Lenalidomide, rituximab, and methotrexate are effective in newly diagnosed primary central nervous system lymphoma

Primary central nervous system (CNS) lymphoma (PCNSL) represents an uncommon aggressive type of non-Hodgkin lymphoma exclusively affecting the brain, spinal cord, eyes, and cerebrospinal fluid, with no systemic non-CNS involvement. The overall prognosis is generally poor despite major advances in the last two decades. High-dose methotrexate (HD-MTX) is considered the mainstay of induction therapy. Autologous hematopoietic stem cell transplantation (ASCT) and whole-brain radiotherapy (WBRT) are similarly effective consolidation treatments, but the latter brings a high risk of significant irreversible neurotoxicity.[1,2] In the long-term follow-up analysis, patients treated with methotrexate, cytarabine, thiotepa, and rituximab (MATRix) induction treatment and ASCT consolidation had a 7-year overall survival (OS) rate of 70%.[3] However, elderly patients account for nearly 70% of all PCNSL and many patients are transplant-ineligible. In a real-world analysis in the modern era, only 23% of patients <60 years old and 2% of patients ≥60 years old received ASCT consolidation treatment.[4] The overall prognosis of those patients without ASCT consolidation is poor. So far, the optimal therapeutic options are limited for transplant-ineligible patients. Thus, an effective and well-tolerated treatment option for those patients ineligible for ASCT is dearly needed.

Lenalidomide is an orally administered small-molecule drug with direct anti-tumor and immunomodulatory effects. Available evidence indicates the effectiveness of lenalidomide maintenance in CNS lymphoma and its tolerability in older individuals.[5] In addition, preclinical findings demonstrated that lenalidomide and rituximab enhance antibody-dependent cell-mediated cytotoxicity to exert synergistic antitumor effects.[6] Lenalidomide, rituximab, and chemotherapy administered in combination in refractory/relapsed PCNSL showed promising anti-tumor effects.[7] Nevertheless, the combination of lenalidomide, rituximab, and methotrexate R2-MTX regimen as first-line therapy in transplant-ineligible PCNSL deserves further verification.

Based on these premises, a multicenter, single-arm, open-labeled, phase II clinical trial was conceived and conducted to evaluate the efficacy and safety of R2-MTX for individuals with newly diagnosed PCNSL. All patients were transplant-ineligible or unwilling to receive upfront ASCT. The study was registered with *clinicaltrials gov. Identifier: NCT04934579*. The trial was approved by the ethics review committee of the Second Affiliated Hospital, Zhejiang University. Signed informed consent was provided by each patient.

Induction treatment was performed with six cycles of lenalidomide (25 mg/day [d], orally, d1-10), rituximab (375 mg/m^2, intravenously [IV], d0), and methotrexate (3.5 g/m^2, IV, d1) every 3 weeks, followed by four cycles of maintenance treatment with lenalidomide (25 mg/day, orally, d1-14, d29-42) and rituximab (375 mg/m^2, IV, d1) (R2 regimen) every 8 weeks. Patients who did not achieve partial response (PR) after four cycles of induction treatment or who experienced disease progression (PD) at any time point were withdrawn from the study. Salvage WBRT was performed for individuals without complete remission (CR) before maintenance treatment. WBRT was performed at 30 Gy (2 Gy/dose, 5 doses/week for 3 weeks) plus local tumor field-size irradiation up to 45 Gy. The primary endpoint was the objective response rate (ORR) at the end of induction therapy. Secondary endpoints were best ORR recorded during induction therapy, progression-free survival (PFS), OS, and safety. As previously reported, the ORR of methotrexate monotherapy for newly diagnosed PCNSL cases varies between 40% and 60%. Meanwhile, the ORR of R2 regimen for refractory/relapse PCNSL was 35.6%.[8] The ORR of R+MTX ± chemotherapy varies between 50% and 89%. Therefore, the standard treatment ORR was assumed to be 0.50 (null hypothesis, P0), and the expected ORR of R2-MTX regimen was 0.85 (P1). Assuming a 2-sided α (type I error) of 0.05 and a power of 0.80, the study required at least 14 evaluable patients. Considering a 15% dropout rate, the minimal enrollment goal was 17 participants in this study. Between Jan 1, 2020 and May 16, 2022, this study screened 20 cases of newly diagnosed PCNSL, of whom 17 were finally included. The full study flow diagram is shown in the *Online Supplementary Figure S1*. Baseline clinicodemographic features are summarized in Table 1. The median patient age at presentation was 60 (range, 44-75) years. Seven cases (41.1%) were male and nine cases (52.9%) were of Eastern Cooperative Oncology Group score >2. Fifteen (88.2%) participants had activated B-cell-like DLBCL. Treatment response was determined by central neuroradiology review with contrast-enhanced brain magnetic resonance imaging every two cycles during induction therapy and every cycle during maintenance therapy, according to the International Primary CNS Lymphoma Collaborative Group (IPCG) criteria. At the end of induction therapy, 13 (76.5%) patients achieved CR, and two (11.8%) patients achieved PR, indicating an ORR of 88.2% (95% confidence interval [CI]: 63.6-98.5) (Figure 1A). The best ORR during induction therapy was 94.1% (95% CI: 71.3-99.9) (Figure 1B). The last

Table 1. Baseline characteristics.

Factors	Total N=17
Age in years, median (range)	60 (44-75)
Male, N (%)	7 (41.1)
ECOG, N (%) 1 2 3	 2 (11.8) 6 (35.3) 9 (52.9)
Multiple lesions, N (%)	7 (41.2)
Deep lesions,* N (%)	12 (70.6)
Pathological subtypes, N (%) Germinal center B-cell Activated B-cell-like	 2 (11.8) 15 (88.2)
C-myc, N (%) Positive Negative	 5 (29.4) 12 (70.6)
Ki67 ≥90%, N (%)	4 (23.5)
IELSG score, N (%) Low risk Intermediate risk High risk	 3 (17.6) 9 (52.9) 5 (29.4)
MSKCC score, N (%) Low risk Intermediate risk High risk	 3 (17.6) 7 (41.2) 7 (41.2)
Previous surgery, N (%) Craniotomy resection Stereotactic biopsy	 5 (29.4) 12 (70.6)

*Deep lesions were located in the thalamus, corpus callosum, brainstem, cerebellum, and ventricles. ECOG: Eastern Cooperative Oncology Group; IELSG: International Extranodal Lymphoma Study Group; MSKCC: Memorial Sloan-Kettering Cancer Center.

follow-up date was September 15, 2023. Following a median follow-up of 23 months (range, 1-41), the median PFS was 29.0 months (Figure 1C), and the median OS was not reached (Figure 1D). The estimated 2-year PFS rate was 58.8% and the estimated 3-year OS rate was 76.0%. In subgroup analysis, participants with low-to-intermediate IELSG risk had better PFS (P=0.0035) and OS (P=0.01) than the high-risk group[9] (*Online Supplementary Figure S2A, B*). PFS and OS were similar among different risk subgroups based on the MSKCC scoring system[10] (P=0.99 and P=0.093, respectively) (*Online Supplementary Figure S2C, D*).

All participants experienced treatment-related adverse events (TRAE). The commonest all-grade TRAE included leukopenia (94.1%), neutropenia (82.4%), increased alanine aminotransferase (ALT) (58.9%), increased aspartate aminotransferase (AST) (52.9%), anemia (47.1%), and constipation (41.2%). Grade ≥3 TRAE included neutropenia (47.1%), leukopenia (23.5%), thrombocytopenia (11.8%), increased ALT (5.9%), and increased AST (5.9%) (Table 2). Severe AE (liver dysfunction) was reported in one patient. No treatment discontinuation occurred due to AE. No unexpected toxicities were observed.

This multicenter, phase II trial first reported the effectiveness of the R2-MTX regimen with a relatively high ORR of 88.2%. The IELSG32 trial applied MATRix for first-line treatment with an ORR of 87%, compared with relatively lower ORR for methotrexate, cytarabine with rituximab group (74%) and methotrexate with cytarabine group (51%).[11] Furthermore, other regimens combining drugs with MTX + rituximab had lower ORR, e.g., temozolomide (MT-R regimen) in the Alliance 50202 study (77%),[12] and procarbazine with/without lomustine in the PRIMAIN study (49.5%).[13] Regarding long-term survival, consolidation with either WBRT or ASCT, achieved 2-year PFS and OS rates of 61% and 69%, respectively in the IELSG32 study.[11] In the PRECIS study,[1] consolidation therapy with either WBRT or ASCT, induced 2-year PFS of 63% and 87%, respectively. In the Alliance 50202 study,[12] consolidation therapy with etoposide plus cytarabine conferred 2-year PFS and OS of 57% and 70%, respectively. No maintenance therapy was applied in the above clinical trials. In this study, R2 maintenance therapy without intended consolidation, produced an estimated 2-year PFS rate of 58.8% and an estimated 3-year OS rate of 76.0%. The advantage of R2-MTX on the anti-tumor effect might be associated with the pharmacological features of lenalidomide, especially its capability to cross the blood-brain barrier. Furthermore, the molecular abnormalities in PCNSL include NF-κB pathway activation, which makes it possible to treat PCNSL with lenalidomide.[14] More specifically, lenalidomide increases the activation and proliferation of natural killer (NK) and T cells, and enhances the generation of immune synapses, causing apoptosis in lymphoma cells, while rituximab induces NK-cell-mediated antibody-dependent cellular cytotoxicity in lymphoma cells, showing a synergistic activation of anti-tumor immunity by combining lenalidomide and rituximab.[6] The immunomodulatory effects of lenalidomide and rituximab make this combination a good prospect for the maintenance of the anti-lymphoma effect.[15] Nevertheless, the survival benefit of R2-MTX followed by R2 maintenance needs to be further verified. In subgroup analysis, we found that participants with low-to-intermediate IELSG risk had better PFS and OS than the high-risk group. It may suggest that low-to-intermediate-risk patients benefit most from such less intensified strategies.

Here, the AE of R2-MTX appeared manageable with no additional safety concerns. Although all patients had TRAE, relatively fewer grade ≥3 TRAE were observed. The grade ≥3 TRAE of R2-MTX in the present study were mainly hematological toxicity (neutropenia: 47.1% and leukopenia: 23.5%). In the IELSG 32 trial,[11] the widely used MATRix regimen resulted in 67% grade ≥3 neutropenia, while HD-MTX with cytarabine induced 52%

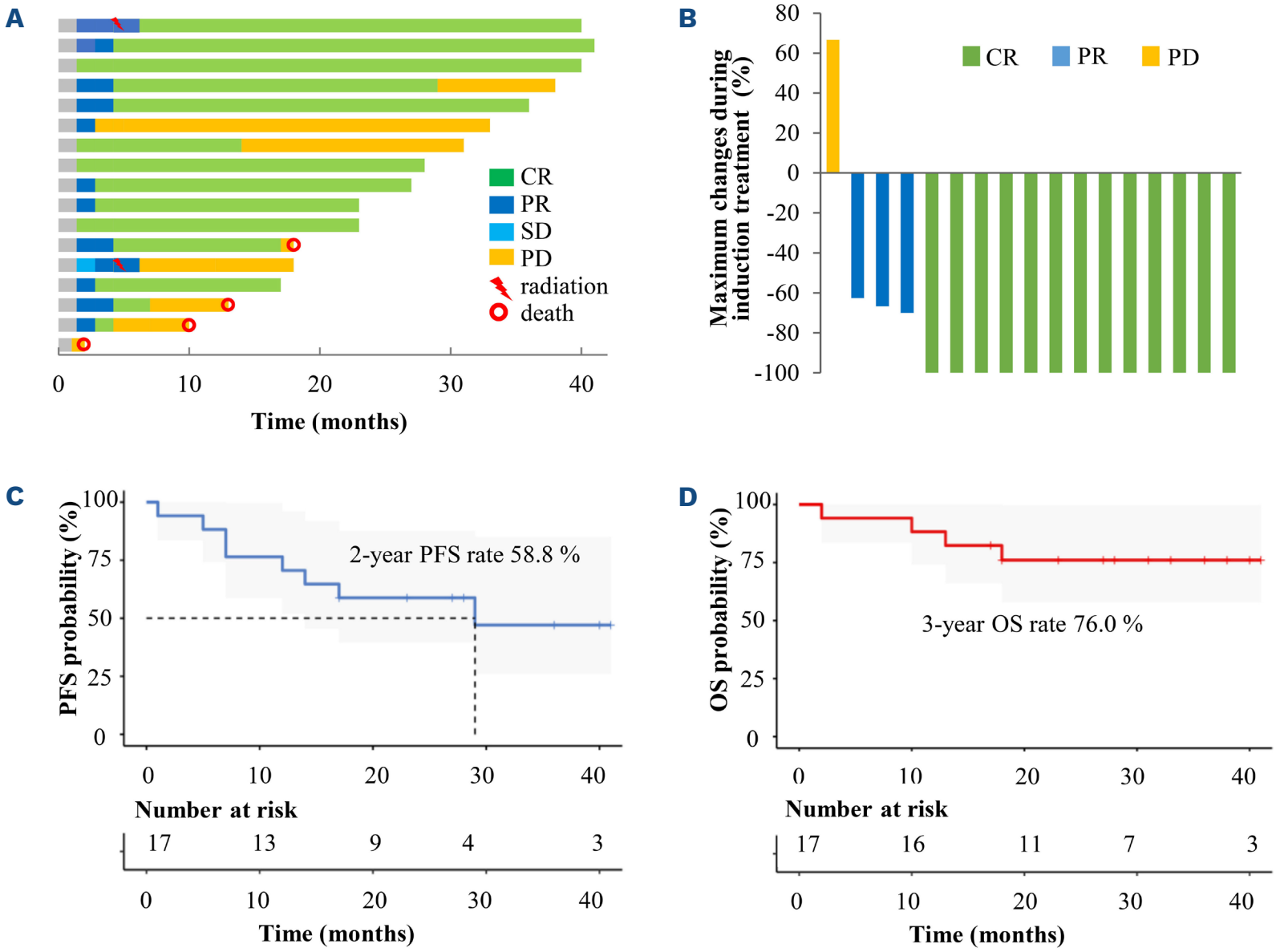

Figure 1. Outcome analysis. (A) Swimmer plot and (B) waterfall plot of best response. (C) Progression-free survival (PFS) and (D) overall survival (OS) in all patients. CR: complete remission; PR: partial response; SD: stable disease; PD: progressive disease.

Table 2. Adverse events.

Adverse events, N (%)	All grades	Grade ≥3
Leukopenia	16 (94.1)	4 (23.5)
Neutropenia	14 (82.4)	8 (47.1)
Anemia	8 (47.1)	0
Thrombocytopenia	4 (23.5)	2 (11.8)
Increased alanine aminotransferase	10 (58.8)	1 (5.9)
Increased aspartate aminotransferase elevation	9 (52.9)	1 (5.9)
Increased bilirubin	0	0
Renal insufficiency	1 (5.9)	0
Skin rash	1 (5.9)	0
Deep vein thrombosis	3 (17.6)	0
Sinus bradycardia	3 (17.6)	0
Numbness of extremities	2 (11.8)	0
Constipation	7 (41.2)	0
Hypotension	1 (5.9)	0
Non-infectious fever	3 (17.6)	0
Urinary tract infection	3 (17.6)	0

grade ≥3 leukopenia. In the PRIMAIN study,[13] R-MP with/without lomustine regimens resulted in 56.7% grade ≥3 leukopenia. Numerically, the R2-MTX regimen showed possible better tolerability.

This study had several limitations. Firstly, among the 17 patients enrolled, 12 patients were transplant-ineligible because of HCT-CI score ≥3 (N=6) or age ≥65 years old (N=6), and the remaining five transplant-eligible patients were unwilling to receive upfront ASCT. The main reasons for refusing ASCT in China included the low acceptability of ASCT, the inaccessibility of thiotepa (a conditioning drug for ASCT) at the initial stage of this study, and unaffordable high costs of ASCT. Secondly, the sample size was small, and the follow-up was short, leading to immature PFS and OS data. Further studies are warranted to address these limitations.

In conclusion, the R2-MTX regimen appears to be effective and well-tolerated in newly diagnosed transplant-ineligible PCNSL, especially for those patients with low-to-intermediate IELSG risk and lack of access to ASCT. Based on its favorable tolerability and good anti-tumor effect, R2-MTX might provide a promising option for newly diagnosed PCNSL.

Authors

Xianggui Yuan,[1*] Yaping Xie,[2*] Nengwen Xu,[3*] Hui Liu,[1] Panpan Chen,[1] Aiqi Zhao,[1] Yun Liang[1] and Wenbin Qian[1,4]

[1]Department of Hematology, the Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou; [2]Department of Hematology, the Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, Hangzhou; [3]Department of Hematology, the Lishui Hospital, Zhejiang University School of Medicine, Lishui and [4]National Clinical Research Center for Hematologic Diseases, the First Affiliated Hospital of Soochow University, Suzhou, China

**XY, YX and NX contributed equally as first authors.*

Correspondence:
W.-B. QIAN - qianwb@zju.edu.cn
Y. LIANG - liangyun@zju.edu.cn

https://doi.org/10.3324/haematol.2023.284834

Received: December 8, 2023.
Accepted: February 2, 2024.

Early view: February 15, 2024.

Disclosures

No conflicts of interests to disclose.

Contributions

WBQ and YL conceived and designed the protocol. XGY, YPX, and NWX collected and analyzed the data. PPC performed data analysis. XGY, HL and AQZ drafted the manuscript. All authors reviewed the manuscript.

Funding

The present study was funded by the National Natural Science Foundation of China (No. 82170219), and Zhejiang province commonweal projects (No. BY24H080013).

Data-sharing statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

References

1. Houillier C, Taillandier L, Dureau S, et al. Radiotherapy or autologous stem-cell transplantation for primary CNS lymphoma in patients 60 years of age and younger: results of the Intergroup ANOCEF-GOELAMS randomized phase II PRECIS study. J Clin Oncol. 2019;37(10):823-833.
2. Ferreri AJM, Cwynarski K, Pulczynski E, et al. Whole-brain radiotherapy or autologous stem-cell transplantation as consolidation strategies after high-dose methotrexate-based chemoimmunotherapy in patients with primary CNS lymphoma: results of the second randomisation of the International Extranodal Lymphoma Study Group-32 phase 2 trial. Lancet Haematol. 2017;4(11):e510-e523.
3. Ferreri AJM, Cwynarski K, Pulczynski E, et al. Long-term efficacy, safety and neurotolerability of MATRix regimen followed by autologous transplant in primary CNS lymphoma: 7-year results of the IELSG32 randomized trial. Leukemia. 2022;36(7):1870-1878.
4. Houillier C, Soussain C, Ghesquières H, et al. Management and outcome of primary CNS lymphoma in the modern era. Neurology. 2020;94(10):e1027-e1039.
5. Vu K, Mannis G, Hwang J, Geng H, Rubenstein JL. Low-dose lenalidomide maintenance after induction therapy in older patients with primary central nervous system lymphoma. Br J Haematol. 2019;186(1):180-183.
6. Wu L, Adams M, Carter T, et al. lenalidomide enhances natural killer cell and monocyte-mediated antibody-dependent cellular cytotoxicity of rituximab-treated CD20+ tumor cells. Clin Cancer Res. 2008;14(14):4650-4657.
7. Yang C, Cui Y, Ren X, et al. Orelabrutinib combined with lenalidomide and immunochemotherapy for relapsed/refractory primary central nervous system lymphoma: a retrospective analysis of case series. Front Oncol. 2022;12:901797.
8. Ghesquieres H, Chevrier M, Laadhari M, et al. Lenalidomide in combination with intravenous rituximab (REVRI) in relapsed/refractory primary CNS lymphoma or primary intraocular lymphoma: a multicenter prospective 'proof of concept' phase II study of the French Oculo-Cerebral lymphoma (LOC) Network and the Lymphoma Study Association (LYSA)†. Ann Oncol. 2019;30(4):621-628.
9. Ferreri AJM, Blay J-Y, Reni M, et al. Prognostic scoring system for primary CNS lymphomas: the International Extranodal Lymphoma Study Group experience. J Clin Oncol. 2003;21(2):266-272.
10. Abrey LE, Ben-Porat L, Panageas KS, et al. Primary central nervous system lymphoma: the Memorial Sloan-Kettering Cancer Center prognostic model. J Clin Oncol. 2006;24(36):5711-5715.
11. Ferreri AJ, Cwynarski K, Pulczynski E, et al. Chemoimmunotherapy with methotrexate, cytarabine, thiotepa, and rituximab (MATRix regimen) in patients with primary CNS lymphoma: results of the first randomisation of the International Extranodal Lymphoma Study Group-32 (IELSG32) phase 2 trial. Lancet Haematol. 2016;3(5):e217-227.
12. Rubenstein JL, Hsi ED, Johnson JL, et al. Intensive chemotherapy and immunotherapy in patients with newly diagnosed primary CNS lymphoma: CALGB 50202 (Alliance 50202). J Clin Oncol. 2013;31(25):3061-3068.
13. Fritsch K, Kasenda B, Schorb E, et al. High-dose methotrexate-based immuno-chemotherapy for elderly

primary CNS lymphoma patients (PRIMAIN study). Leukemia. 2017;31(4):846-852.
14. Hernández-Verdin I, Kirasic E, Wienand K, et al. Molecular and clinical diversity in primary central nervous system lymphoma. Ann Oncol. 2023;34(2):186-199.
15. Yilmaz U, Salihoglu A, Soysal T. An overview of lenalidomide in combination with rituximab for the treatment of adult patients with follicular lymphoma: the evidence to date. Drug Des Devel Ther. 2021;15:3809-3820.