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RESEARCH

Efficacy and safety of the R2-MTX regimen in primary central nervous system lymphoma (PCNSL): a single-center retrospective analysis

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Abstract

Purpose Primary central nervous system lymphoma (PCNSL) has a poor prognosis, mainly because of the significant challenges with the efficacy and tolerability of induction chemotherapy. This retrospective study aimed to evaluate the efficacy and safety of the R2-MTX regimen in PCNSL patients.

Methods We conducted a retrospective analysis of 39 PCNSL patients treated with the R2-MTX regimen, focusing on treatment outcomes and adverse events (AEs).

Results The overall response rate (ORR) was 72.2%, with a complete response (CR) rate of 69.4% and a partial response (PR) rate of 2.8%. With a median follow-up of 37.2 months (interquartile range [IQR] 24.2–47.5), the estimated 2-year progression-free survival (PFS) and overall survival (OS) rates were 54.9% (95% CI, 37.2–69.5%) and 78.5% (95% CI, 59.8–89.2%), respectively. The most common grade 3 or 4 AEs included neutropenia (33.3%), leukopenia (13.9%), anemia (2.8%), and thrombocytopenia (2.8%). Consolidation or maintenance therapy was associated with prolonged survival in PCNSL patients (2-year OS rates 100% vs. 42.9%, $P=0.067$). Survival analysis revealed that clinicopathological factors, such as double-expressor lymphoma (DEL), ECOG PS≥2, and high-risk classification based on the Memorial Sloan Kettering Cancer Center model (MSKCC), predicted poor survival.

Conclusions Our results underscore the therapeutic potential of the R2-MTX regimen in managing newly diagnosed PCNSL patients. Further prospective studies with larger patient cohorts are imperative to solidify these preliminary findings.

Keywords Primary central nervous system lymphoma (PCNSL) · R2-MTX regimen · Consolidation therapy · Maintenance therapy · Clinicopathological factors

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Introduction

Primary central nervous system lymphoma (PCNSL) is a rare form of extranodal non-Hodgkin lymphoma that occurs within the central nervous system, representing 4% of intracranial tumors and 4–6% of extranodal lymphomas (Campo et al. 2011; Darlix et al. 2017; Ferreri et al. 2023). Most PCNSLs are classified as diffuse large B-cell lymphomas (DLBCL), with over 95% falling into this category, and they are typically identified as the non-germinal center B-cell (non-GCB) subtype (Camilleri-Broët et al. 1998, 2006; Grommes et al. 2017). Compared to systemic DLBCL, PCNSL is more aggressive and associated with a poorer prognosis. The median overall survival (OS) for patients with PCNSL is 1.3 years, with an estimated 3-year OS rate of 37.7% and a 5-year OS rate of 30.5% (Fallah et al. 2016). The current most effective treatment strategy for newly diagnosed PCNSL involves intensive induction using

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a multi-agent chemoimmunotherapy regimen that includes high-dose methotrexate (HD-MTX), followed by consolidation therapy with either autologous stem cell transplantation (ASCT) or whole-brain radiotherapy (WBRT) (Ferreri et al. 2016a, 2017). However, there are few phase 3 randomized clinical trials focusing on PCNSL treatment, and as a result, there is no established standard induction strategy. Multi-agent induction chemotherapy regimens typically include drugs such as thiotepa, temozolomide, carmustine, and cytarabine (Bromberg et al. 2019; Ferreri et al. 2009, 2016b; Rubenstein et al. 2013). Although standard induction regimens, such as the MATRix regimen, have been established, elderly or less fit patients have poor tolerance to highly toxic regimens. Consequently, there is a pressing need to explore milder and more effective induction strategies (Ferreri et al. 2016b).

Lenalidomide, an oral immunomodulatory drug, has shown promise due to its diverse immunomodulatory mechanisms, including inhibiting angiogenesis and directly inducing tumor cytotoxicity. Preclinical studies suggest that lenalidomide is more effective in inhibiting non-GCB DLBCL cells, with this proliferation inhibition associated with the down-regulation of interferon regulatory factor 4 (IRF4) (Riches and Gribben 2016). Additionally, lenalidomide influences the NF-κB pathway and works in conjunction with rituximab, providing therapeutic benefits against DLBCL (Garciaz et al. 2016). In cases of recurrent PCNSL, lenalidomide has demonstrated effectiveness, often leading to prolonged survival as a monotherapy (Ghesquieres et al. 2019; Houillier et al. 2015; Salati et al. 2017; Warren et al. 2011). Some studies have explored the R2-MTX regimen, which combines lenalidomide, rituximab, and HD-MTX as a first-line treatment option for PCNSL, showing preliminary indications of good remission rates and acceptable toxicity. However, these studies involved relatively small patient cohorts and had a short follow-up period (Yuan et al. 2024; Zhang et al. 2022).

Given this context, we conducted a retrospective study of newly diagnosed PCNSL to evaluate the remission rate and tolerability of the R2-MTX regimen as well as the impact of clinical factors on patient survival.

Methods

Study population

This study retrospectively included 39 newly diagnosed PCNSL-DLBCL patients from September 2018 to September 2023 at West China Hospital of Sichuan University. None of the patients were immunosuppressed due to HIV infection, organ transplantation, or other causes. The diagnosis was confirmed by pathological examination following craniotomy biopsy or stereotactic puncture biopsy, and systemic imaging indicated that the patients had no evidence of involvement outside the central nervous system.

The study was approved by the Biomedical Ethics Committee of West China Hospital of Sichuan University (2023/883) and complied with ethical requirements. All research procedures adhered to the Declaration of Helsinki.

Treatment regimens

In the induction phase, patients received a total of six cycles of the R2-MTX regimen, consisting of rituximab (375 mg/m^2 on day 0), MTX (3.5 g/m^2 on day1), and lenalidomide (25 mg once daily on days 3–17), for a duration of 3 weeks per cycle until the occurrence of progression disease (PD), intolerable toxicity, or refusal to continue. Some patients continued to undergo ASCT or WBRT (23.40 Gy in 1.8 Gy fractions × 13) as consolidation therapy or lenalidomide maintenance therapy after remission with induction chemotherapy.

Therapeutic evaluation

All patients were assessed for efficacy primarily through imaging (gadolinium-enhanced brain MRI), ocular examination, and cerebrospinal fluid cytology, with reference to IPCG response criteria (Abrey et al. 2005). Progression-free survival (PFS) was defined as the time from the start of treatment until disease progression or death from any cause. Overall survival was defined as the time from the start of treatment to death from any cause. The objective response rate (ORR) was defined as the sum of partial response (PR) and CR. The primary endpoint of this study was ORR, and the secondary endpoints included CR rate, PFS, and OS. The National Cancer Institute's Common Terminology Criteria for Adverse Events (version 5.0) were used to define adverse events (AEs).

Statistical analysis

Patient demographic and clinical data were analyzed using descriptive statistical analysis. Continuous variables were expressed as medians (ranges). The Kaplan-Meier curves were employed to estimate OS and PFS, and the log-rank test was used to compare differences in survival. A two-sided p-value of <0.05 was considered statistically significant. All statistical analyses were conducted using SPSS version 25.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 10.1.2 (GraphPad Software, Inc.).

Results

Patient characteristics

From September 2018 to September 2023, a total number of 39 patients with PCNSL were included, all of whom had received at least 1 cycle of the R2-MTX regimen. Unfortunately, two patients discontinued treatment after the first cycle (C1) due to methotrexate-induced nephrotoxicity and one patient died after the first cycle due to rapid disease progression. Ultimately, 36 patients were assessable for response (Fig. 1). The characteristics of these 36 patients are detailed in Table 1. The median age of the cohort was 60 years (range 18–74 years), with 16 patients (44.4%) aged 65 years or older. Approximately half of the patients ($n=19$, 52.8%) had a good Performance Status (PS; 0 or 1). A total of 34 patients (94.4%) had isolated parenchymal brain lesions, while the remaining 2 patients (5.6%) exhibited both brain and ocular involvement. Most patients (77.8%) were classified as non-GCB subtypes, while 22.2% were classified as GCB subtypes. Fourteen patients (38.9%) were identified as having double-expression lymphoma (DEL). According to the Memorial Sloan Kettering Cancer Center (MSKCC) model, only 4 patients (11.1%) were classified as low-risk, while 16 patients were categorized as intermediate-risk and 16 as high-risk (Table 1).

Treatment response

The median number of induction treatment cycles in the analyzed cohort was 6 (range 2–6; interquartile range [IQR] 4–6). After C2, C4, and C6 induction, 15 (41.7%), 21 (58.3%), and 25 (69.4%) patients achieved a CR/uCR, respectively (Table 2). Twenty-six patients completed the 6-cycle induction phase, resulting in an ORR of 72.2% (26/36) at the end of induction treatment.

Patients who had CR, uCR, or PR after induction therapy were assigned to receive different consolidation/maintenance regimens after adequate assessment of age, physical function, and performance scores by the physician and in conjunction with the patient's preference (Supplemental Table 2; Supplemental Fig. 1). Among the 26 patients achived remmison, 14 received consolidation therapy, which included WBRT ($n=8$) or ASCT ($n=6$). Five patients received maintenance therapy with lenalidomide. Nevertheless, seven patients did not proceed to consolidation/maintenance therapy due to patient refusal ($n=6$), and disease progression ($n=1$) (Fig. 1). Four patients completed the 2-year maintenance phase, but one relapsed after 9 months. At the last follow-up, three patients were still in CR, and one patient relapsed 5 months after the end of maintenance. Details of the patients' treatment assessments are shown in Table 2; Fig. 2.

Outcome

During the follow-up period, 17 patients experienced PD, and 9 patients died. Among them, 12 patients received salvage treatment, including targeted drugs ($n=1$), chemotherapy combined with targeted drugs ($n=8$), chemotherapy combined with radiotherapy ($n=1$), chemotherapy combined with targeted drugs and radiotherapy ($n=2$). Overall,

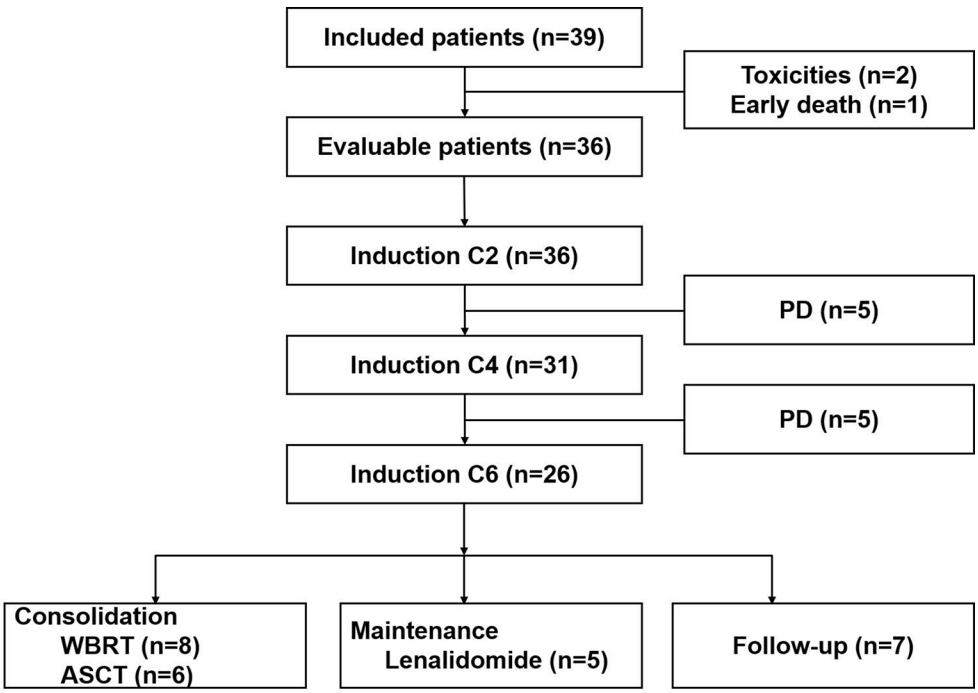

Fig. 1 Patient inclusion and treatment overview. Abbreviations: ASCT, autologous stem-cell transplantation; PD, progressive disease; WBRT, whole-brain radiotherapy

Table 1 Baseline characteristics

	N (%)
Age, years	
Median(range)	60(18–74)
%< 60	17(47.2)
≥60	19(52.8)
Sex	
Male	14(38.9)
Female	22(61.1)
ECOG performance status	
0–1	19(52.8)
≥2	17(47.2)
Increased serum lactate dehydrogenase concentration	2(5.6)
Increased cerebrospinal fluid protein	22(61.1)
Increased β2-microglobulin	21(58.3)
Deep lesions	26(72.2)
Multiple lesions	22(61.1)
Localization at inclusion	
Brain alone	34(94.4)
Brain + eye	2(5.6)
GCB/non-GCB profile	
GCB	28(77.8)
non-GCB	8(22.2)
DEL	
Yes	14(38.9)
No	18(50.0)
Unknown	4(11.1)
IELSG risk score	
Low	7(19.4)
Intermediate	13(36.1)
High	7(19.4)
Unknown	9(25.0)
MSKCC risk score	
Low	4(11.1)
Intermediate	16(44.4)
High	16(44.4)

Abbreviations: DEL, double-expression lymphoma; ECOG, Eastern Cooperative Oncology Group; GCB, germinal center B-cell; IELSG, International Extranodal Lymphoma Study Group; MSKCC, Memorial Sloan Kettering Cancer Center

Table 2 Responses to induction treatment

Response	Patients, *n*	CR + uCR, *n*(%)	PR, *n*(%)	SD, *n*(%)	PD, *n*(%)
After C2	36	15(41.7)	16(44.4)	1(2.8)	5(13.9)
After C4	31	21(58.3)	5(13.9)	0(0)	5(13.9)
After C6	26	25(69.4)	1(2.8)	0(0)	0(0)

Abbreviations: CR, complete response; uCR, unconfirmed CR; PR, partial response; SD, stable disease; PD, progressive disease

the ORR (25%) for salvage therapy is relatively low, with a median PFS of 5.4 months (Supplemental Table 1). With a median follow-up of 37.2 months (IQR, 24.2–47.5), 17 patients experienced PD, and 9 patients died during the follow-up period. Median PFS and OS were not reached. The estimated 2-year PFS and OS rates in the evaluable population were 54.9% (95% CI, 37.2–69.5%) and 78.5% (95% CI, 59.8–89.2%), respectively (Fig. 3A, B).

The 2-year PFS rate for patients receiving consolidation or maintenance therapy was 84.2% (95% CI, 58.7-94.6%), whereas the 2-year PFS rate for patients without such therapy was 47.6% (95% CI, 7.5-80.9%); however, this difference was not statistically significant (HR, 0.34; 95% CI, 0.054–2.14; $P=0.13$) (Fig. 3C). The 2-year OS rates were 100% for patients who underwent consolidation or maintenance therapy and 42.9% (95% CI, 5.8-77.7%) for those who did not. There was a statistically significant difference in OS between the two groups (HR, 0.13; 95% CI, 0.012–1.39; $P=0.067$) (Fig. 3D). There was no statistically significant difference in survival between the ASCT/WBRT consolidation group and lenalidomide maintenancegroup (Supplemental Fig. 2).

Clinicopathological prognostic variables

The good PS (0 or 1) group had a 2-year PFS rate of 73.7%, while the poor PS (≥2) group had a rate of 34.3% (HR, 0.29; 95% CI, 0.11–0.75; $P=0.011$) (Fig. 4A). Similarly, the good PS (0 or 1) group achieved superior OS (2-year OS rate, 89.5% vs. 65.4%; $P=0.027$) (Fig. 4B). The cutoff values for the DEL were MYC≥40% and BCL2≥50%. Patients with DEL had a significantly shorter PFS than those without DEL (2-year PFS rate, 43.8% vs. 78.6%; $P=0.040$) (Fig. 4C). However, there was no significant difference in OS between these two groups ($P=0.062$) (Fig. 4D). Since only 4 patients had a low MSKCC risk, we combined the low-risk and intermediate-risk groups into a low-intermediate-risk group. Compared to the low-intermediate-risk group, survival was significantly worse in the high-risk group (HR, 0.21; 95% CI, 0.057–0.79; $P=0.032$), with a 2-year OS rate of 90.0% and 64.8%, respectively (Fig. 4F). Nevertheless, we did not find a statistically significant difference in PFS between the two groups (2-year PFS rate, 65.0% vs. 42.9%; $P=0.18$) (Fig. 4E).

In the subgroup analyses, factors such as gender, age, cell origin, elevated β2-MG, elevated cerebrospinal fluid protein levels, lesion location, number of lesions, and IELSG risk scores did not show significant differences in PFS and OS.

Safety

The R2-MTX regimen was generally well tolerated, with no treatment-related deaths or unexpected toxicities. The most common non-hematological AEs included fatigue (35.9%), liver function anomalies (28.2%), paresthesia (20.5%), and rashes (17.9%), with most events classified as grades 1–2 (Table 3). Hematological AEs, such as neutropenia (30.8%), leukopenia (12.9%), anemia (2.6%), and thrombocytopenia

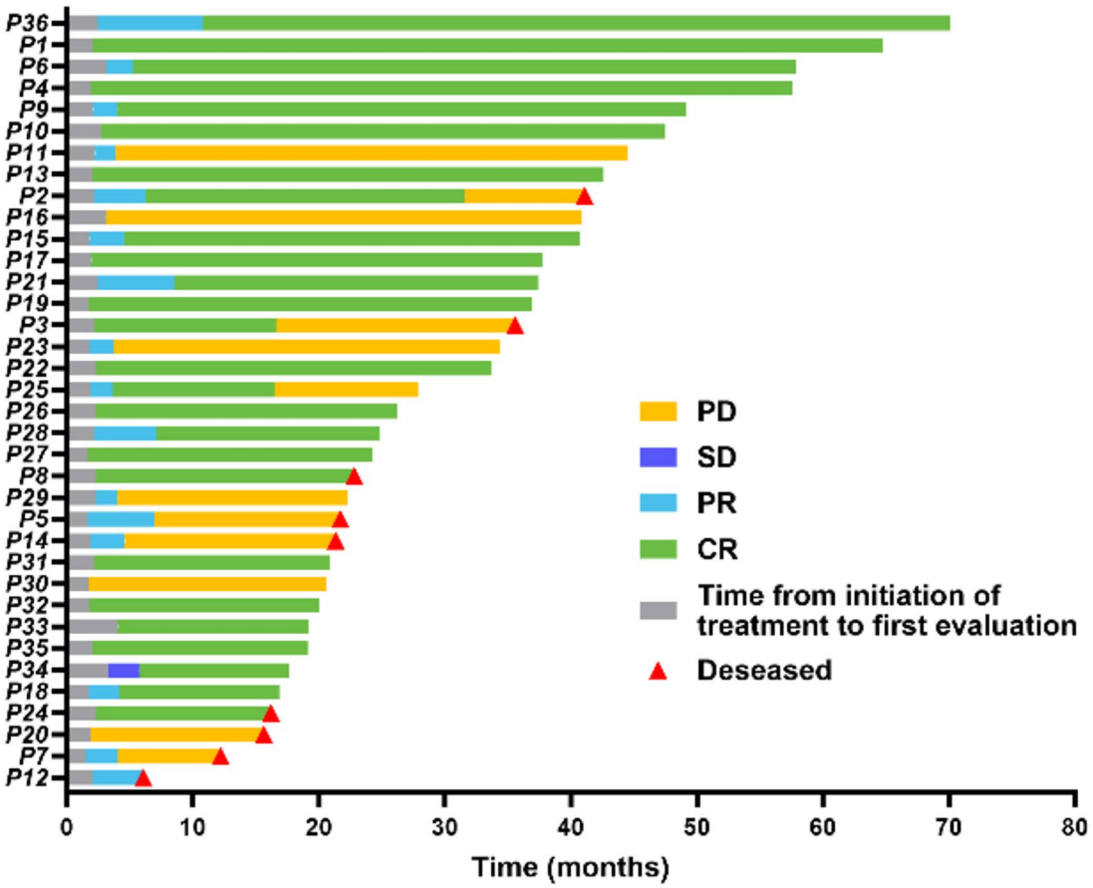

Fig. 2 Swimmer plot. Each bar represents a single patient

(2.6%), were the most frequently observed grade 3 or 4 AEs. Two patients discontinued induction therapy due to grade 3 nephrotoxicity. There were no treatment-related deaths. Only 1 patient died early on due to disease progression. The dose of HD-MTX was reduced for two patients, and treatment was delayed in one patient, primarily due to hematological toxicity (Table 3).

Discussion

The management of PCNSL remains a clinical challenge, highlighting the need for effective treatment regimens that deliver durable responses while minimizing toxicity. To our knowledge, this is the first real-world study to report on the favorable efficacy and safety of the R2-MTX regimen in patients with newly diagnosed PCNSL. Our findings indicate that R2-MTX induction chemotherapy achieves a high response rate, with a CR rate of 69.4%, demonstrating its feasibility and effectiveness in this patient population. However, given the relatively limited sample size and the absence of comparisons with other combination regimens, further verification is needed to establish the superiority of this regimen.

Consolidating ASCT after HD-MTX-containing induction therapy is currently the preferred approach for fit patients, with WBRT as an alternative option (Ferreri et al. 2017; Kasenda et al. 2016; Thiel et al. 2010). Two randomized controlled studies, the IELSG32 study, and the ANOCEF-GOELAMS study, have demonstrated that effective disease control can be achieved with either WBRT or ASCT consolidation. However, long-term neurological adverse effects were more pronounced in the WBRT group (Ferreri et al. 2016a; Houillier et al. 2019). Research has indicated some benefits from maintenance therapy using low-dose lenalidomide and Bruton tyrosine kinase inhibitors, though evidence from randomized controlled studies is still lacking (Chen et al. 2020; Zhang et al. 2022). This study also highlighted the survival benefits of consolidation or maintenance therapy following induction therapy, which is consistent with previous research. Due to the limited sample size, statistical comparisons between ASCT/WBRT consolidation and lenalidomide maintenance were not feasible. However, preliminary observations suggest a trend toward prolonged PFS with consolidation therapy.

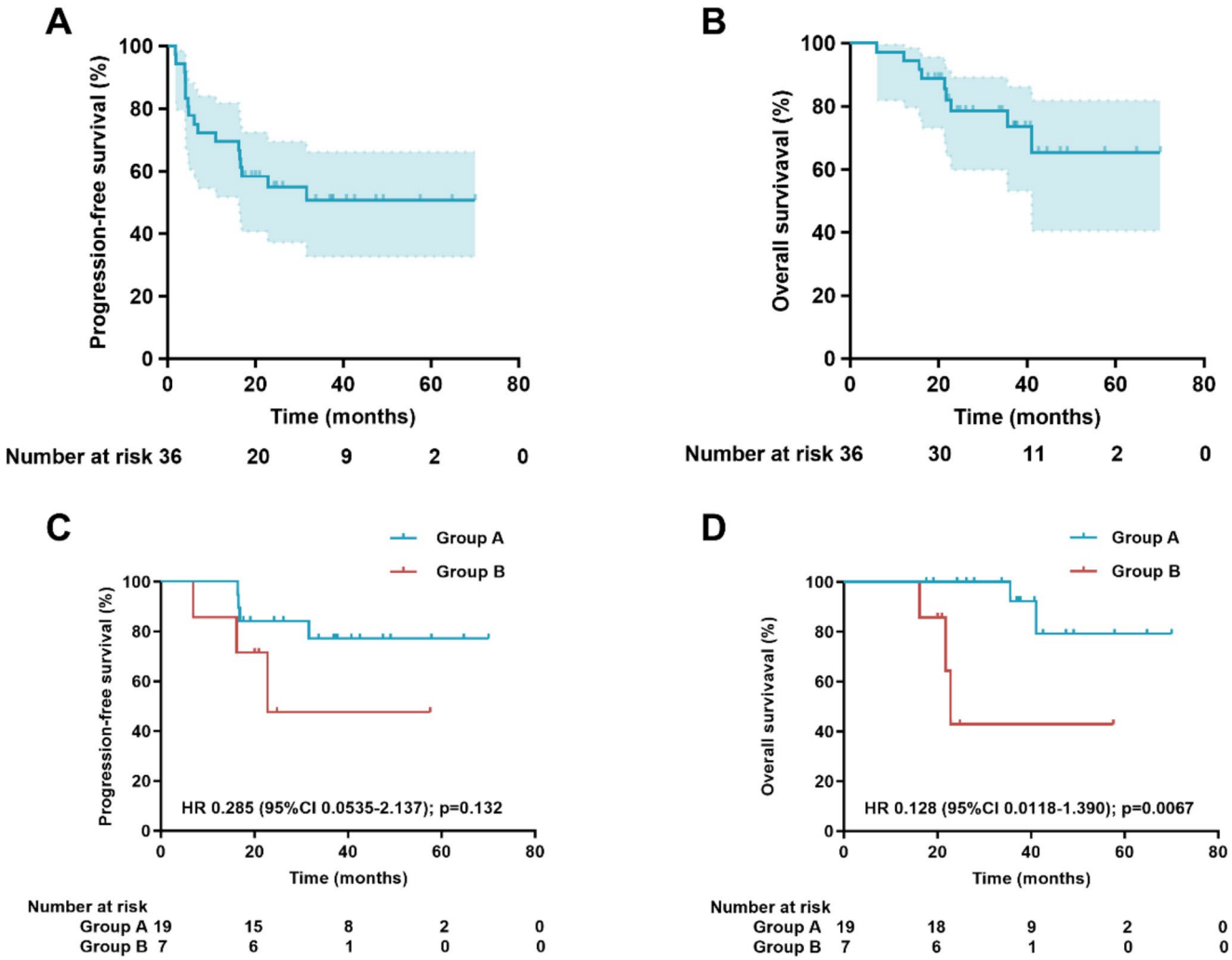

Fig. 3 Survival outcomes. (**A**) PFS and (**B**) OS of the 36 patients treated with the R2-MTX regimen. (**C**) PFS and (**D**) OS of the patients in remission after induction chemotherapy, categorized according to subsequent therapy. Group A (R2-MTX regimen + ASCT/WBRT/lenalidomide maintenance therapy); Group B (R2-MTX regimen alone)

On the other hand, we explored the factors associated with the prognosis of PCNSL patients. The two widely used prognostic scoring systems for PCNSL, the IELSG and MSKCC prognostic models, have been validated in several studies (Abrey et al. 2006; Ferreri et al. 2003). The MSKCC prognostic model, proposed by Abrey et al., utilizes the Karnofsky Performance Status (KPS) score and age at diagnosis to classify patients into three risk groups (Abrey et al. 2006). Our study demonstrated that the MSKCC prognostic model is predictive of OS in PCNSL patients receiving the R2-MTX regimen. However, lumbar punctures were not performed in some patients due to contraindications, refusals, or other reasons. This may explain why we did not observe prognostic value in the IELSG risk model, potentially due to missing or critical cerebrospinal fluid protein levels. With the availability of new targeted immune drugs, there is a need to examine genetic markers to create a more precise and reliable prognostic model.

Age and PS are important prognostic factors included in several existing prognostic models (Abrey et al. 2006; Ahn et al. 2017; Ferreri et al. 2003). Additionally, age and PS are major considerations when deciding on the optimal treatment regimen, significantly influencing the treatment intensity. Our study demonstrated shorter PFS and OS in PCNSL patients with ECOG PS ≥ 2. Notably, we did not find a significant effect of age (> 60 years) on survival; this discrepancy from previous studies may be attributed to sample size.

MYC proteins play a crucial role in energy metabolism, protein synthesis, and cell proliferation, which can promote lymphoma progression and lead to drug resistance through interaction with the BCL-2 protein (Chang et al. 2008; Letai 2008; Nguyen et al. 2017; Riedell and Smith 2018; Schmitt and Lowe 2001; van Riggelen et al. 2010). DEL, defined as

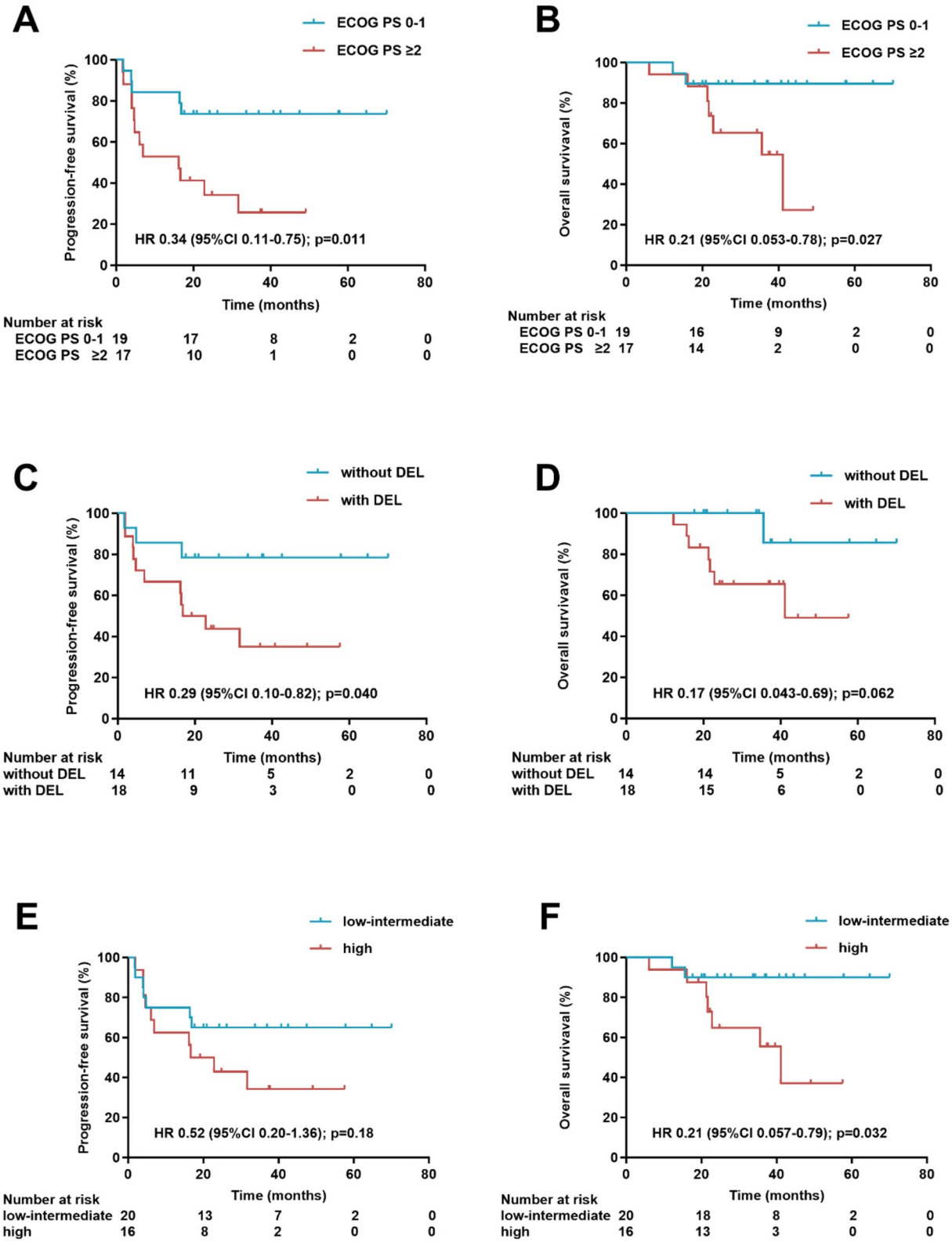

Fig. 4 Clinical prognostic variables and their relationship to PFS and OS. (**A**) Patients with an ECOG PS of 2 to 3 had shorter PFS ($P=0.011$). (**B**) Patients with an ECOG PS of 2 to 3 had shorter OS ($P=0.027$). (**C**) DEL patients had significantly shorter PFS compared to non-DEL patients ($P=0.040$). (**D**) There was a trend toward shorter OS in DEL patients ($P=0.062$). (**E**) The high-risk MSKCC score group did not have significantly shorter PFS (low-intermediate vs. high; $P=0.18$). (**F**) A shorter OS was associated with the high-risk groups of MSKCC score (low-intermediate vs. high; $P=0.032$)

Table 3 Adverse events during induction treatment

Type of toxicity	Grade 1–2	Grade 3	Grade 4
Leukopenia	6(15.4%)	4(10.3%)	1(2.6%)
Neutropenia	8(20.5%)	9(23.1%)	3(7.7%)
Thrombocytopenia	4(10.3%)	1(2.6%)	0
Anemia	17(43.6%)	1(2.6%)	0
Infection	1(2.6%)	0	0
Hepatotoxicity	11(28.2%)	2(5.1%)	0
Nephrotoxicity	4(10.3%)	0	0
Fatigue	14(35.9%)	0	0
Nausea	7(17.9%)	0	0
Paresthesia	8(20.5%)	0	0
Rash	7(17.9%)	0	0

overexpression in MYC and BCL2 proteins, is associated with poor outcomes of DLBCL cases (Bettelli et al. 2021; Johnson et al. 2012). The prognosis of the DEL subtype in PCNSL patients has not been conclusively established. Although several studies reported a poorer prognosis for the DEL subtype in PCNSL (Guo et al. 2016; Hatzl et al. 2020; Shi et al. 2017), others did not find a significant relationship (Gill et al. 2014; Makino et al. 2018). In this study, PCNSL-DLBCL with DEL had worse PFS ($P=0.040$) and a trend toward shorter OS ($P=0.062$). Nevertheless, given the retrospective and single-center nature of the study, future validation in prospective studies with larger cohorts is warranted.

Our study indicates that the R2-MTX regimen has a manageable safety profile. In our study, 13 patients (33.3%) experienced grade 3–4 hematological AEs and 3 patients (7.7%) experienced grade 3 non-hematological AEs, with no treatment-related deaths reported. Previous studies have shown that older patients with PCNSL are more susceptible to treatment-related toxicity, with no substantial improvement in prognosis (Houillier et al. 2020; Kasenda et al. 2015). The favorable tolerability of the R2-MTX regimen suggests it could be a preferred regimen for older or less fit PCNSL patients. These findings are particularly encouraging, given the historically aggressive nature of PCNSL and the limited treatment options available. Nevertheless, the efficacy and safety of R2-MTX must be validated through high-quality, large-scale prospective randomized trials.

Conclusions

In this retrospective study, we provided preliminary evidence that the R2-MTX regimen may serve as a promising therapeutic option for patients with PCNSL, demonstrating favorable outcomes and tolerability. Our findings also confirmed that consolidation or maintenance therapy is associated with improved survival in these patients. Additionally, we identified clinicopathological factors, such as DEL and ECOG PS≥2, as predictors of poor survival. The feasibility of the MSKCC model for prognostic prediction was also confirmed. Moving forward, it is essential to conduct prospective studies with larger patient cohorts and extended follow-up periods to strengthen these preliminary insights and develop reliable prognostic models for PCNSL.

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Data availability The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval This study was conducted in accordance with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Biomedical Research, West China Hospital of Sichuan University.

Consent to participate Not applicable.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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