Management of secondary central nervous system involvement in systemic aggressive B cell lymphoma using R-MIADD chemotherapy: a single-center experience

Yuchen Wu

Beijing Tiantan Hospital

Xuefei Sun

Beijing Tiantan Hospital

Xueyan Bai

Beijing Tiantan Hospital

Jun Qian

Beijing Tiantan Hospital

Hong Zhu

Beijing Tiantan Hospital

Qu Cui

Beijing Tiantan Hospital

Ruixian Xing

Beijing Tiantan Hospital

Yuedan Chen

Beijing Tiantan Hospital

Qing Liu

Beijing Tiantan Hospital

Wenyuan Lai

Beijing Tiantan Hospital

Nan Ji

Beijing Tiantan Hospital

Shengjun Sun

Beijing Tiantan Hospital

Yuanbo Liu (✉ yuanbol@ccmu.edu.cn)

Capital Medical University Affiliated Beijing Tiantan Hospital <https://orcid.org/0000-0003-1703-6774>

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Abstract

Introduction Secondary central nervous lymphoma(SCNSL) was defined as lymphoma involvement of both within and outside CNS at initially diagnosis or CNS relapse of a systemic disease. The prognosis of SCNSL was poor and the most appropriate treatment remained unestablished. **Methods** We conducted a retrospective study addressing the feasibility of R-MIADD regimen which comprised rituximab, high dose methotrexate, ifosfamide, cytarabine, liposomal formulation of doxorubicin, dexamethasone in 19 consecutive SCNSL patients. **Results** Nineteen SCNSL patients with newly diagnosed CNS lesions were included with median age of 58 years (range 20 to 72 years). Eleven out of 19(57.9%) patients achieved complete remission(CR) and 2(10.5%) patients achieved partial remission by the end of induction treatment, the overall response rate (ORR) was 68.4%. The median follow-up time after the onset of CNS was 11.1 (3.2-35.5) months, the median progression-free survival after CNS was 28.0 months (95% CI: 11.0-44.9), and the median overall survival after CNS were 34.5months, by the time of this report, 8 patients remained CR. Treatment-related deaths was found in only one patient. **Conclusions** This is the largest series of SCNSL patients in China, and these data underscore the feasibility and efficacy of R-MIADD as induction treatment of SCNSL, further investigation is warranted.

Background

Secondary central nervous system lymphoma (SCNSL) refers to secondary involvement of brain, eye, spine, meningeal by systemic lymphoma.[1, 2] It's a devastating complication of systemic lymphoma which occurred in 5–10% diffuse large B cell lymphoma(DLBCL) patients with very few long-term survivors under conventional treatment.[3] SCNSL can occur in combination of systemic disease or presented as an isolated relapse. The prognostic model to assess the risk of CNS disease included the International Prognostic Score, involvement of the kidneys and/or adrenal gland.[4, 5] In addition, dual expression of MYC and BCL2,[6] breasts/testis involvement[7] were also considered substantial risk factors of SCNSL according to recent researches. The prognosis of SCNSL was poor comparing to PCNSL, in the current largest cohort of SCNSL, less than half patients reached complete remission by the end of the induction treatment, and the median post-CNS overall survival(OS) was only 3.9 months.[8] Therefore, further explorations on the treatment of SCNSL especially initial induction are needed to improve CR rate and improve outcomes.

High dose Methotrexate(HD-MTX) based regimens were the most commonly used therapy, HD-MTX in combination with high dose cytarabine(Ara-C) can improve survival significantly. Procarbazine, etoposide, ifosfamide(IFO), thiotepa, carmustine and other drugs which can cross the blood-brain barrier (BBB) were also included in combination with HD-MTX and/or Ara-C to further improve outcomes. Doxorubicin which is a vital component for the treatment of systemic DLBCL, was not included in regimens primary central nervous system lymphoma(PCNSL) for its incapability of penetrate the BBB,[9] but with an alternative liposomal formulation, doxorubicin can overcome this intervention and was proved an promising drug for CNSL in several studies.[10] In addition, high dose chemotherapy followed by autologous stem cell transplantation (ASCT) were introduced and showed benefit effect. However, ASCT was offered to only a

small part of younger patients with favorable response to induction treatment. Therefore, several studies explored the effectiveness of non-transplant regimens in SCNSL and indicated that this can be an effective treatment for SCNSL.[11–13]

Nijland et al retrospectively investigated the outcome of SCNSL patients treated with HD-MTX and R-CHOP(rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone regimen) without ASCT, the 3-year OS was 49% which was comparable to patient outcomes with more intensive treatment including ASCT. [11] Moreton et al carried out a pilot study using IDARAM regimen in 16 SCNSL among which 12 achieved CR, seven remained CR at median follow-up of 24 months.[14]

We observed an promising response in SCNSL treated with the combination of rituximab, HD-MTX, ifosfamide, cytarabine, liposomal formulation of doxorubicin, thus we retrospectively analyze the effectiveness of this regimen in order to explore novel treatment combination for SCNSL patients.

Methods And Materials

Study design and patient identification

Clinical data of a total 19 SCNSL patients were retrospectively reviewed in electronical medical records at the Department of hematology, Beijing Tiantan hospital hematology, Capital Medical University from January 2015 to August 2019. All patients were diagnosed with systemic lymphoma histologically, and SCNSL were determined by stereotactic biopsy, cerebrospinal fluid (CSF) cytology/flow cytometry or brain magnetic resonance imaging(MRI). All patients had newly diagnosed intracranial parenchymal lesion without prior CNS-directed therapy for CNS involvement of DLBCL.

Treatment

Patients were treated with R-MAIDD regimen in 21-day cycles. R-MIADD regimen: rituximab 375 mg/m² infusion day0, HD-MTX 3.5 g/ m² infusion 3.5-h day1(with folinic acid rescue), ifosfamide 1.2 g/ m² infusion day2, cytarabine 1 g/ m² infusion day3, liposomal doxorubicin infusion 20–25 mg/m² day4, dexamethasone 10 mg i.v. Day1-3.

Treatment after R-MIADD regimen. Patients who didn't achieve complete remission were proceed to salvage treatment with whole brain radiotherapy. Patients received post-R-MIADD CNS radiotherapy or consolidation chemotherapy according to clinical response.

Response and toxicity assessment

Response assessment was performed within 4 weeks of the final R-MIADD chemotherapy. Enhanced MRI and whole body CT with PET scan were used for assessment. Treatment response of systemic lymphoma were graded according to 2014 Lugano criteria. Clinical response in CNS disease was assessed using International Workshop to Standardize Baseline Evaluation and Response Criteria for Primary CNS Lymphoma,[15] MRI of all patients were assessed by two experienced neuro radiologists.

Toxicities were assessed and recorded using the Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0.[16] Post CNS overall survival (post CNS OS) was defined as the time from initiation CNS disease to last follow-up or death from any cause, post CNS progression free survival (post CNS PFS) was calculated from initiation of CNS disease to disease progression or last follow-up.

Statistical analysis

Survival analyses were performed using the Kaplan-Meier methodology with SPSS statistics 24.0 software. Univariate Cox regression was used to analyze the impact of baseline characteristics on PFS and OS. There were not enough subjects to perform reliable multivariate analysis. All tests were two sided and a p-value of < 0.05 was considered statistically significant.

Results

Clinical characteristics of systemic disease in SCNSL patients (Table 1)

Table 1
Clinical characteristics of systemic disease in
SCNSL patients.

Characteristics	N	%
Age		
Median	58	
Range	20–72	
≤60	10	52.6
>60	9	47.4
Gender		
Male	9	47.4
Female	10	52.6
Initial disease location		
Breasts	3	15.8
Testis	2	10.5
Lymph node	11	57.9
Others	3	15.9
Ann Arbor Stage		
I-II	5	26.3
III-IV	14	73.7
Treatment of initial disease		
R-CHOP like regimen	9	47.4
Other regimen	10	52.6
CNS prophylaxis		
Yes	2	10.5
No	17	89.5

The median age at initial of systemic disease was 58 (20–72) years. Among all nineteen SCNSL patients, ten(52.6%)had simultaneous involvement of both inside and outside CNS when initially diagnosed which were ‘new disease’, five(26.3%) had CNS disease in the latter part or within 3 months of completion of primary therapy which were defined as ‘refractory disease’, four(21.1%) had CNS relapse either combined

with systemic disease which were called 'relapse disease'. Extranodal involvement as initial systemic disease was observed in nine patients including breasts(n = 3), testis(n = 2), bone marrow(n = 1), prostate(n = 1), and stomach(n = 1). The histological findings were DLBCL in eighteen(94.7%) patients, and mantle cell lymphoma was diagnosed in one(15.3%)patient. Fourteen(73.7%) patients were graded to Ann Arbor staging III-IV at initial diagnosis.

For treatment after onset of systemic disease, nine(47.7%) patients received R-CHOP or similar regimens in which two patients received of intrathecal(IT) injection of methotrexate as CNS prophylaxis. One patient received ASCT after achieving complete remission of systemic disease and developed CNS disease afterward. Ten patients with new disease type SCNSL received CNS targeting treatment which will be described latter in this section.

Clinical characteristics of CNS disease in SCNSL patients(Table 2)

Table 2
Clinical characteristics of CNS disease in SCNSL patients.

CNS characteristics	N	%
CNS age		
Median, Range	59, 20–76	
≤ 60	10	52.6
> 60	9	47.4
Initial Symptoms		
Headache	5	26.3
Dizziness	5	26.3
Blurred vision	2	10.5
limb weakness	2	10.5
Seizure	1	5.3
Somnolence	1	5.3
Focal neurological deficits	3	15.8
ECOG-PS		
≤1	6	31.6
> 1	13	68.4
Type of CNS relapse		
New disease	10	52.6
Relapse	4	21.1
CNS only	3	
Combined CNS & systemic disease	1	
Refractory	5	26.3
Multiplicity		
Single	6	31.6
Multiple	13	68.4
Enhancement		

ABC: activated B cell, GCB: germinal center B cell, NA: not available.

CNS characteristics	N	%
Homogenous	11	57.9
Patchy	7	36.8
None	1	5.3
Location of disease		
White matter	16	84.2
Cerebellum	3	74.2
Brain stem	3	15.8
Deep grey matter	10	47.4
Diagnosis approaches		
Biopsy	10	52.6
Surgery section	4	21.1
Enhanced MRI	4	21.1
CSF cytology	1	5.3
Histology at relapse		
ABC	10	52.6
GCB	4	21.1
NA	5	26.3
ABC: activated B cell, GCB: germinal center B cell, NA: not available.		

The median age at onset of CNS disease was 59 (20–76) years. The most common symptoms at the initial of CNS disease were increased intracranial pressure symptoms and dizziness, which were seen in five(26.3%) SCNSL patients respectively. Other symptoms included blurred vision(n = 2), limb weakness(n = 2), seizure(n = 1), somnolence(n = 1) and focal neurological deficits(n = 3). For radiological features, brain parenchymal lesions were found in all nineteen patients, six (31.6%) were single lesion and in thirteen (68.4%) patients the lesions were multiple; Ten (47.4%) had tumors involving the deep part of the brain including cerebellum, basal ganglia, corpus callosum, and brain stem.

As for diagnostic approaches, four(21.1%) patients were diagnosed with typical radiological manifestations on enhanced MRI, ten(52.6%) were diagnosed with stereotactic biopsy and four(21.1%) patients received tumor resection, one(5.3%) patient was diagnosed with cerebrospinal fluid cytology. Histologically, four(4/10) cases showed germinal center B cell (GCB) phenotypes (CD10 + BCL-6 +/- MUM1

+/-), and ten(10/14) cases were peripherally activated B cell (ABC) phenotypes (CD10-BCL- 6 +/- MUM-I + or CD10-BCL-6-MUMI-).

Treatment and responses (Fig. 1)

All patients were treated with R-MIADD regimen, one with CSF dissemination received IT MTX (MTX 10 mg, dexamethasone 5 mg) simultaneously. After 1–3 cycles of induction, six patients reached CR, eight patients were assessed as PR, three had stable disease while one patient had progression disease(PD). One patient died of neutropenic sepsis after the 2nd cycle of chemotherapy.

All 6 patients with CR and 7 patients with PR continued R-MIADD treatment, by the end of the induction treatment, 11 patients attained CR and 2 attained PR (Table 3). Patients with SD and PD proceeded with whole brain radiotherapy(WBRT), one patient with PR also turned to WBRT due to financial difficulties. All 5 patients achieved CR after WBRT.

Table 3
Response of SCNSL patients after induction therapy.

Response	Total		New disease		Refractory disease		Relapse disease	
	N = 19	%	N = 10	%	N = 5	%	N = 4	%
CR	11	57.9	7	70	2	40	2	50
PR	2	10.5	1	10	0	0	1	25
WBRT*	5	26.3	2	20	2	40	1	25
Death	1	5.3	0	0	1	20	0	0
CR: complete remission, PR: partial remission, SD: stable disease, PD: progression disease, WBRT: whole brain radiotherapy, *WBRT indicated SCNSL who turned to WBRT during the induction treatment.								

Progression free and overall survival

By the end of induction treatment, 11(57.9%) patients achieved complete remission and 2(10.5%) patients achieved partial remission for an overall response rate(ORR) of 68.4%. Of the new disease patients, (7/10) attained CR and (1/10) attained PR. Of Refractory and relapse patients, ORR of 40% (CR40%) and 75%(CR50%) respectively.

The median follow-up time after the onset of CNS disease was 11.1 (3.2–35.5) months, the median post CNS PFS was 28.0 months (95% CI: 11.0-44.9)(Fig. 2), and the post CNS OS was 34.5months(Fig. 3).

Post R-MIADD treatment

After achieving complete remission, 10 patients continued with chemotherapy for consolidation treatment with combination of ifosfamide, etoposide and cytarabine every three months, 1 did not receive further treatment; For the five patients who did not respond to R-MIADD and proceeded to WBRT, all attained CR and proceeded with ifosfamide, etoposide and cytarabine consolidation every three months.

Toxicity, relapses and cause of death

Hematologic toxicity 16(84.2%) was most frequently seen in the treatment with 3(15.8%) patients experienced grade 4 myelosuppression. In isolated relapse and concurrent disease the number of patients with 3–4 grade myelosuppression was 2(20%) and 6(66.7%) though without statistical difference($p = 0.07$). Aminotransferases elevated was observed in 8(42.1%) and bilirubin elevated in 2(10.5%). No severe mucosa damage was observed during treatment. Two(10.5%) patients experienced temporarily creatinine elevated after applying MTX, and their renal function returned to normal after alkalinized urine and hydration to accelerate the excretion of MTX.

One patient with refractory disease died during the induction treatment due to myelosuppression and severe pneumonia after chemotherapy, which resulted in toxic shock of infection. Of 11 patients who obtain CR with R-MIADD alone, 3 had isolated relapsed in CNS (2 new disease and 1 relapse disease initially) of which 1 relapse in spine 2 in brain parenchymal, and 1 patients died of progression of CNS disease(Fig. 4).

Discussion

With the emerging of novel treatment strategies, more regimens were introduced to CNS lymphoma. However, comparing to the general favorable treatment response and survival of PCNSL, SCNSL have inferior outcome and remained a fatal complication of aggressive B-cell lymphoma with a post CNS OS between 3.9-7.2months according to previous reports.[17–19] In this research, we use the combination of R-MAIDD to treat SCNSL patients with an ORR of 68.4%, and post CNS PFS 28.0months(95%CI: 11.0-44.9), this result indicated that non-transplant regimen of R-MIADD could be a potential effective treatment for SCNSL.

There's no current randomized study define the optimal regimen of SCNSL due to the rarity of this disease. Few prospective studies have demonstrated improved outcome favoring ASCT in young and fit SCNSL patients.[20–24] In a prospective study undertaken by korfel et al, 30 SCNSL patients were treated with intravenous HD-MTX, IFO, dexamethasone with IT liposomal cytarabine, non-responding were converted to thiotepa and cytarabine for the second cycle, responding patients received thiotepa, carmustine, etoposide conditioned ASCT with a CR response of 50% and PR 7%;[21] Ferreri et al carried out regimen including high doses of MTX and Ara-C, followed by Rituximab, cyclophosphamide, Ara-C +/- etoposide targeting residual systemic disease prior to ASCT, and BEAM-conditioned ASCT were used in responding patients, the CR rate was 63% in this trial with a 2-year event free survival rate of 50%.[20] Despite the encouraging results of highly selective chemo-responsive fit patients, majority patients with SCNSL could not proceeded to ASCT due to the poorly response to initial treatment. In a large

international cohort study included 291 cases of secondary central involvement of DLBCL, 173 patients received systemic chemotherapy in which only 25 received high-dose chemotherapy followed by ASCT. Moreover, the author indicated that when considering only patients in CR after initial therapy, ASCT consolidation did not prolong OS with isolated SCNSL.[8]

Therefore, several researches turned to non-transplant regimen for SCNSL and focus on improving the responding rate of initial treatment. Marcel Nijland et al used MBVP (methotrexate, etoposide, carmustine, and methylprednisolone) combined with R-CHOP as induction therapy. After achieving remission, whole brain radiotherapy was given for consolidation. The complete response rate 57%, with 3 years PFS and OS 45% (95% CI 34–56%) and 49% (95% CI 38–60%);[11] Those were comparable to figures reported here. In another pilot study, Dai Chihara treated 8 patients with DA-EPOCH-R combined with HD-MTX and all 8 patients achieved CR;[12] Nagle SJ et al reported HD-MTX combined with temozolomide for the treatment of SCNSL, with median OS of 4.8 months and 4 years OS of 25%.[13]

In our research, the regimen contain HD-MTX/cytarabine/IFO, in addition to liposomal doxorubicin, but the dose of all regimen was reduced comparing to the study mentioned above which lead to better treatment response without additional treatment toxicity. By the end of the induction therapy, 57.9% patients achieved CR, post CNS PFS was 28.0months(95%CI: 11.0-44.9) which was comparable to ASCT containing regimen. Much longer survival than median PFS were seen in two patients(Patient 6 and 7) at the age of 39 and 20, there's previous reports indicated that long-term survival was seen in a small albeit clinically relevant proportion of younger SCNS patients, younger patients may have better prognosis despite the overall disappointing survival of SCNSL.[20]

In this study, patients with new disease possessed higher CR rate than relapse/refractory patients(70% vs 50% and 40%). We postulated this due to patients with relapse and refractory disease were more likely to be drug resist and more likely to develop treatment toxicity, this indicate that SCNSL patients require more individualized treatment regarding their disease condition and regimen prior to CNS disease. In addition, timely treatment was crucial, the only treatment related death in our study were found in an refractory SCNSL patient with atypical MRI manifestation who were initially diagnosed as anti-NMDA-receptor encephalitis, while treated by high dose corticosteroids, his neurological symptoms continuous deteriorate, by the time the patients was diagnosed SCNSL by biopsy, he was already in coma and had hypostatic pneumonia making treatment option extremely challenging. Eventually, he received reduced dose R-MIADD and became conscious after the first cycle, therefore we proceeded with the second cycle of R-MIADD. Unfortunately, even with carefully supportive treatment, the patient died of severe sepsis. This case suggested the significance of early recognize and early CNS targeting treatment, for patients with inferior ECOG-PS score, even they can response to CNS targeting treatment, adverse event of treatment may greatly influence outcome of the patient.

Benefit from the use of Rituximab in PCNSL is controversial.[25] In a meta-analysis published in 2019, two randomize control studies were included, and it was concluded that Rituximab could improve PFS, but without significant improvement in OS (HR 0.76; 95%CI 0.52–1.12, low certainty); Nevertheless, the

majority research on SCNSL treatments included Rituximab (some were as part of the peripheral lymphoma treatment). [11–13, 20, 22] T.C El - Galaly et al concluded that Rituximab may reduce the risk of death in patients with isolated SCNSL, they also emphasized that in this subgroup, Rituximab plays a role even comparable to ASCT.[8] Thus we also included Rituximab as part of SCNSL treatment.

In conclusion, treatment of SCNSL has always been challenging, this is current largest cohort report of SCNSL treatment in Chinese population, our single center experience indicated that R-MIADD were effective in SCNSL, the outcome of patients receiving R-MIADD were comparable to previous reports of ASCT contained regimens. This study naturally has some limitations for it's a retrospective study with relative small sample size. Larger cohort prospective studies were needed to define the most effective treatment strategies in SCNSL.

List Of Abbreviations

Secondary central nervous lymphoma(SCNSL); complete remission(CR); partial remission(PR); overall response rate (ORR); diffuse large B cell lymphoma(DLBCL); overall survival(OS); High dose Methotrexate(HD-MTX); cytarabine(Ara-C); ifosfamide(IFO); blood-brain barrier (BBB); primary central nervous system lymphoma(PCNSL); autologous stem cell transplantation (ASCT); R-CHOP(rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone regimen); cerebrospinal fluid (CSF); magnetic resonance imaging(MRI); Post CNS overall survival (post CNS OS); post CNS progression free survival (post CNS PFS); intrathecal(IT); germinal center B cell (GCB); activated B cell (ABC); progression disease(PD); whole brain radiotherapy(WBRT)

Declarations

Conflict of interest:

The authors declare that they have no competing interests.

Ethics approval and consent to participate

Ethical approval was provided by Beijing Tiantan Hospital Ethics Committee, Capital medical university (Ethical approval reference number: KYSB2016-170).

Consent to participate

Informed consent was written obtained when patients were admitted to Department of Hematology before initiation of chemotherapy.

Consent for publication

Not applicable.

Availability of data and materials

The datasets supporting the conclusions of this study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

LYB and WYC designed the study; JN provided the patient samples; SSJ revised neuroimaging; WYC analyzed the data and wrote the manuscript; SXF, CQ, ZH and QJ performed the experiments; BXY, XRX, CYD, LQ and WYL collected and analyzed the data; and all the authors have read the manuscript and approved its submission.

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Figures

Figure 1

Course of therapy, responses and clinical outcomes. CR, complete response; PR, partial response; PD, progressive disease; SD, stable disease; WBRT, whole brain radiotherapy.

Figure 2

Post CNS progression free survival of 19 SCNSL patients.

Figure 3

Post CNS Overall survival of 19 SCNSL patients.

Figure 4

Swim lane plot of treatment duration and response for all patients. CR, complete response; PR, partial response; PD, progressive disease; SD, stable disease.