Efficacy and safety of first-line combination therapy versus monotherapy for vitreoretinal lymphoma: A systematic review and meta-analysis

Jing Gao
Capital Medical University

Xiaoyan Peng
Capital Medical University

Liang Wang (wangliangtrhos@126.com)
Capital Medical University

Research Article

Keywords: vitreoretinal lymphoma, combination therapy, monotherapy, BTK inhibitors, meta-analysis

Posted Date: May 22nd, 2023

DOI: https://doi.org/10.21203/rs.3.rs-2772423/v1

License: ©  This work is licensed under a Creative Commons Attribution 4.0 International License.  Read Full License
Abstract

Background

Vitreoretinal lymphoma (VRL) is usually treated with a combo of intraocular methotrexate, high-dose intravenous methotrexate, and local radiotherapy as the first options. The effectiveness and safety of monotherapy such as BTK inhibitors, temozolomide, and pomalidomide for PVRL remain uncertain.

Methods

A systematic review and meta-analysis of clinical trial data and conference abstracts in VRL patients treated with first-line combination therapy and monotherapy were conducted through a search of PubMed, Embase, and Scopus databases until December 2022. A total of 17 studies comprising 278 patients were included, and survival data were extracted from 151 patients due to inconsistent units across studies.

Results

The combined treatment group used ioMTX + chemotherapy (in 3 studies), bilateral RT + chemotherapy (in 2 studies), ioMTX/IV HD-MTX based regimen (in 2 studies), ioMTX + chemotherapy + rdWBRT (in 2 studies), and ioMTX + lenalidomide/BTKi (in 2 studies). The monotherapy group used pomalidomide, temozolomide, and BTKi. The combination therapy had a higher overall response rate (ORR) and complete response rate (CRR) than monotherapy (ORR: 95% vs. 72%, CRR: 94% vs. 63%). Combination therapy also resulted in a longer median progression-free survival (33 months vs. 13 months, p = 0.0059). However, the combination therapy group had more severe side effects (grade 3/4 toxicity) than the monotherapy group (46% vs. 8%).

Conclusion

The study showed combination therapy had better OR and CR rates, longer survival, and more toxicity than monotherapy. While BTK inhibitors were well-tolerated, long-term effectiveness needs confirmation from prospective studies.

Systematic review registration: CRD42023400305

1 Introduction

Vitreoretinal lymphoma (VRL), also known as intraocular lymphoma (IOL), is a rare variant of central nervous system lymphoma (CNSL). It is a highly extranodal, non-Hodgkin's lymphoma, typically of the B-cell type, which predominantly affects the vitreous and retina of the eye, while also potentially involving the optic nerve without any infiltration of the brain parenchyma. It is important to note that VRL is an exceptionally aggressive lymphoma subtype, often posing significant challenges for diagnosis and treatment.

VRL is a highly rare disease, with only approximately 50 new cases reported annually in the United States, mostly affecting elderly patients. Additionally, women appear to be more susceptible than men. Nonetheless, there exists a close association between VRL and CNSL, as some CNSL may ultimately develop an ocular manifestation, while most VRL-origin lymphomas may eventually progress to CNSL. Hence, despite its low prevalence, the severity of VRL should not be underestimated, making it crucial to find an appropriate treatment strategy that can minimize the risk of CNS recurrence while alleviating ocular symptoms.

The first-line treatment for VRL typically includes both local treatment, such as intravitreal injection of chemotherapy, ocular radiotherapy, etc., and systemic therapy based on high-dose (HD) methotrexate (MTX). Nevertheless, the contribution of the combination of these two first-line treatments to improved outcomes remains controversial. In addition to local and systemic treatments, there are currently several other therapeutic modalities that have gained widespread attention in research. Various single agents, including temozolomide, and targeted agents such as Bruton tyrosine kinase inhibitors (BTKi), are also emerging as potential treatment options for VRL. However, the specific advantages and disadvantages between the two first-line therapy modalities and monotherapy remain unclear. Thus, the objective of this study is to conduct a systematic review and meta-analysis comparing the efficacy and safety of first-line combination therapy versus monotherapy, in order to provide recommendations for future clinical management.

2 Methods

2.1 Search strategy and selection criteria

This systematic review and meta-analysis adhered to a previously published protocol registered on the PROSPERO registry (CRD42023400305) and followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A comprehensive search of the literature was conducted to identify articles published in PubMed, Embase, and Scopus up to December 2022. Furthermore, relevant data from conference abstracts were included in the analysis if available. The complete search algorithm is provided in Supplementary Table 1. The outcome measure of interest is the median progression-free survival, which is defined as the duration of time during which 50% of patients remain free of disease progression.

The inclusion criteria for this review consisted of the following: (1) Prospective and retrospective studies; (2) Studies published in English language; (3) Patients diagnosed with VRL or IOL; (4) Various treatment options, such as monotherapy or MTX-based first-line therapy; (5) Studies reporting extractable endpoints, including the overall response rate (ORR), complete response (CR), partial response (PR), survival data, and adverse events (AEs). Meanwhile, studies meeting any of the following criteria were excluded from this review: (1) Duplicate literature; (2) Reviews, case reports, and cellular or animal studies;
(3) Non-therapeutic or diagnostic studies; (4) Studies from which data could not be extracted; (5) Updates of previous results; (6) Lymphoma with primary site in the ciliary body or choroid.

The study selection process can be broadly divided into two stages. First, two investigators (Jing Gao, Lang Wang) independently evaluated the title and abstract of each article to determine its eligibility for inclusion in the meta-analysis. Subsequently, the two investigators compared the full text of the studies that met the criteria established in the first stage, with any discrepancies resolved through discussion or consultation with a third researcher (Xiaoyan Peng).

2.2 Data analysis

The data collection process from eligible studies was conducted independently by two authors, with any discrepancies being resolved through joint discussion with a third author. An Excel sheet was utilized to extract information from the studies, which included the name of the first author, publication year, country, study period, study design (type of study and trial phase), median follow-up time, disease status, sample size, median age, patient gender, primary intervention, and main outcomes (response, survival, and AEs).

The ORRs, CRRs, and 3/4 AEs from the included literature were analyzed and combined using forest plots. The survival data units were inconsistent among the included literature, and only three studies had results for mPFS. Therefore, the extractable survival data from the literature were pooled and analyzed using the Kaplan-Meier method and the log-rank test to plot survival curves, perform survival comparisons, and calculate mPFS for each group. The Engauge digitizing software version 10.8 was used to obtain a portion of the survival data from Kaplan-Meier curves.

Heterogeneity across studies was assessed using Cochran’s Q test and I² statistics. A fixed effects model was used for data combination when heterogeneity was not significant (I² < 50% or p-value > 0.1), and a random effects model was used when heterogeneity was significant. Egger’s test was utilized to investigate publication bias, with P-values indicating the significance of bias and P < 0.05 indicating a significant publication bias. All statistical analyses were performed using R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

3 Results

3.1 Study Selection

Upon an initial search, 680 pertinent records were acquired. After eliminating 150 duplicates, we meticulously examined the titles and abstracts of the remaining 530 publications. Out of these, 450 studies were disregarded for failing to meet the eligibility criteria: reviews (n = 38), research on different maladies (n = 91), case reports (n = 171), diagnostic studies (n = 63), animal studies (n = 10), and non-therapeutic studies (n = 77). From the remaining 80 records, the complete text was scrutinized and 63 of them were dismissed due to the following reasons: inability to extract data (n = 55), and update of results (n = 8). Eventually, 17 full-text articles or conference abstracts qualified for assessment, which comprised of 7 retrospective studies and 10 prospective studies. The specific studies screening process is depicted in Fig. 1.

3.2 Study Characteristics

Out of the aforementioned 17 studies, 12 studies received first-line combination regimens, which included intraocular MTX injections, systemic high-dose MTX chemotherapy, local radiotherapy, and other targeted therapy regimens such as Lenalidomide and BTKi. Meanwhile, 5 studies utilized monotherapy, including the administration of pembrolizumab, BTKi, and temozolomide. A total of 278 patients with vitreoretinal lymphoma were included in these studies, with 224 having gender data, out of which 77 were male and 147 were female. The gender information of 54 patients was missing. The age range of the patients was 31–90 years, with a median age of 65 years. The follow-up duration of all studies ranged from 0.2–123.3 months, with a median follow-up time of 30.03 months. Four of the included studies had a median follow-up time of less than 24 months (Two using BTKi alone and two ioMTX in combination with lenalidomide/BTKi). The patient characteristics of the studies included are showed in Table 1.
## Table 1
Baseline clinical characteristics of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Design</th>
<th>Study period</th>
<th>Median follow-up time, months (range)</th>
<th>Disease status</th>
<th>Sample size</th>
<th>Median age, years (range)</th>
<th>Gender male/female</th>
<th>Primary intervention</th>
<th>Main outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaburaki, et al.</td>
<td>2017</td>
<td>Japan</td>
<td>One-arm Prospective Trial</td>
<td>2008/8-2015/3</td>
<td>48.9(15.3–95.1)</td>
<td>Primary intraocular lymphoma (PIOL)</td>
<td>17</td>
<td>63(43–72)</td>
<td>9/8</td>
<td>ioMTX + R-MPV + rdWBRT</td>
<td>CR, OR, PFS, OS, AEs</td>
</tr>
<tr>
<td>Hoang-Xuan, et al.</td>
<td>2020</td>
<td>France</td>
<td>Prospective Multi-center, Open-label, Phase II trial</td>
<td>2017/7-2019/10</td>
<td>6.7(0.2–27.4)</td>
<td>Primary CNS lymphoma (PCNSL) and PVRL</td>
<td>50(9)</td>
<td>72(43–83)</td>
<td>/</td>
<td>Pembrolizumab</td>
<td>CR, OR, PFS, AEs</td>
</tr>
<tr>
<td>Akiyama, et al.</td>
<td>2016</td>
<td>Japan</td>
<td>Single-arm Prospective study</td>
<td>2007/1-2013/12</td>
<td>29.5</td>
<td>PIOL</td>
<td>10</td>
<td>68.5</td>
<td>4/6</td>
<td>ioMTX + systemic high-dose MTX</td>
<td>CR, OR, AEs</td>
</tr>
<tr>
<td>Soussain, et al.</td>
<td>2019</td>
<td>France</td>
<td>Prospective Multi-center, Open-label, Phase II trial</td>
<td>2015/9-2016/7</td>
<td>25.7(0.7–30.5)</td>
<td>R/R PCNSL and PVRL</td>
<td>44(14)</td>
<td>70(52–81)</td>
<td>/</td>
<td>Ibrutinib</td>
<td>CR, OR, OS, PFS, AEs</td>
</tr>
<tr>
<td>Zhang, et al.</td>
<td>2022</td>
<td>China</td>
<td>Prospective Multi-center, Open-label, Phase II trial</td>
<td>2020/8-2022/1</td>
<td>12.4(0.3–18.1)</td>
<td>PVRL</td>
<td>10</td>
<td>55(39–70)</td>
<td>3/7</td>
<td>Btki + ioMTX</td>
<td>PFS, AEs</td>
</tr>
<tr>
<td>Guan, et al.</td>
<td>2022</td>
<td>China</td>
<td>Prospective Single-center, Open-label, Phase II trial</td>
<td>2020/10-2022/4</td>
<td>8.3(2.5–21.4)</td>
<td>Vitreoretinal lymphoma (VRL)</td>
<td>10</td>
<td>/</td>
<td>/</td>
<td>Ibrutinib, zanubrutinib, orelabrutinib</td>
<td>CR, OR, PFS, OS</td>
</tr>
<tr>
<td>Baron, et al.</td>
<td>2020</td>
<td>France</td>
<td>Retrospective</td>
<td>/</td>
<td>42(9-115)</td>
<td>PVRL</td>
<td>21</td>
<td>75(35–90)</td>
<td>/</td>
<td>Temozolomide</td>
<td>CR, OR, PFS, OS</td>
</tr>
<tr>
<td>Hsu, et al.</td>
<td>2022</td>
<td>China</td>
<td>Retrospective</td>
<td>2013/1-2018/1</td>
<td>/</td>
<td>Intraocular lymphoma (IOL)</td>
<td>12</td>
<td>/</td>
<td>5/7</td>
<td>ioMTX + systemic high-dose MTX</td>
<td>CR, OR, OS, PFS, AEs</td>
</tr>
</tbody>
</table>

Abbreviations: PVRL, primary vitreoretinal lymphoma; PIOL, primary intraocular lymphoma; PCNSL, primary central nervous system lymphoma; VRL, vitreoretinal lymphoma; MTX, methotrexate; ioMTX, intravitreal MTX; R-MPV, rituximab, methotrexate, procarbazine, vincristine, rdWBRT; reduced-dose whole-brain radiotherapy; Btki, Bruton tyrosine kinase inhibitors; OR, overall response; CR, complete response; OS, overall survival; mPFS, median progression-free survival; AEs, adverse event; DFS, disease-free survival.
demonstrates a combined mPFS of 42 months (95% CI, 16.8 to NA) and 11 months (95% CI, 9.0 to NA) in the combination (n = 30) and monotherapy groups.

24) In eight prospective studies, demonstrating a significant difference (p = 0.046), with the survival curves depicted in Fig.

demonstrating a significant difference (p = 0.0059). In a subgroup analysis based on the prospective article, the median progression-free survival was 33 months (95% CI, 10.0 to 40) in the combined treatment group (n = 95) versus the monotherapy group (n = 56) from a total of 13 publications, respectively.

data extraction. Figure Nine prospective studies and four retrospective studies provided extractable survival data tables or K-M survival curves for a total of 151 patients following This finding suggests that BTK inhibitors may be a promising treatment option for vitreoretinal lymphoma.

single drugs. The results indicated that the combined ORR value of the BTK inhibitor group is significantly higher than that of the non-BTK inhibitor group.

analyses on the monotherapy treatment group and found that among the five studies, three employed BTK inhibitors while the other two used different single (pooled value of 0.93, 95% CI: 0.85-1.00) was higher than that of the BTKi group (pooled value of 0.79, 95% CI: 0.54-1.00). We further performed subgroup analyses on the monotherapy treatment group and found that among the five studies, three employed BTK inhibitors while the other two used different single drugs. The results indicated that the combined ORR value of the BTK inhibitor group is significantly higher than that of the non-BTK inhibitor group.

We have also conducted a comparative analysis of the pooled overall response rate (ORR) and complete response rate (CRR) between the combination treatment group and the BTKi monotherapy group. Figure 3 showed that the combination treatment group demonstrated a pooled ORR comparable to that of the BTKi group, with values of 0.95 (95% CI, 0.89-1.00) and 0.89 (95% CI, 0.79-0.99), respectively. However, the CRR of the combination treatment group (pooled value of 0.93, 95% CI: 0.85-1.00) was higher than that of the BTKi group (pooled value of 0.79, 95% CI: 0.54-1.00). We further performed subgroup analyses on the monotherapy treatment group and found that among the five studies, three employed BTK inhibitors while the other two used different single drugs. The results indicated that the combined ORR value of the BTK inhibitor group is significantly higher than that of the non-BTK inhibitor group.

This finding suggests that BTK inhibitors may be a promising treatment option for vitreoretinal lymphoma.

3.4 Efficacy

3.4.1 Tumor Response

A total of 14 publications reported complete response (CR), partial response (PR), as well as overall response (CR + PR) to measure the tumor response to treatment. CR is defined as the patient achieving symptom remission after treatment, having no residual lesions in the anterior chamber, vitreous body, or retina, and returning to normal IL-10 levels. In contrast, PR is defined as partial remission of the disease after treatment, as evidenced by mild anterior chamber, vitreous or retinal lesions. The pooled overall response rate (ORR) was 0.88 (95% CI, 0.76 to 0.99) for the entire cohort, and 0.95 (95% CI, 0.89 to 1.00) and 0.72 (95% CI, 0.43 to 1.00) for the combination and monotherapy groups, respectively. In addition, the pooled complete response rate (CRR) for the entire cohort was 0.82 (95% CI, 0.68 to 0.95), while the pooled CRR for the combination and monotherapy groups was 0.94 (95% CI, 0.87 to 1.00) and 0.63 (95% CI, 0.34 to 0.93), respectively. The forest plots depicting these results are shown in Fig. 2.

We have also conducted a comparative analysis of the pooled overall response rate (ORR) and complete response rate (CRR) between the combination treatment group and the BTKi monotherapy group. Figure 3 showed that the combination treatment group demonstrated a pooled ORR comparable to that of the BTKi group, with values of 0.95 (95% CI, 0.89-1.00) and 0.89 (95% CI, 0.79-0.99), respectively. However, the CRR of the combination treatment group (pooled value of 0.93, 95% CI: 0.85-1.00) was higher than that of the BTKi group (pooled value of 0.79, 95% CI: 0.54-1.00). We further performed subgroup analyses on the monotherapy treatment group and found that among the five studies, three employed BTK inhibitors while the other two used different single drugs. The results indicated that the combined ORR value of the BTK inhibitor group is significantly higher than that of the non-BTK inhibitor group.

This finding suggests that BTK inhibitors may be a promising treatment option for vitreoretinal lymphoma.

3.4.2 Survival

Nine prospective studies and four retrospective studies provided extractable survival data tables or K-M survival curves for a total of 151 patients following data extraction. Figure 4 displays the survival curves for the combined median progression-free survival (mPFS) of 33 months (95% CI, 22 to NA) and 13 months (95% CI, 10.0 to 40) in the combined treatment group (n = 95) versus the monotherapy group (n = 56) from a total of 13 publications, respectively, demonstrating a significant difference (p = 0.0059). In a subgroup analysis based on the prospective article, the median progression-free survival was 33 months (95% CI, 25 to NA) in the combination treatment group (n = 65) compared to 19 months (95% CI, 9.1 to NA) in the combined monotherapy group (n = 24) in eight prospective studies, demonstrating a significant difference (p = 0.046), with the survival curves depicted in Fig. 5. Meanwhile, Figure S3 demonstrates a combined mPFS of 42 months (95% CI, 16.8 to NA) and 11 months (95% CI, 9.0 to NA) in the combination (n = 30) and monotherapy groups (n = 32), respectively, in the five retrospective studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Design</th>
<th>Study period</th>
<th>Median follow-up time, months (range)</th>
<th>Disease status</th>
<th>Sample size</th>
<th>Median age, years (range)</th>
<th>Gender male/ female</th>
<th>Primary intervention</th>
<th>Main outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ma et al.</td>
<td>2016</td>
<td>China</td>
<td>Retrospective</td>
<td>2003/1-2013/12</td>
<td>40.2(4.4-123.3)</td>
<td>PIOL</td>
<td>19</td>
<td>57(39–77)</td>
<td>6/13</td>
<td>ioMTX + systemic high-dose MTX</td>
<td>CR, OR, OS, AEs</td>
</tr>
<tr>
<td>Lam et al.</td>
<td>2021</td>
<td>French</td>
<td>Retrospective</td>
<td>2011/1-2018/3</td>
<td>61(50–71)</td>
<td>PVRL</td>
<td>59</td>
<td>70(39–88)</td>
<td>14/45</td>
<td>IV HD-MTX based systemic therapy</td>
<td>CR, OR, mPFS, AEs</td>
</tr>
<tr>
<td>Wang et al.</td>
<td>2021</td>
<td>China</td>
<td>Retrospective</td>
<td>2020/5-?</td>
<td>7.5(4–15)</td>
<td>VRL</td>
<td>11</td>
<td>61(41–73)</td>
<td>4/7</td>
<td>zanubrutinib orelabrutin</td>
<td>CR, OR, PFS, AEs</td>
</tr>
</tbody>
</table>

Abbreviations: PVRL, primary vitreoretinal lymphoma; PIOL, primary intraocular lymphoma; PCNSL, primary central nervous system lymphoma; VRL, vitreoretinal lymphoma; MTX, methotrexate; ioMTX, intravitreal MTX; R-MPV, rituximab, methotrexate, procarbazine, vincristine; rdWBRT, reduced-dose whole-brain radiotherapy; Btki, Bruton tyrosine kinase inhibitors; OR, overall response; CR, complete response; OS, overall survival; mPFS, median progression-free survival; AEs, adverse event; DFS, disease-free survival.
Furthermore, four publications were included in the monotherapy group with treatments comprising temozolomide monotherapy and BTK inhibitors, and the two groups did not exhibit a significant difference in mPFS (p = 0.58) (Figure S4). In the combination treatment group, there was no significant survival difference between the three-approach combination regimen and the two-approach combination regimen or the ioMTX-based regimen, while age, gender, and whether or not bilateral eye onset were not found to be associated with survival time (Figure S5-S8). In contrast, the analysis revealed that targeted-agent such as Lenalidomide and BTKi combined with ioMTX therapy had poorer survival outcomes compared to other combination therapies (Figure S9). This implies that systemic chemotherapy regimens based on MTX may be more efficacious when used in conjunction with ioMTX as opposed to lenalidomide and BTKi.

### 3.5 Toxicity and Replase

Nine publications reported grade 3/4 adverse events (AEs), consisting mainly of cataract, neutropenia, keratitis, anemia, and hepatic and renal toxicity. In the overall analysis, the pooled grade 3/4 toxicity was 0.46 (95% CI: 0.21–0.71) for the combination therapy group compared to 0.08 (95% CI: 0.0-0.20) for the monotherapy group, and the overall pooled value was 0.33 (95% CI: 0.13–0.53), indicating that less severe toxicity occurred in the monotherapy group than in the combination therapy group, as depicted in Fig. 6. Moreover, in the combination treatment group, major serious toxic reactions included cataract (pooled value of 0.43 95% CI: 0.26–0.61), keratitis (pooled value of 0.48 95% CI: 0.28–0.68), and neutropenia (pooled value of 0.35 95% CI: 0.00-0.77), as illustrated in Figure S10-S12. While in the monotherapy group, only four cases of grade 3/4 toxicity were reported in the literature using temozolomide, which consisted of 3 cases of grade 3 anemia and vomiting and 1 case of grade 4 neutropenia and thrombocytopenia.

The forest plot in Figure S13 shows that central nervous system (CNS) relapse was reported in 9 publications in the combination therapy group, while only 2 publications reported it in the monotherapy group. The incidence rate of CNS relapse was 0.27 (95% CI: 0.19–0.35) in the combination therapy group, with a median follow-up time of 35.38 months (ranging from 0.3 to 123.3 months). In the monotherapy group, only one trial provided information on CNS relapse, with a 30% incidence and a median follow-up time of 8.3 months (ranging from 2.5 to 21.4 months). Seven publications in the combination therapy group reported ocular recurrence with a combined incidence of 0.23 (95% CI, 0.13 to 0.33) (Figure S14), while one publication in the monotherapy group reported ocular recurrence in 2 of 10 patients. However, due to the limited number of studies and small sample size in the monotherapy group, further research is needed to better understand any potential differences in ocular recurrence between the two treatment approaches.

### 4 Discussion

Intraocular lymphoma, being an uncommon ailment, can be mistakenly identified as uveitis during diagnosis. Additionally, a treatment approach that achieves both effectiveness and safety remains elusive. Moreover, the long-term prognosis for PVRL patients is bleak, as around 60%-80% of them eventually develop PCNSL, as reported in 1999 by Akeyte. Treatment modalities for PVRL are variable and include methotrexate-based local/systemic therapy, local/whole-brain radiation therapy, various monotherapy and intensive chemotherapy plus hematopoietic stem cell transplantation (IC + ASCT), the optimal treatment modality has not yet been identified.

Intravitreal methotrexate (ioMTX) is an early proposed local treatment with a high remission rate but usually a poor prognosis, with most patients experiencing CNS progression within a short period of time (2004 Coupland). Anthony et al. designed a small sample single-center retrospective study to investigate the efficacy of ioMTX alone in the treatment of PVRL. Although all achieved CR or PR, their time until disease recurrence was not promising (mean time to first recurrence was 6.5 months). Based on the anatomical and functional similarities of PVRL to PCNSL at the blood-brain barrier (BBB) and blood-retinal barrier (BRB), intravenous high-dose methotrexate injection (IV HD-MTX) has also been used as an empirical agent for PVRL treatment and is often combined with ioMTX and local radiotherapy to improve efficacy (Akiyama, de la Fuente).

Lam et al. gathered data pertaining to 59 patients who were diagnosed with isolated primary vitreoretinal lymphoma (PVRL) from the French LOC network database, in order to examine the effectiveness and adverse effects of intravenous high-dose methotrexate (HD-MTX)-based systemic chemotherapy in treating PVRL patients. Despite the fact that 70% of patients attained a complete response (CR) or unconfirmed complete response (uCR), the relapse rate was not insignificant (with a median follow-up of 61 months, 37% of patients experienced central nervous system recurrence and 58% had ocular recurrence), and the occurrence of grade 3/4 toxicity in 53% of patients implied poor tolerability. Furthermore, there are instances of using more than two regimens for treating PVRL. Kaburaki et al.’s R-MTX + ioMTX + rDWBR (reduced-dose whole brain radiation therapy) regimen for PVRL resulted in long-term progression-free survival (PFS) and overall survival (OS) (with a 4-year PFS of 74.9% and a 4-year OS of 86.3%), as well as a low overall relapse rate (23.5%). However, it is important to note that this regimen was associated with significant grade 3/4 hematologic toxicity.

In recent times, various monotherapy regimens have been investigated to identify an effective and safe treatment combination. Temozolomide (TMZ), a second-generation alkylating agent that is well-tolerated, has been found to have good penetrative capacity into the central nervous system and cerebrospinal fluid (CSF) (Reni, 2007). Baron et al. conducted a retrospective study using TMZ for the treatment of PVRL, which produced encouraging results (with an overall response rate [ORR] of 81%, median progression-free survival [mPFS] of 12 months, and a central nervous system [CNS] relapse rate of 23.8%). Bruton tyrosine kinase (BTK) is a crucial mediator molecule in B-cell proliferation, and its inhibitors have the potential to serve as therapeutic agents in various B-cell malignancies. However, it is yet to be determined whether such inhibitors can offer therapeutic benefit to patients with primary vitreoretinal lymphoma (PVRL). To address this, Soussain et al. designed a multicenter, open-label phase II clinical trial aimed at evaluating the efficacy of Ibrutinib as a single agent in patients with both primary central nervous system lymphoma (PCNSL) and PVRL. Of the 14 patients with PVRL included in the study, 86% achieved remission after 2 months of treatment, with a median progression-free survival (PFS) value of 22.7 months. Moreover, single-agent combination intracranial methotrexate (ioMTX) regimens have also been investigated. Zhang et al. sequentially tried a regimen of R2 (lenalidomide plus rituximab) + ioMTX induction, lenalidomide maintenance therapy, and ZR (zanubrutinib plus rituximab) + ioMTX to further investigate the optimal treatment strategy for PVRL.
Moreover, a prospective study designed by Soussain et al. evaluating the feasibility of intensive chemotherapy (consisting of high-dose thiopeta, busulfan and cyclophosphamide) plus hematopoietic stem cell transplantation as a treatment modality for relapsed or refractory CNS lymphoma and intraocular lymphoma with an ultimate 3-year overall survival rate of 63.7%. demonstrating the benefit of IC + ASCT in patients with relapsed PVRL, but this modality is only indicated for younger relapsed patients younger than 60 years of age who are well tolerated, and its safety is difficult to guarantee in patients older than 60 years of age.25

In this meta-analysis, we compared the efficacy and safety of combination therapy versus monotherapy regimens for the treatment of VRL. In the combination therapy group, specific interventions included ioMTX + chemotherapy (3 studies), bilateral RT + chemotherapy (2 studies), ioMTX/IV HD-MTX based regimen (2 studies), ioMTX + chemotherapy + rdWBRT (2 studies), and ioMTX + lenalidomide/BTKi (2 studies). In the monotherapy group included in our study, interventions included Pomalidomide, Temozolomide, and BTKi.

We found that patients receiving combination therapy demonstrated a higher overall response rate (ORR) and complete response rate (CRR), as well as a relatively longer median progression-free survival (PFS) compared to those receiving monotherapy. BTKi, as a single agent, achieved an ORR that approximated that of the combination group, suggesting a strong potential for the treatment of VRL. The analysis also explored whether the number of treatment approaches in the combination group had an impact on survival time. Interestingly, the results showed that there were no significant survival differences between treatment regimens combining three approaches versus those combining two or less approaches. This suggests that the number of treatment approaches may not be the primary factor influencing survival time in patients receiving combination therapy for the condition under study. Moreover, this study investigated the potential influence of demographic and clinical characteristics on survival time, including age, gender, and whether the onset of the condition was bilateral. The study results indicated that none of these factors demonstrated a significant association with survival time. In further subgroup analysis, we found that ioMTX plus monotherapy did not show superior survival compared to other combination therapies, suggesting that MTX-based systemic chemotherapy regimens may be more effective when combined with ioMTX compared to lenalidomide and BTKi, but the data on ioMTX plus monotherapy is limited and requires more data to confirm its true benefits.

In addition, we also observed that the combination therapy group exhibited a higher incidence of grade 3/4 toxicities. Grade 3/4 toxicities mainly included ocular and systemic toxicities, with ocular toxicities mainly consisting of cataracts and keratitis, and systemic toxicities mainly consisting of neutropenia and anemia. We found that the combination therapy group had more significant grade 3/4 toxicities than the monotherapy group, suggesting that the safety of monotherapy may be better than that of combination therapy. Furthermore, we observed similar recurrence rates between the two groups. Whether it was a combination therapy or monotherapy, the CNS recurrence rate was approximately 30%. However, the ocular recurrence rate appeared to be relatively higher in the combination therapy group, but the number of studies included in the monotherapy treatment group was limited, and further research is needed to better understand the potential differences between the two treatment methods in terms of ocular recurrence.

In general, these results suggest that a treatment approach that combines efficacy and safety still needs to be explored to achieve better management of intraocular lymphoma. The long-term efficacy of systemic therapy with one drug alone is not satisfactory, and the combination of systemic and local therapy for intraocular lymphoma is the future trend. The use of single drugs such as BTK inhibitors and temozolomide in combination with high-dose systemic MTX chemotherapy regimens may also be a potential new research direction. Future research may focus on identifying the optimal treatment combination that can provide VRL patients with a longer period of remission, extended survival time, and prevention of recurrence in the central nervous system and ocular region.

The limitations of this article stem from the rarity of VRL, which results in a relatively small sample size. Additionally, the diverse treatment methods employed across various studies introduce significant heterogeneity, leading to some conclusions drawn from the combined data lacking statistical support. Moreover, the average follow-up time in the literature involving the use of new BTKi-like drugs is not yet long and may lead to some uncertainty in the results. Nonetheless, our analysis provides a comprehensive summary of the efficacy and safety of various VRL treatment methods and serves as a valuable reference for further exploration of more optimal solutions.

5 Conclusion

Based on the available evidence, first-line combination therapy for VRL appears to be more effective than monotherapy, with higher OR and CR rates and longer median progression-free survival. However, combination therapy also has higher rates of grade 3/4 toxicity compared to monotherapy. While BTK inhibitors as monotherapy for VRL appear to be well tolerated, further studies are needed to confirm their long-term efficacy. Prospective studies are necessary to evaluate the optimal treatment approach for VRL.

Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests

Funding: This work was supported by grants from the National Natural Science Foundation of China (grant No.82170181), Beijing Hospitals Authority Youth Programme (code: QML20200201), and Beijing Natural Science Foundation (No.7222027) to Liang Wang.
Acknowledgements: Not applicable

References


Figures

**Figure 1**
Flow diagram of study selection.
**Figure 2**

Forest plot for pooled overall response rate (A) and complete response rate (B) across the combined treatment group and the monotherapy group.
Figure 3

Forest plot for pooled overall response rate (A) and complete response rate (B) across the combined treatment group and the BTKi group.
Survival curves in the combined treatment group versus the monotherapy group.

Figure 4
Figure 5

Survival curves in the combined treatment group versus the monotherapy group in the prospective study subgroup.

Log-rank $p = 0.046$
Figure 6

Forest plot for pooled grade 3/4 adverse events (AEs) across the combined treatment group and the monotherapy group.

**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- FigureS1.pdf
- FigureS10.pdf
- FigureS11.pdf
- FigureS12.pdf
- FigureS13.pdf
- FigureS14.pdf
- FigureS2.pdf
- FigureS3.pdf
- FigureS4.pdf
- FigureS5.pdf
- FigureS6.pdf
- FigureS7.pdf
- FigureS8.pdf
- FigureS9.pdf
- SupplementaryTable1.docx
- SupplementaryTable2.docx