10.0%), and 1 PD (3.3%). The 28 patients in the MTX alone group had the following outcomes: 9 CR (32.1%), 10 PR (35.7%), 5 SD (17.9%), and 4 PD (14.3%).

Table I: Clinical Characteristics of Primary Central Nervous System Lymphomas

Characteristic	Craniotomy plus MTX n=30 (%)	MTX alone n=28 (%)	p	Total Number n=58 (%)
Age	56.3 ± 0.99	49.6 ± 0.73	-	54.5 ± 0.82
Gender				
Male	19	16	0.63	35
Female	11	12		23
Number of lesion				
1	21	13	0.37	34
At least 2	9	15		24
Deep structure involvement				
Presence	26	20	0.186	46
Absence	4	8		12
Induction treatment response				
CR	21	9	**0.021**	30
Without CR	9	19		28

***CR:** Complete remission, **MTX:** Methotrexate.*

A total of 53 patients had sufficient follow-up data. The median PFS rates in the MTX plus craniotomy and MTX alone groups were 54.4 months [95% confidence interval (CI) 29.4–49.7] and 16.3 months (95% CI 4.9–23.0), respectively (Table III). Multivariate analysis revealed that craniotomy for surgical resection was an independent predictor for improved PFS (Table IV).

Complications from treatment for all patients are summarized in Table V. The most common adverse events were hematological toxicity, liver toxicity, and gastrointestinal reaction were similar between groups.

DISCUSSION

Although surgical resection is the standard treatment formost malignant brain tumors, including gliomas and large brain metastases, resection for PCNSL has not been advocated because of historical studies showing poor outcomes and high complication rates (4,5). However, more recent studies have shown that resection is possibly beneficial. The advantages of surgery are not only resolution of mass effect and neurological symptoms, but also oncologic control. In this study, the post-resection neurological complication rate was significantly lower than those seen in historical series (12), and we observed a higher CR rate and improved PFS in patients treated with combined MTX and craniotomy compared with those treated with MTX alone.

There is increasing evidence demonstrating that surgical resection may improve outcomes and survival in certain systemic lymphomas. Lee et al. reported that patients with intestinal diffuse large B-cell lymphoma who were treated with surgical resection followed by chemotherapy had improved

Table II: Response to Induction Therapy

Response to Therapy	Craniotomy plus MTX n=30 (%)	MTX alone n=28 (%)	Total Number n=58 (%)
Complete remission	21 (70.0)	9 (32.1)	30 (51.7)
Partial remission	5 (16.7)	10 (35.7)	15 (25.9)
Stable disease	3 (10.0)	5 (17.9)	8 (13.8)
Progression disease	1 (3.3)	4 (14.3)	5 (8.6)
Died during therapy	0 (0)	0 (0)	0 (0)

Table III: Overall Survival and Progression-Free Survival

Survival	Craniotomy plus MTX n=27	MTX alone n=26	p
median OS (months 95% CI)	-	-	-
median PFS (months 95% CI)	54.4 (29.4-49.7)	16.3 (4.9-23.0)	0.002

OS: *Overall survival,* ***PFS:*** *Progression-free survival.*

Table IV: Univariate and Multivariate Analyses of OS and PFS for Patients

	OS						PS					
Variable	**Univariate analysis**			**Multivariate analysis**			**Univariate analysis**			**Multivariate analysis**		
	HR	**95%CI**	**p**	**HR**	**95%CI**	**p**	**HR**	**95%CI**	**p**	**HR**	**95%CI**	**p**
Age	0.18	0.03-1.42	0.074	0.27	0.02-3.52	0.292	0.79	0.41-3.02	0.92	1.83	0.69-4.96	0.275
Gender	1.03	0.34-3.87	0.937	-	-	-	0.75	0.27-1.86	0.462	-	-	-
Number of lesion	0.58	0.11-2.19	0.323	0.46	0.05-2.53	0.375	0.84	0.24-2.63	0.790	0.91	0.25-2.79	0.746
Deep structure involvement	2.61	0.32-27.59	0.520	5.09	0.18-148.73	0.382	1.03	0.26-3.99	0.826	0.927	0.13-5.019	0.915
Induction treatment response	3.02	0.59-15.81	0.162	9.84	0.76-129.43	0.060	3.37	1.03-7.98	0.028	4.92	1.58-16.82	**0.008**

Age, ≥60yvs.<60y; Gender, male vs. female; Number of lesion,1 vs. ≥2 lesions; Deep structure involvement, presence vs. absence; Induction treatment response, MTX, plus craniotomy vs. MTX alone.

Table V: Complication from PCNSL by Craniotomy Plus MTX-Base Chemistry and only Chemotherapy

Response to Therapy	Craniotomy plus MTX n=30 (%)	MTX only n=28 (%)	Total Number n=58 (%)
Gastrointestinal reaction			
Nausea	3 (5.2%)	3 (5.2%)	6 (10.3%)
Vomiting	1 (1.7%)	0 (0)	1 (1.7%)
Diarrhea	1 (1.7%)	0 (0)	1 (1.7%)
Constipation	5 (16.7)	3 (5.2%)	8 (13.8%)
Hematological toxicity			
Neutropenia	19 (63.3%)	10 (35.7%)	29 (50.0%)
Infection	3 (5.2%)	2 (7.1%)	5 (17.9%)
Anemia	3 (5.2%)	3 (5.2%)	6 (10.3)
Thrombocytopenia	2 (6.7%)	1 (3.6%)	3 (5.2%)
Liver toxicity	17 (56.7%)	11 (39.3%)	28 (48.3%)
Nephrotoxicity	4 (13.3%)	2 (7.1%)	6 (10.3%)
Complications after resection			
Surgical site infection	5 (17.9%)	0 (0)	5 (17.9%)
Subdural hygroma	3 (5.2%)	0 (0)	3 (5.2%)
CSF leak	1 (1.7%)	0 (0)	1 (1.7%)

CSF: *Cerebrospinal fluid.*

OS compared with those treated with chemotherapy alone (10). In a large report of 248 PCNSL patients, Bataille et al. showed that 1-year OS was 56.6% in those who underwent gross total resection, 31.8% in subtotal resection, and 48.6% in biopsy alone (1).

This study was designed to investigate surgical treatment's role in PCNSL patients treated with MTX. A better outcome was demonstrated in patients who additionally underwent craniotomy for surgical resection.The observed improvement in PFS was independent of age, sex, and chemotherapy treatment response. In addition, surgical resection was an independent predictor for improved PFS (Table IV). With technological developments in modern imaging, intraoperative monitoring, and navigation techniques, surgical resection is likely considerably safer today than in the past. Although this was a retrospective study, it suggests a survival benefit is associated with cytoreductive surgery for PCNSL.

Adding craniotomy to chemotherapy did not increase complications in this study. The most common adverse events, including neutropenia, anemia, thrombocytopenia, elevated aminotransferase level, and gastrointestinal reaction, were similar between the two treatment groups. Complications from craniotomy included surgical site infection, subdural hygroma, and cerebrospinal fluid (CSF) leak. One patient developed a CSF leak, which resolved after administration of cerebrospinal fluid.

The limitations of this study are as follows: patient-selection bias, a limited number of cases, single non-eloquent area lesion, and single-center study. Further multicenter prospective studies are necessary to confirm our results.

CONCLUSION

Early studies that examined the surgery's role in PCNSL found no advantage for surgical resection; however, these studies were biased. More recent data suggests that resection might provide a therapeutic benefit. Combining craniotomy with MTX chemotherapy may be useful; further study is needed.

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REFERENCES

1. Bataille B, Delwail V, Menet E: Primary intracerebral malignant lymphoma: Report of 248 cases. J Neurosurg 92:261-266, 2000
2. Batchelor T, Carson K, O'Neill A, Grossman SA, Alavi J, New P, Hochberg F, Priet R: Treatment of primary CNS lymphoma with methotrexate and deferred radiotherapy: A report of NABTT 96–07. J Clin Oncol 21:1044-1049,2003

3. Batchelor TT, Grossman SA, Mikkelsen T, Ye X, Desideri S, Lesser GJ: Rituximab monotherapy for patients with recurrent primary CNS lymphoma. Neurology 76:929-930, 2011
4. Bellinzona M, Roser F, Ostertag H, Gaab RM, Saini M: Surgical removal of primary central nervous system lymphomas (PCNSL) presenting as space occupying lesions: A series of 33 cases. Eur J Surg Oncol 31:100-105,2005
5. DeAngelis LM, Yahalom J, Heinemann MH, Cirrincione C, Thaler HT, Krol G: Primary CNS lymphoma combined treatment with chemotherapy and radiotherapy. Neurology 40:80-86,1990
6. Ekenel M, Deangelis LM: Treatment of primary central nervous system lymphoma. Curr Treat Options Neurol 9:271-282, 2007
7. Henry JM, Heffner RR, Dillard SH, Earle KM, Davis RL: Primary malignant lymphomas of the central nervous system. Cancer 34:1293-1302, 1974
8. Herrlinger U, Schabet M, Brugger W, Kortmann RD: German Cancer Society NeuroOncology Working Group NOA-03 multicenter trial of single-agent high-dose methotrexate for primary central nervous system lymphoma. Ann Neurol 51:247-252, 2002
9. Jahnke K, Thiel E: Treatment options for central nervous system lymphomas in immunocompetent patients. Expert Rev Neurother 9:1497-1509, 2009
10. Lee HS, Park LC, Lee EM, Shin SH, Ye BJ: Comparison of therapeutic outcomes between surgical resection followed by R-CHOP and R-CHOP alone for localized primary intestinal diffuse large B-cell lymphoma. Am J Clin Oncol 37:182-187, 2014
11. Liu J, Sun XF, Qian J, Bai XY, Zhu H, Cui QU, Li XY, Chen YD, Wang YM, Liu YB: Immunochemotherapy forprimary central nervous system lymphoma with rituximab, methotrexate, cytarabine and dexamethasone: Retrospective analysis of 18 cases. Mol Clin Oncol 3:949-953, 2015
12. Michael BC, Adam MS, Jonathan Y: The safety of resection for primary central nervous system lymphoma: A single institution retrospective analysis. J Neurooncol 132:1-9,2017
13. Schabet M: Epidemiology of primary CNS lymphoma. J Neurooncol 43:199-201,1999
14. Trotti A, Colevas AD, Setser A, Rusch V, Jaques D, Budach V, Langer C, Murphy B, Cumberlin R, Coleman CN, Rubin P: CTCAE v3.0: Development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol 13:176-181, 2003
15. Weller M, Martus P, Roth P, Thiel E, Korfel A: Surgery for primary CNS lymphoma? Challenging a paradigm. Neuro Oncol 14:1481-1484, 2012