Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/survophthal

Review article

Primary central nervous system lymphoma – ocular variant: an interdisciplinary review on management

Vishal Raval, MD[a], *Elaine Binkley, MD*[b], *Mary E. Aronow, MD*[c], *Juan Valenzuela, MD*[d], *David M. Peereboom, MD*[e], *Arun D. Singh, MD*[a,*]

[a] *Department of Ophthalmic Oncology, Cole Eye Institute, Cleveland Clinic, Cleveland, OH, USA*
[b] *Department of Ophthalmology & Visual Sciences, University of Iowa, Iowa City, IA, USA*
[c] *Retina Service, Massachusetts Eye and Ear, Harvard Medical School, Boston, MA, USA*
[d] *Department of Retina and Ophthalmic Oncology, Consultores Oftalmológicos, Buenos Aires, Argentina*
[e] *The Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center, Cleveland Clinic, Cleveland, OH, USA*

ARTICLE INFO

Article history:
Received 10 October 2020
Revised 8 March 2021
Accepted 15 March 2021
Available online 21 March 2021

Keywords:
Primary central nervous system lymphoma
Primary CNS lymphoma- ocular variant
Primary vitreoretinal lymphoma
Treatment
Systematic review
Neuro-oncology

ABSTRACT

Primary central nervous system lymphoma-ophthalmic variant (PCNSL-O) is an ocular subset of PCNSL predominantly involving subretinal pigment epithelium space, retina, and vitreous. The ophthalmic manifestations can precede, occur simultaneously, or follow other compartments of the CNS. Clinical trials have resulted in a significantly improved outcome in PCNSL patients over the past 2 decades, with a higher proportion of patients receiving frontline high dose methotrexate-based polychemotherapy regimens with curative intent; however, the current management of PCNSL-O remains controversial owing to lack of prospective data. The goals of PCNSL-O treatment are both to achieve local (ocular) control and to prevent tumor-specific mortality from further CNS involvement. Despite achieving high rates of ocular control with intravitreal agents like methotrexate and rituximab, the overall survival is poor, as 65-85% of patients eventually succumb to CNS disease. Few studies define the role of systemic chemotherapy with/without local treatment as a first line induction treatment for PCNSL-O considering limiting factors such as ocular penetration of systemically administered drugs and treatment related neurotoxicity. Also, the role of adjuvant treatment for PCNSL-O to prevent CNS progression and to improve overall survival is unknown. In this systematic review of the literature, we analyze treatment outcomes of various regimens (local, systemic, and combination) in terms of local control, CNS progression, and overall survival.

* Corresponding author: Arun D. Singh, MD, Department of Ophthalmic Oncology, Cole Eye Institute, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195, Phone: 216-445-9479.
E-mail address: singha@ccf.org (A.D. Singh).

0039-6257/$ – see front matter © 2021 Elsevier Inc. All rights reserved.
https://doi.org/10.1016/j.survophthal.2021.03.004

1. Introduction

Primary central nervous system lymphoma (PCNSL) is a subtype of non-Hodgkin lymphoma confined to the CNS compartments. As per the 2017 World Health Organization classification of hematopoietic and lymphoid tumors [22], PCNSL is classified as primary diffuse large B-cell lymphoma (DLBCL) of the CNS. The CNS compartments include the brain (deep cortical regions, periventricular regions, and basal ganglia), spinal cord, meninges, and the eyes [14]. The most recent population standardized rate of PCNSL in the United States reported by the Central Brain Tumor Registry of the United States (CBTRUS) was calculated at 4.4 per million person-years between 2010 and 2014, representing approximately 2% of all brain neoplasms [45]. The incidence of PCNSL-ophthalmic variant (PCNSL-O), a subset of PCNSL, has increased in recent years as a result of an overall increase in life expectancy, newer diagnostic and molecular techniques, the use of newer chemotherapeutic treatment regimens, and an increase in the number of patients with immunodeficiency and immunosuppression [50]. The majority of individuals who present with PCNSL-O are over 50 years of age with no clear sex predilection [8]. The involvement of the eye and other CNS compartments varies as ophthalmic manifestations can precede, occur simultaneously with or follow disease in other CNS sites. Sixty to 90% of patients with PCNSL-O ultimately involve other CNS compartments, while 20 % of patients with PCNSL present with concurrent PCNSL-O [8,29], The median interval between the progression of lymphoma from the eye to other CNS compartments and vice versa varies over a follow up of 8-29 months [8,50]. In a recent review by Farrall and coworkers the prevalence of ocular involvement at any time during the course of PCNSL was 16%, with greater prevalence (69%) of CNS involvement with ocular involvement [14]. As PCNSL is an aggressive lymphoma, the longterm prognosis is poor (5-year overall survival of 30%). The overall prognosis of PCNSL-O is also poor, with 5-year survival rates between 25% and 40% [27].

2. Terminology

There is lack of consensus regarding appropriate terminology for primary CNS lymphoma involving the ocular compartment. Historically CNS lymphoma involving the eye was described as reticulum cell sarcoma [56] and microgliomatosis [49]. These terms, however, are no longer favored as they are misleading regarding the cell of origin. In the last two decades terminology such as primary intraocular lymphoma (PIOL) has been introduced; however, this term is confusing as lymphoma involving such as the retina, vitreous, and optic nerve often is typically DLBCL subtype (high grade), whereas lymphoma involving the uveal tract is usually of the extranodal marginal zone subtype (low grade) [11]. Primary vitreoretinal lymphoma (PVRL) is the most commonly used term in the literature; however, it implies that the disease originates in the eye. Also, in a few cases there is selective involvement of the sub-retinal pigment epithelial (RPE) space or optic nerve, and in these cases PVRL, VRL, or retinal lymphoma would not be appropriate. We have therefore used PCNSL-O as the preferred term to emphasize that it is an ocular variant or subset of PCNSL [4]. Those with concurrent CNS and ocular disease were labelled as (PCNSL-CNS/O), in contrast to patients with CNS only involvement (PCNSL-CNS) at presentation who are not included in this review.

Systemic large B-cell lymphoma component rarely may manifest with retinal infiltrates or vitreous cells similar to those observed in PCNSL-O [51]; however, some recent studies have reported that 20-28% of PCNSL-O patients may have systemic large B-cell lymphoma [34,43]. Therefore, a thorough systemic evaluation is needed to rule out lymphoma elsewhere in the body before confirming a diagnosis of PCNSL/PCNSL-O. There are only a few case reports and series and such cases were not included in this review.

3. Treatment of PCNSL

Safe and efficient treatment for patients with PCNSL should be performed by an experienced multidisciplinary team comprised of ophthalmologists, neurologists, oncologists and/or radiation oncologists. Treatment of PCNSL has evolved over the last two decades based on a few randomized clinical trials, single-arm phase II trials, and many retrospective studies, but no consensus on the optimal treatment regimen exists currently [19].

The rational for the choice of chemotherapeutic agents for the treatment of PCNSL depends on the penetration of the blood-brain barrier. The use of high dose methotrexate (HD-MTX) is the backbone of multimodal therapy because of its ability to achieve reasonable therapeutic levels in the CNS. HD-MTX, alone or in combination with other chemotherapeutic agents such as other antimetabolites (high dose cytarabine), alkylating agents (thiotepa) and monoclonal antianti-CD20 antibodies (rituximab) are the first line induction treatment used in most centers [18].

Once remission is achieved, *consolidation treatment* to improve progression free survival (PFS) includes whole brain radiotherapy, high dose chemotherapy with autologous stem cell transplantation (HDC/ASCT), and non-myeloablative chemotherapy [19]. The role of maintenance therapy in PCNSL is under investigation and is particularly useful in elderly patients who are unsuitable for consolidation treatments like WBRT or HDC/ASCT [46].

4. Treatment of PCNSL-O

Optimal management is not well established owing to lack of evidence-based, randomized clinical trials, as only a few PCNSL trials have included patients with PCNSL-O [44]. The current treatment strategies for management of PCNSL-O are focused primarily on local ocular control with the use of either intravitreal agents such as methotrexate and rituximab or local radiation treatment [37]. Even though these local treatments achieve good intraocular response, they are not intended to be curative as these interventions do not improve overall survival and have no effect on progression/relapse in other CNS compartments [32]. Therefore, ocular therapy by design is palliative; however, the primary goal in management

of PCNSL-O should not be limited to controlling the ocular disease (palliative approach), but rather a curative approach should be undertaken considering the high tendency for CNS progression/relapse. Taking cues from management of PCNSL, a multidisciplinary team approach is needed for management of patients with PCNSL-O.

In patients diagnosed with PCNSL-O, there is no consensus among ophthalmologists regarding the use of either local or systemic treatment or a combination of both local and systemic treatment regimens. There is also no consensus regarding the choice of first line local agents, the dosing schedule of injections, or the treatment endpoint. There are contradictory reports, with some showing no effect on progression of disease into the CNS compartment when comparing local therapy only (radiation with or without intravitreal chemotherapy) with a combination of local and systemic chemotherapy [8,24,31,48]. Others have shown that the use of systemic treatment along with ocular radiation have improved progression free survival (PFS) from 10 months to 37 months. but not overall survival (OS) [31,40,58].

Staging evaluation for the patient, an important part of management, is usually done in patients with biopsy confirmed diagnosis of PCNSL-O to rule out extraocular sites of involvement like the CNS or testis. Magnetic resonance imaging of the brain with contrast, along with lumbar puncture for cerebrospinal fluid (CSF) evaluation, should be obtained in all patients diagnosed with PCNSL-O since 80% of these patients ultimately develop lymphoma in other areas of their central nervous system [63]. Testicular ultrasound can also be considered, as the testes represent a relatively immune privileged site where lymphoma can be detected [62]. Serological testing for HIV, hepatitis B and C, plus quantification of serum lactate dehydrogenase, should also be considered as standard-of-care at baseline.

5. Review of literature related to treatment for PCNSL-O

5.1. *Inclusion criteria*

All of studies, including case series and clinical trials, in which immunocompetent patients with newly diagnosed PCNSL-O either prior to or with concurrent CNS involvement and without previous history of systemic lymphoma were selected for this analysis. All patients treated for intraocular and CNS disease with various treatment regimens were included. Patients were categorized into two groups on the basis of the ocular involvement. Group 1 included patients with PCNSL-O only at presentation and Group 2 (PCNSL-CNS/O) included patients with concurrent involvement of the eye and other CNS compartments. Group 1 patients were further categorized into 1A who received local ocular therapy such as intravitreal chemotherapy and/or radiation treatment; 1B received systemic intravenous chemotherapy ± whole brain radiation, and 1C received a combination of local ocular therapy and systemic treatment. Group 2 patients received either systemic chemotherapy alone or a combination of local ocular and systemic chemotherapy.

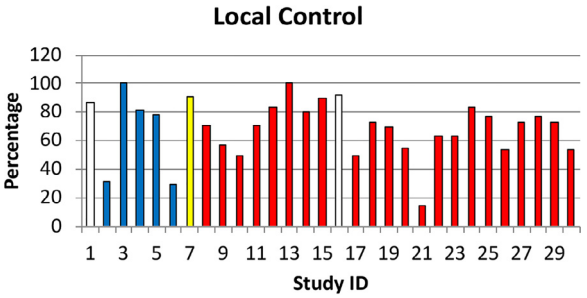

Fig. 1. – Ocular control in Group 1 (PCNSL-O). The studies are categorized by the treatment approach. Local ocular therapy such as intravitreal chemotherapy ± radiation treatment (A-Blue), systemic chemotherapy ± whole brain radiation (B-yellow) and a combination of local ocular therapy and systemic treatment (C-Red). Studies 1 and 16 included patients treated by all three methods (white). (Color version of figure is available online.)

5.2. *Exclusion criteria*

Studies were excluded if the case series was less than 5 patients, treatment regimens were not clearly stated, or treatment outcomes such as PFS and OS were not specified. There was no restriction on language, as long as the abstract was available in English

5.3. *Outcome measures*

The main outcomes in our review analysis were median time to CNS progression, PFS (defined as time from treatment initiation until disease progression or death (whichever occurred first) and OS (defined as the duration of patient survival from the time of initial treatment).

6. Results

We identified 737 potentially eligible reports. After removal of 102 duplicates, we screened 635 abstracts, excluded 576 as ineligible, and reviewed full texts of the remaining 59 studies. Ultimately, 30 cohort studies [3,5,7,9,10,12,13,16,20,23,24,26,27,30–33,35,36,38,39,40–42,48,54,58,59,60,65] met eligibility criteria. In Group 1, studies with initial manifestation of the disease in the ocular compartment (PCNSL-O) without CNS involvement were included.

a. Group 1A (128 patients) included all studies where local treatment (intravitreal chemotherapy with or without ocular radiation) was the primary mode of treatment to the eye (Table 1). From 7 studies (128 patients), 5 studies (intravitreal chemotherapy with or without ocular radiation) and 2 studies (only ocular radiation) were identified. The median age at presentation was 65 years (range, 57-70 years). Local control was achieved in 93 out of 128 patients (73%) with CNS progression in 68 patients (53%) (Figs. 1 and 2). The median time to CNS progression was 28 months (range: 14-32 months) and the median time to death was 36 months

Table 1 – PCNSL-O treated with local ocular therapy (Group 1A).

Study ID	Author (year)	Total patients	Eye first	Eye –> CNS	Primary treatment	Ocular relapse	Time to CNS progression (median) months	Overall Survival (median) months	Death	Follow-up (median) months
1	Riemens A (2015)	78	31	10	MTX (IVT) ± RT	4	28	44	11	48
2	Hashida N (2012)	13	13	9	MTX ± RTX (IVT)	9	32	NA	NA	47
3	Frenkel S (2008)	19	6	6	MTX (IVT)	0	14	NA	NA	24
4	Larkin K (2013)	34	21	15	RTX ± MTX (IVT)	4	18	28	7	11
5	Teckie S (2014)	18	18	6	RT	4	19	27	5	25
16	Castellino A (2019)	33	17	10	IVT (MTX/RTX) or RT	12	31*	48*	NA*	36
6	Mikami R (2013)	22	22	12	RT	2	28	36	7	NA

CNS = central nervous system; MTX = methotrexate; IVT = intravitreal; RT = radiation; RTX = rituximab; NA = not applicable.
* Data available for entire cohort (33 patients).

Table 2 – PCNSL-O treated with systemic chemotherapy (Group 1B).

Study ID	Author (year)	Total patients	Eye first	Eye –> CNS	Primary treatment	Ocular relapse	Time to CNS progression (median) months	Overall Survival (median) months	Death	Follow-up (median) months
1	Riemens A (2015)	78	21	9	Sys Chemo	6	29	44	2	44
16	Castellino A (2019)	33	7	2	Sys Chemo	3	31*	48*	NA*	36*
7	Batchelor T (2003)	9	4	3	Sys Chemo	2	9	12.5	1	17

CNS = central nervous system; Sys Chemo = systemic chemotherapy.
* Data available for entire cohort (33 patients).

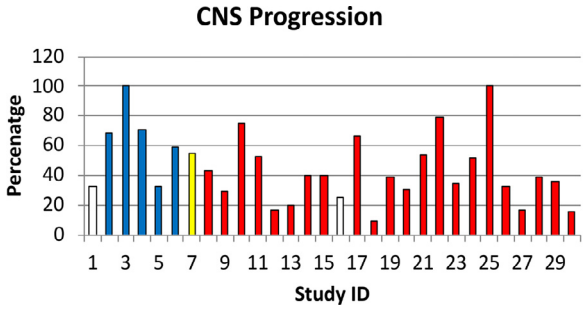

Fig. 2. – CNS progression in Group 1 (PCNSL-O). The studies are categorized by the treatment approach. Local ocular therapy such as intravitreal chemotherapy ± radiation treatment (A-Blue), systemic intravenous chemotherapy ± whole brain radiation (B-yellow) and a combination of local ocular therapy and systemic treatment (C-Red). Studies 1 and 16 included patients treated by all three methods (white). (Color version of figure is available online.)

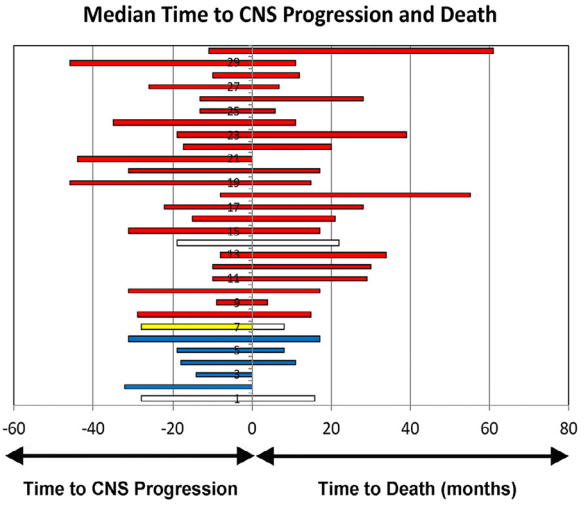

Fig. 3. – Median time to CNS progression and death for Group 1 studies (PCNSL-O). Time 0 represents CNS involvement. Local ocular therapy such as intravitreal chemotherapy ± radiation treatment (A-Blue), systemic intravenous chemotherapy ± whole brain radiation (B-yellow) and a combination of local ocular therapy and systemic treatment (C-Red). Studies 1 and 16 included patients treated by all three methods (white). (Color version of figure is available online.)

(range 27-48 months). When corrected for lead time bias (time to CNS progression), the corrected time to death was 11 months with OS of 67% (62 out of 92) (Fig. 3).

b. Group 1B (32 patients) included all studies where systemic treatment (systemic chemotherapy +/- whole brain radiation) was the primary mode of treatment (Table 2). The median age at presentation was 59 years (range, 52-67 years). Local ocular control was achieved in 21 out of 32 patients

Table 3 – PCNSL-O treated with combination of local ocular therapy and systemic therapy (Group 1C).

Study ID	Author (year)	Total patients	Eye first	Eye –> CNS	Primary treatment	Ocular Relapse	Time to CNS progression (median) months	Overall Survival (median) months	Death	Follow-up (median) months
8	Hormigo A (2004)	31	17	9	Sys Chemo+ RT	5	10	39	8	NA
9	Sfefanovic A (2010)	6	6	1	Sys Chemo+ RT	1	10	21	1	44
10	Taoka K (2012)	5	5	1	Sys Chemo+ WBR+ MTX (IVT)	0	8	22	0	32
11	Akiyama H (2016)	10	10	4	Sys Chemo+ MTX (IVT)	2	18.5	28	3	40
12	Klimova A (2018)	20	10	4	Sys Chemo+ MTX (IVT)	1	31	48	2	53
13	de la Fuente M (2019)	12	12	3	Sys Chemo+ RT	1	15	36	2	68
14	Hoffman PM (2003)	10	6	4	Sys Chemo+ RT	3	21.5	49	4	NA
15	Kaburaki T (2017)	17	11	1	Sys Chemo+ WBR+ MTX (IVT)	3	8	63	1	49†
1	Riemens A (2015)	78	23	9	Sys Chemo + RT/MTX (IVT)	7	46	61	10	78
16	Castellino A (2019)	33	8	0	Sys Chemo+ MTX/RTX (IVT)	3	31*	48*	14*	36†
28	Hashida N (2014)	26	26	14	Sys Chemo/ MTX (IVT)	NA	44	NA	NA	44
18	Cho BJ (2018)	53	14	11	Sys Chemo+ MTX (IVT) ± RT	NA	17.4	37	10	39
19	Grimm S (2007)	83	83	29	Sys Chemo/ MTX ± RT	21	19	58	33	NA
20	Dalvin L (2020)	77	27	14	Sys Chemo/ MTX ± RT	10	35	46	11	NA
21	Smith J (2002)	16	8	8	Sys Chemo+ MTX (IVT) ± RT	3	13	18.5	2	19.5
22	Lee S (2015)	20	6	2	Sys Chemo+ MTX (IVT)	NA	13	41	1	NA
23	Levasseur S (2013)	22	12	2	Sys Chemo+ RT	2	26	33	4	NA
24	Jahnke K (2006)	19	13	5	Sys Chemo+ MTX (IVT) ± RT	3	10.2	22.5	3	NA
25	Cheah C (2016)	11	11	4	Sys Chemo+ RT	3	45.6	56.4	2	NA
26	Ma Wei-Li (2016)	19	13	2	Sys Chemo+ MTX (IVT)	6	11.4	NR	4	NA

CNS = central nervous system; Sys Chemo = systemic chemotherapy; RT = radiation; WBR = whole brain radiation; MTX = methotrexate; IVT = intravitreal; NA = not applicable; NR = not reached.

* Data available for entire cohort (33 patients).

† Follow-up mentioned for entire cohort.

(66%) (Figs. 1 and 2). Of the 32 patients, CNS progression was reported in 14 patients (44%) with a median time to CNS progression of 29 months (range: 9-31 months) and median time to death of 28 months (range: 13-44 months). When corrected for lead time bias (time to CNS progression), the corrected time to death was 15 months with OS of 88% (22 out of 25). (Fig. 3)

c. Group 1C (321 patients) included all studies where systemic treatment (systemic chemotherapy and/or whole brain radiation) and local ocular therapy (intravitreal local chemotherapy and/or radiation) was the primary mode of treatment (Table 3). The median age at presentation was 64 years (range, 56-69 years). Local control was achieved in 201 out of 275 patients (73%) (Figs. 1 and 2). Of the total 321 patients, progression to the CNS was reported in 127 patients (40%). The median time to CNS progression was 18 months (range: 8-46 months) and median time to death was 41 months (range: 19-72 months). When corrected for lead time bias (time to CNS progression), the corrected time to death was 21 months with OS of 65% (186 out of 287) (Fig. 3).

d. Group 2 (PCNSL-CNS/O (462 patients) included all studies where concurrent involvement of the ocular and other CNS compartments were identified (Table 4). The primary mode of treatment in this group was systemic treatment (systemic chemotherapy ± whole brain radiation) with/without local ocular therapy (intravitreal local chemotherapy ± ocular radiation). Of 16 studies, 15 studies (systemic chemotherapy + local ocular therapy) and 1 study (only systemic chemotherapy) were identified. The median age at presentation was 61 years (range, 53-67 years). Of the 462 patients, CNS and ocular control rate was reported in 57% (200 out of 351) and 75% (263 of 351), respectively (Fig. 4). The median time to CNS/ocular recur-

Table 4 – PCNSL with concurrent eye and CNS involvement treated with combination of local ocular therapy and systemic therapy (Group 2).

Study ID	Author (year)	N	Concurrent	Primary CNS treatment	CNS Relapse	Ocular Relapse	Time to CNS progression (median) months	Overall Survival (median) months	Death	Follow-up (median) months
8	Hormingo A (2004)	31	14	Sys Chemo+ RT	7	3	16	24	13	23
7	Batchelor T (2003)	9	5	Sys Chemo	1	1	20	18	1	20
14	Hoffman PM (2003)	10	4	Sys Chemo+ RT	0	0	0	7	4	NA
15	Kaburaki T (2017)	17	6	Sys Chemo+ WBR+ MTX (IVT)	1	1	8.8	48	1	49*
12	Klimova A (2018)	20	10	Sys Chemo+ RT+ MTX (IVT)	3	3	12	29	4	56
16	Castellino A (2019)	59	27	Sys Chemo+ MTX (IVT) ± RT	9	8	24	48	11	42*
17	Zhuang L (2019)	21	21	Sys Chemo+ MTX (IVT) ± RT	9	12	13	51	8	21
18	Cho BJ (2018)	53	39	Sys Chemo+ MTX (IVT) ± RT	NA	NA	NA	18	20	19
19	Grimm S (2008)	221	221	Sys Chemo+ MTX (IVT) ± RT	98	48	13	31	150	36
20	Dalvin L (2020)	77	50	Sys Chemo+ MTX (IVT) ± RT	NA	NA	NA	57	32	NA
21	Smith J (2002)	16	8	Sys Chemo+ MTX (IVT) ± RT	NA	NA	NA	14	4	18.5
27	Ferreri A (2002)	21	21	Sys Chemo+ RT	15	8	12	53	14	NA
22	Lee S (2015)	20	14	Sys Chemo+ MTX (IVT) ± RT	NA	NA	NA	17	5	NA
23	Levasseur S (2013)	22	10	Sys Chemo+ RT	5	2	NA	21	8	NA
24	Jahnke K (2006)	19	6	Sys Chemo+ MTX (IVT) ± RT	2	1	NA	13	1	NA
26	Ma Wei-Li (2016)	19	6	Sys Chemo+ MTX (IVT)	1	1	12	40	1	NA

CNS = central nervous system; Sys Chemo = systemic chemotherapy; RT = radiation; WBR = whole brain radiation; MTX = methotrexate; IVT = intravitreal; NA = not applicable.
* Follow-up mentioned for entire cohort.

rence was 13 months (range: 9–24 months) and median time interval to death was 27 months (range: 7–57 months) with OS of 40% (185/462) (Fig. 5).

7. Discussion

7.1. *Reporting outcomes*

The method of reporting data for PCNSL-O is problematic. Relevant outcomes can be considered as primary, secondary, or tertiary outcomes.

i. Primary outcomes can be considered as complete response, refractory. or relapse. Complete response (CR) is no evidence of residual disease within the anterior eye chamber, vitreous cavity, or retina. Refractory disease may be defined as no modifications or <50% reduction of observable findings. Relapse is local disease recurrence after a defined period of CR. Another outcome measure, ocular recurrence-free survival, would more accurately capture both ocular response rates and time to local ocular recurrence. The concept of minimal residual disease (MRD) which represents subclinical levels of tumor burden present after treatment completion is used frequently in management of leukemias as it serves as an important prognostic disease marker and holds information about probability of future relapses and mortality [52]. A similar concept of MRD in treatment and staging of vitreoretinal lymphoma is recommended [57], as most of the patients at the end of treatment are left with residual vitreous opacities/debris that seems to be clinically inactive; however, without sure knowledge of the origin of those opacities, it is not entirely correct to label such a patient as a CR. Therefore, at minimum ophthalmologists should document the presence or absence of all vitreous opacities using a graded scale.
ii. Secondary outcome measure of progression free survival (PFS) may represent inter compartmental progression to previously uninvolved compartment such as ocular to CNS compartments or vice versa. In patients presenting with PCNSL-O, it would be more accurate and meaningful to report PFS (time to CNS progression) so as to adjust for lead time bias as the death in PCNSL-O is from CNS progression.
iii. The tertiary outcome measure of overall survival (OS) defined as the duration from diagnosis until death.

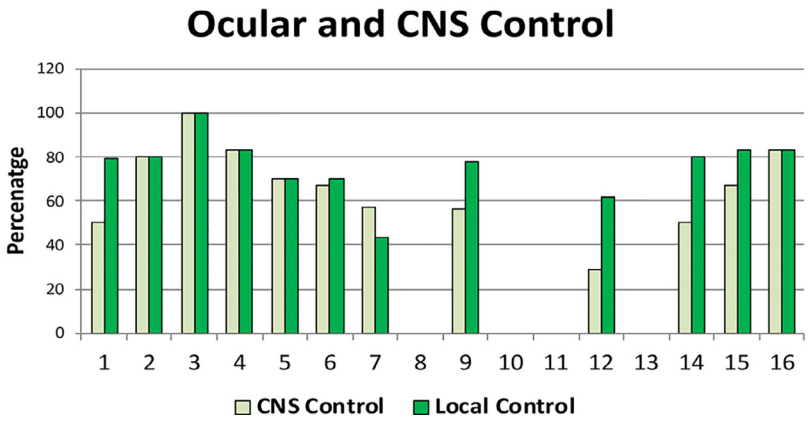

Fig. 4. – Ocular and CNS control in patients with concurrent involvement of the eye and CNS compartments (Group 2 studies; PCNSL-CNS/O).

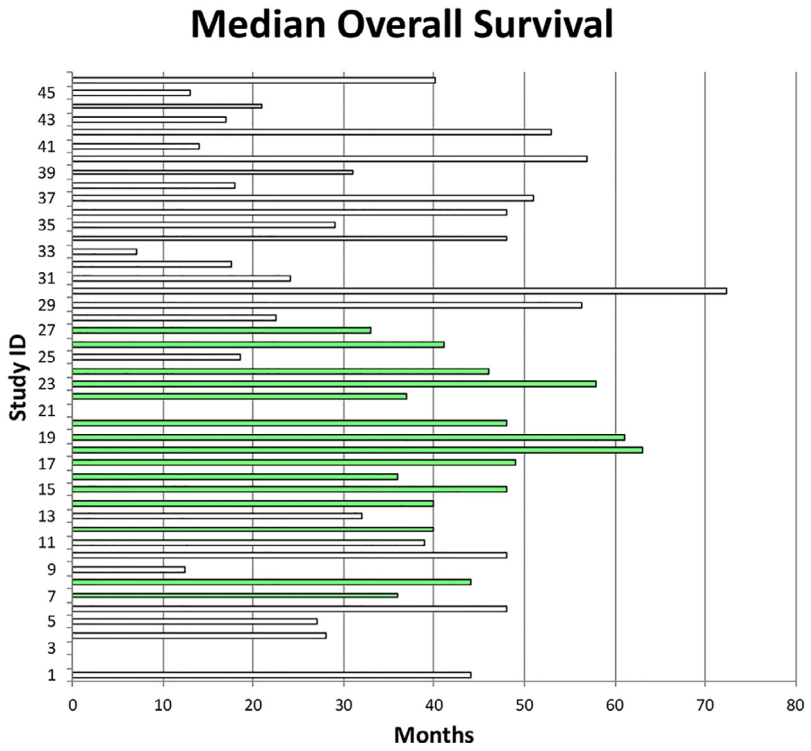

Fig. 5. – Median time to death. Comparison of Group 1 (PCNSL-O only at presentation: White) and Group 2 studies (PCNSL-CNS/O; concurrent involvement of the eye and CNS: Green).

7.2. *PCNSL-O: prognostic impact on overall survival in CNS lymphoma*

The prognosis reported as OS is thought to be worse in patients with PCNSL-O with CNS involvement compared to those with isolated CNS disease, attributable to increased disease burden, lymphoma involving a compartment that is difficult to treat, or a more aggressive histology associated with widespread dissemination. The results from a recent randomized phase III clinical trial indicated that intraocular involvement at diagnosis of PCNSL was an independent negative prognostic indicator for both PFS and OS [36]. Others have reported that the presence of ocular involvement does not appear to be an independent prognostic variable [2,17]. This includes the report from the International PCNSL Collaborative Group in which the median OS of patients with PCNSL with or without ocular involvement was similar [24]. This study, however, included only patients with concomitant ocular and CNS involvement at diagnosis. In a recent study, Zhuang and coworkers have shown that patients with intraocular disease had an inferior PFS, but similar OS, when compared to those without intraocular disease. Multiple factors may influence

OS such as heterogeneity of systemic treatments and the use of eye-specific therapy in some patients with intraocular involvement [65].

7.3. PCNSL-O: local ocular therapy

Before the advent of intravitreal chemotherapy, external beam radiotherapy (EBRT) was considered the first line therapy for intraocular lymphoma. Currently, it is used for intravitreal chemotherapy refractory or recurrent disease; however, it may still be used as a first line therapy in circumstances such as bilateral involvement, older age, or inability to return for frequent injections. Local radiation-related side effects include optic neuropathy, retinopathy, conjunctivitis, dry eye, cataract, and glaucoma .[32] Some studies have reported excellent local ocular control with EBRT as the primary treatment for PCNSL-O with acceptable toxicities [42,60].

Intravitreal chemotherapy is the most frequent first-line treatment for PCNSL-O. The most commonly used agent is MTX, followed by rituximab (RTX) [20,26,38,54]. The largest series of patients treated with intravitreal methotrexate is reported by Pe'er and coworkers where 122 eyes of 74 patients with PCNSL-O achieved remission in all of cases (100%) after a range of 2 to 16 intravitreal injections [55].

The total number of injections required to achieve complete response varied widely. The major drawback with multiple injections is local ocular side effects including rise in intraocular pressure, cataract, conjunctival hyperemia, keratopathy, and cystoid macular edema. The Israeli group used 400 micrograms in lower injection volume (0.05 mL), as opposed to the 0.10 mL volume that has more reflux and risk for keratopathy. The standard injection regimen, as reported by the original group from Israel [20], was a total of 25 injections in a year, whereas others have tried to achieve similar ocular control rates with fewer injections and lower incidence of keratopathy [64]. In a large study by Larkin and coworkers of 48 treated eyes, 31 (65%) demonstrated complete remission, 11 (23%) demonstrated partial remission, and 4 (8%) had no response. The median number of injections required to achieve complete remission was 3, with fewer instances of cataract and anterior uveitis [38]. Drug resistance following multiple injections of MTX is a concern [53]. Rituximab has been tried either alone or in combination with MTX in patients who had ocular recurrence or partial response to initial MTX injections [26,38].

Review of all Group 1A studies where local treatment (intravitreal chemotherapy ± ocular radiation) was the primary mode of treatment to the eye local control was achieved in 93 out of 128 patients (73%) and ocular relapse occurred in 35 out of 128 patients (27%) (Fig. 1 and Table 1).

A role of therapeutic complete vitrectomy, particularly in patients who are refractory to local and systemic chemotherapy, might be considered in special cases. The rationale for this procedure is to reduce the disease burden, thereby allowing improved penetration of systemic chemotherapy, and to eliminate the vitreous scaffold where the majority of lymphoma cells are located [6,61].

7.4. PCNSL-O: systemic therapy: local ocular effect

The role of high-dose MTX based systemic chemotherapy as first-line treatment in the management of PCNSL-O remains controversial [1,19]. Treatment outcomes of PCNSL-O have failed to limit the CNS progression of the disease and OS despite achieving good ocular control [24]. Considering pharmacokinetic studies showing micromolar concentrations of MTX present in both aqueous as well as vitreous humor following systemic administration [28], the role of systemic chemotherapy in management of PCNSL-O is worth exploring. Batchelor and coworkers observed an initial response to high dose systemic MTX for treatment of intraocular lymphoma, where 7 of 9 patients showed good response (6 complete responses and one partial response), whereas two patients had persistent disease despite achieving micromolar concentrations of MTX [5]. Given the high incidence of systemic neurotoxicity and risk of infections in patients receiving systemic chemotherapy; however, it is not widely accepted as the primary method of treatment in patients diagnosed with PCNSL-O. Currently, the role of systemic chemotherapy with/without local treatment is limited to refractory/relapsed cases of PCNSL-O or patients who have concurrent CNS involvement [47].

In those Group 1B studies where systemic treatment (systemic chemotherapy with or without whole brain radiation) was the primary mode of treatment, local ocular control was achieved in 21 out of 32 patients (66%) (Fig. 1 and Table 2).

Recently, a newer treatment regimen, "MATRix" (methotrexate, cytarabine, thiotepa, and rituximab), which includes MTX, RTX, and alkylating agents has shown to improve treatment outcomes and OS in patients with refractory/relapsed PCNSL and PCNSL-O [19]. Various novel immunotherapy drugs, including ibrutinib, lenalidomide, and temozolomide, are in clinical trials for refractory/relapsed PCNSL with/without ocular involvement [21,25].

7.5. PCNSL-O: local ocular therapy vs systemic therapy: effect on progression free survival

Review of all Group 1 studies treated with local ocular therapy (Group 1A: intravitreal chemotherapy ± ocular radiation), systemic treatment (Group 1B: systemic chemotherapy with or without whole brain radiation) or a combination of systemic treatment and local ocular therapy (Group 1C) revealed comparable median time to CNS progression of 28 months (range: 14–32 months), 29 months (range: 9–31 months), and 18 months (range: 8–46 months), respectively (Fig. 3).

7.6. PCNSL-O: local vs systemic therapy: effect on overall survival

Review of all Group 1 studies treated with local ocular therapy (Group 1A: intravitreal chemotherapy with or without ocular radiation) and systemic treatment (Group 1B: systemic chemotherapy with or without whole brain radiation) revealed comparable median time to death of 36 months (range 27–48 months) and 28 months (range: 13-44 months), respectively. The median time to death of 41 months (range: 19–72 months) was longest in patients treated with combination of systemic treatment and local ocular therapy (Group 1C). However, when

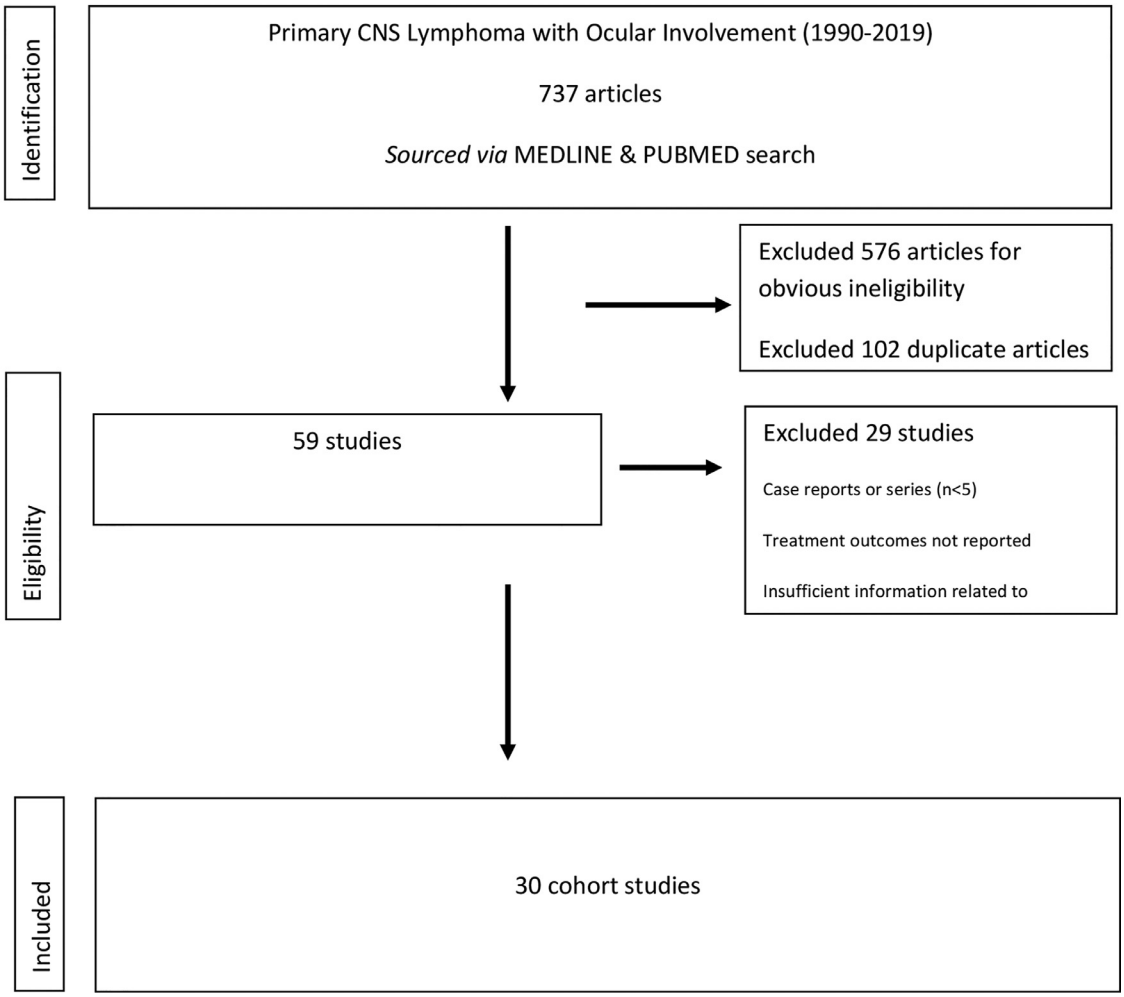

Fig. 6. – PRISMA flow diagram for systematic literature search and review.

adjusted for lead time bias, i.e., time to death from CNS involvement, the median time interval was comparable within Group 1 studies (Fig. 3) and also with Group 2 studies (Fig. 5); however, the worst OS (65%) was observed in those treated with combination therapy (Group 1C) compared to 67%, 88% in Groups 1A and 1B respectively.

7.7. *PCNSL-O: role of adjuvant chemotherapy*

Considering that 60%–90% of patients with PCNSL-O eventually progress to involve the CNS, the debate for administering adjuvant systemic chemotherapy in patients with PCNSL-O is justified [8,24]. A prospective one-arm clinical trial suggested that the combination of systemic chemotherapy and prophylactic reduced dose WBRT (23.8 Gy) may reduce the subsequent risk of CNS involvement, although the number of cases was small (11 patients) [33].

A 17-Center European Collaborative Study on PCNSL-O demonstrated that aggressive systemic chemotherapy for ocular disease alone did not change the rates of CNS progression when compared with local ocular therapy alone [48]. Follow-up period in the local therapy and systemic chemotherapy group (no ocular treatment) of 48 and 44 months was significantly shorter than 78 months of follow up in local ocular therapy plus systemic chemotherapy group. This may be one of the reasons why CNS progression may be high in the local plus systemic therapy group. Multiple regimens of systemic chemotherapy used over the long study span of more than 20 years may be another reason.

Several retrospective studies comparing local therapy alone versus a combination of systemic and local ocular therapy have not shown reduction in the rates of CNS progression [23,31]. On the contrary, large multicenter studies have shown lower rates of CNS progression in patients treated with systemic chemotherapy along with local ocular therapy (ocular radiation with or without intravitreal chemotherapy) [3,7,40,58]. In our review, patients for whom adjuvant systemic chemotherapy was administered along with local ocular therapy, the rate of CNS progression was lower (31%) as compared to patients in whom the systemic chemotherapy was started after CNS progression had already occurred (47%). In addition, the median OS was similar (24 months) in those who received adjuvant systemic treatment (Fig. 3; green bars) compared with those receiving systemic treatment after CNS progression (20 months) (Fig. 3, white bars).

8. Limitations

Several limitations are apparent in our analysis, and hence the results should be interpreted with caution. As the source data are largely derived from retrospective studies, there are inherent biases in the results. Despite our best efforts to sort through individual cases, errors in correct allocation to disease and treatment groups may exist. The timing and nature of chemotherapy in studies reviewed herein was variable. Similarly, there is variability in the radiation therapy intended for local control of the ocular disease or WBRT with some ocular exposure. Variability in follow up duration among studies adds another layer of uncertainty to the data interpretation. Most retrospective studies have defined PFS as time from onset of symptoms [48] or diagnosis to progression or relapse/death [3,16,23,24]. PFS defined in this way results in heterogenous outcomes such as local relapse, progression, and death making results amongst studies non-comparable. The lack of well-defined outcome measures, particularly those related to progression, further hampers valid comparisons between published studies.

9. Design for a multicenter, prospective randomized clinical trial

The current knowledge about the management of PCNSL-O lacks evidence-based randomized clinical trials and is currently based on single-arm trials and multicenter retrospective studies that results in variability for formulating treatment guidelines and lack of agreement on primary end points like PFS and OS [44]. The major limitation applied to all of the large, retrospective multicenter studies is of case selection bias depending on whether PCNSL-O or PCNSL disease is the presenting manifestation. Studies reported by neuro-oncologists suffer from unfavorable patient selection, mostly because many of the included patients had a diagnosis of PCNSL-O only after histopathological assessment of relapsing CNS lesions, whereas patients with PCNSL-O who do not experience CNS symptoms are often treated exclusively by ophthalmologists. Conversely, studies reported by ophthalmologists are biased in selecting predominantly those with PCNSL-O [23]. The largest reported PCNSL series are 2 clear examples of this selection bias: the CNS relapse rate was 60% at a median follow-up of 33 months in the series by neuro-oncologists [23], and 36% at 49 months in the series reported by ophthalmologists [48]. The other major limitation in all retrospective studies is the limited sample size in the subgroup of patients with various treatment regimens that thus lack statistical power. There is also a possibility of lead-time bias for patients with PCNSL-O. A multicenter collaborative international registry and clinical trials to explore current therapies and new target agents are required [15].

10. Conclusions

The ultimate goal of any treatment approach in patients of PCNSL/PCNSL-O is to achieve long term local control, prevent progression into other compartments, and improve overall survival; however, important factors like the age of the patient; involvement of ocular, CNS, or both compartments; treatment benefits, and risk of complications need to be considered before initiating the treatment. In patients older than 70 with low Karnofsky performance status scores and associated systemic comorbidities, the use of toxic systemic chemotherapy is not advisable, and the decision to pursue only palliative local ocular therapy is appropriate. In the absence of such constraints, however, the clinician should aim for curative and long-term remission strategies. This is even more important in patients with PCNSL-O where current treatment strategies are palliative with no apparent impact on OS and CNS progression. Therefore, we recommend a multidisciplinary approach, comprised of ophthalmologists, neuro-oncologists, pathologists, and radiation oncologists, for early diagnosis, staging, and treatment of the disease. In view of the increased likelihood of subsequent CNS progression in the absence of demonstrable CNS involvement at the time of PCNSL-O presentation, the role of adjuvant systemic chemotherapy needs to be explored in clinical trials.

11. Literature search

A thorough literature search including all publication on primary CNS lymphoma with ocular involvement published between 1990 through 2019 was performed (Fig. 6). We searched MEDLINE, PUBMED and clinicalTrials.gov databases in the English language using the following keywords: Non-Hodgkin lymphoma [MeSH] AND central + nervous + system AND eye/ocular/intraocular; Non-Hodgkin lymphoma [MeSH] AND CNS AND intraocular/ocular/eye; vitreoretinal + lymphoma; primary + vitreoretinal + lymphoma; primary + CNS + lymphoma AND eye/intraocular/ocular; primary + central + nervous + system + lymphoma AND ocular/intraocular/eye; reticulum + cell + sarcoma AND intraocular; microglioma AND central + nervous + system. There was no restriction on language, as long as the abstract was available in English.

Financial disclosure

None.

REFERENCES

1. Abrey LE, Batchelor TT, Ferreri AJ, et al. Report of an international workshop to standardize baseline evaluation and response criteria for primary CNS lymphoma. J Clin Oncol. 2005;23:5034–43.
2. 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;24:5711–15.
3. Akiyama H, Takase H, Kubo F, et al. High-dose methotrexate following intravitreal methotrexate administration in preventing central nervous system involvement of primary intraocular lymphoma. Cancer Sci. 2016;107:1458–64.

4. Aziz HA, Peereboom DM, Singh AD. Primary central nervous system lymphoma. Int Ophthalmol Clin. 2015;55:111–21.
5. Batchelor TT, Kolak G, Ciordia R, et al. High-dose methotrexate for intraocular lymphoma. Clin Cancer Res. 2003;9:711–15.
6. Bever GJ, Kim DJ, Afshar AR, et al. Therapeutic vitrectomy as an adjunct treatment to systemic chemotherapy for intraocular lymphoma. Retin Cases Brief Rep. 2020;14:116–19.
7. Castellino A, Pulido JS, Johnston PB, et al. Role of systemic high-dose methotrexate and combined approaches in the management of vitreoretinal lymphoma: a single center experience 1990-2018. Am J Hematol. 2019;94:291–8.
8. Chan CC, Rubenstein JL, Coupland SE, et al. Primary vitreoretinal lymphoma: a report from an International Primary Central Nervous System Lymphoma Collaborative Group symposium. Oncologist. 2011;16:1589–99.
9. Cheah CY, Milgrom S, Chihara D, et al. Intensive chemoimmunotherapy and bilateral globe irradiation as initial therapy for primary intraocular lymphoma. Neuro Oncol. 2016;18:575–81.
10. Cho BJ, Kim DY, Park UC, et al. Clinical features and treatment outcomes of vitreoretinal lymphoma according to its association with CNS lymphoma. Ocul Immunol Inflamm. 2018;26:365–71.
11. Coupland SE, Damato B. Understanding intraocular lymphomas. Clin Exp Ophthalmol. 2008;36:564–78.
12. Dalvin LA, Lim LS, Ancona-Lezama D, et al. Clinical features predictive of survival in patients with vitreoretinal lymphoma: analysis of 70 patients at a single ocular oncology center. Asia Pac J Ophthalmol (Phila). 2020;9:110–16.
13. de la Fuente MI, Alderuccio JP, Reis IM, et al. Bilateral radiation therapy followed by methotrexate-based chemotherapy for primary vitreoretinal lymphoma. Am J Hematol. 2019;94:455–60.
14. Farrall AL, Smith JR. Eye involvement in primary central nervous system lymphoma. Surv Ophthalmol. 2020;65:548–61.
15. Fend F, Ferreri AJ, Coupland SE. How we diagnose and treat vitreoretinal lymphoma. Br J Haematol. 2016;173:680–92.
16. Ferreri AJ, Blay JY, Reni M, et al. Relevance of intraocular involvement in the management of primary central nervous system lymphomas. Ann Oncol. 2002;13:531–8.
17. Ferreri AJ, Blay JY, Reni M, et al. Prognostic scoring system for primary CNS lymphomas: the International Extranodal Lymphoma Study Group experience. J Clin Oncol. 2003;21:266–72.
18. 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:e217–27.
19. Ferreri AJM. Therapy of primary CNS lymphoma: role of intensity, radiation, and novel agents. Hematology Am Soc Hematol Educ Program. 2017;2017(1):565–77 2017.
20. Frenkel S, Hendler K, Siegal T, et al. Intravitreal methotrexate for treating vitreoretinal lymphoma: 10 years of experience. Br J Ophthalmol. 2008;92:383–8.
21. 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)dagger. Ann Oncol. 2019;30:621–8.
22. Grimm KE, O'Malley DP. Aggressive B cell lymphomas in the 2017 revised WHO classification of tumors of hematopoietic and lymphoid tissues. Ann Diagn Pathol. 2019;38:6–10.
23. Grimm SA, Pulido JS, Jahnke K, et al. Primary intraocular lymphoma: an International Primary Central Nervous System Lymphoma Collaborative Group Report. Ann Oncol. 2007;18:1851–5.
24. Grimm SA, McCannel CA, Omuro AM, et al. Primary CNS lymphoma with intraocular involvement: International PCNSL Collaborative Group Report. Neurology. 2008;71:1355–60.
25. Grommes C, Tang SS, Wolfe J, et al. Phase 1b trial of an ibrutinib-based combination therapy in recurrent/refractory CNS lymphoma. Blood. 2019;133:436–45.
26. Hashida N, Ohguro N, Nishida K. Efficacy and complications of intravitreal rituximab injection for treating primary vitreoretinal lymphoma. Transl Vis Sci Technol. 2012;1(3):1.
27. Hashida N, Nakai K, Saitoh N, Nishida K. Association between ocular findings and preventive therapy with onset of central nervous system involvement in patients with primary vitreoretinal lymphoma. Graefes Arch Clin Exp Ophthalmol. 2014;252:687–93.
28. Henson JW, Yang J, Batchelor T. Intraocular methotrexate level after high-dose intravenous infusion. J Clin Oncol. 1999;17:1329.
29. Hochberg FH, Miller DC. Primary central nervous system lymphoma. J Neurosurg. 1988;68:835–53.
30. Hoffman PM, McKelvie P, Hall AJ, et al. Intraocular lymphoma: a series of 14 patients with clinicopathological features and treatment outcomes. Eye (Lond). 2003;17:513–21.
31. Hormigo A, Abrey L, Heinemann MH, DeAngelis LM. Ocular presentation of primary central nervous system lymphoma: diagnosis and treatment. Br J Haematol. 2004;126:202–8.
32. Jahnke K, Korfel A, Komm J, et al. Intraocular lymphoma 2000-2005: results of a retrospective multicentre trial. Graefes Arch Clin Exp Ophthalmol. 2006;244:663–9.
33. Kaburaki T, Taoka K, Matsuda J, et al. Combined intravitreal methotrexate and immunochemotherapy followed by reduced-dose whole-brain radiotherapy for newly diagnosed B-cell primary intraocular lymphoma. Br J Haematol. 2017;179:246–55.
34. Karakawa A, Taoka K, Kaburaki T, et al. Clinical features and outcomes of secondary intraocular lymphoma. Br J Haematol. 2018;183:668–71.
35. Klimova A, Heissigerova J, Rihova E, et al. Combined treatment of primary vitreoretinal lymphomas significantly prolongs the time to first relapse. Br J Ophthalmol. 2018;102:1579–85.
36. Kreher S, Strehlow F, Martus P, et al. Prognostic impact of intraocular involvement in primary CNS lymphoma: experience from the G-PCNSL-SG1 trial. Ann Hematol. 2015;94:409–14.
37. Kvopka M, Lake SR, Smith JR. Intraocular chemotherapy for vitreoretinal lymphoma: a review. Clin Exp Ophthalmol. 2020;48:240–8.
38. Larkin KL, Saboo US, Comer GM, et al. Use of intravitreal rituximab for treatment of vitreoretinal lymphoma. Br J Ophthalmol. 2014;98:99–103.
39. Lee S, Kim MJ, Kim JS, et al. Intraocular lymphoma in Korea: the Consortium for Improving Survival of Lymphoma (CISL) study. Blood Res. 2015;50:242–7.
40. Levasseur SD, Wittenberg LA, White VA. Vitreoretinal lymphoma: a 20-year review of incidence, clinical and cytologic features, treatment, and outcomes. JAMA Ophthalmol. 2013;131:50–5.
41. Ma WL, Hou HA, Hsu YJ, et al. Clinical outcomes of primary intraocular lymphoma patients treated with front-line systemic high-dose methotrexate and intravitreal methotrexate injection. Ann Hematol. 2016;95:593–601.
42. Mikami R, Nakayama H, Goto H, et al. Preliminary results of radiotherapy for primary intraocular non-Hodgkin lymphoma. Leuk Lymphoma. 2013;54:2181–4.

43. Mochizuki M, Singh AD. Epidemiology and clinical features of intraocular lymphoma. Ocul Immunol Inflamm. 2009;17:69–72.
44. Nguyen DT, Houillier C, Choquet S, et al. Primary oculocerebral lymphoma: MTX polychemotherapy alone on intraocular disease control. Ophthalmology. 2016;123:2047–50.
45. Ostrom QT, Gittleman H, Liao P, et al. CBTRUS Statistical Report: Primary brain and other central nervous system tumors diagnosed in the United States in 2010-2014. Neuro Oncol. 2017;19:v1–v88.
46. Pulczynski EJ, Kuittinen O, Erlanson M, et al. Successful change of treatment strategy in elderly patients with primary central nervous system lymphoma by de-escalating induction and introducing temozolomide maintenance: results from a phase II study by the Nordic Lymphoma Group. Haematologica. 2015;100:534–40.
47. Pulido JS, Johnston PB, Nowakowski GS, et al. The diagnosis and treatment of primary vitreoretinal lymphoma: a review. Int J Retina Vitreous. 2018;4:18.
48. Riemens A, Bromberg J, Touitou V, et al. Treatment strategies in primary vitreoretinal lymphoma: a 17-center European collaborative study. JAMA Ophthalmol. 2015;133:191–7.
49. Russell DS, Marshall AH, Smith FB. Microgliomatosis; a form of reticulosis affecting the brain. Brain. 1948;71:1–15.
50. Sagoo MS, Mehta H, Swampillai AJ, et al. Primary intraocular lymphoma. Surv Ophthalmol. 2014;59:503–16.
51. Salomao DR, Pulido JS, Johnston PB, et al. Vitreoretinal presentation of secondary large B-cell lymphoma in patients with systemic lymphoma. JAMA Ophthalmol. 2013;131:1151–8.
52. Schuurhuis GJ, Heuser M, Freeman S, et al. Minimal/measurable residual disease in AML: a consensus document from the European LeukemiaNet MRD Working Party. Blood. 2018;131:1275–91.
53. Sen HN, Chan CC, Byrnes G, et al. Intravitreal methotrexate resistance in a patient with primary intraocular lymphoma. Ocul Immunol Inflamm. 2008;16:29–33.
54. Smith JR, Rosenbaum JT, Wilson DJ, et al. Role of intravitreal methotrexate in the management of primary central nervous system lymphoma with ocular involvement. Ophthalmology. 2002;109:1709–16.
55. Smith JR, Pe'er J, Belfort RN, et al. Proceedings of the association for research in vision and ophthalmology and champalimaud foundation ocular oncogenesis and oncology conference. Transl Vis Sci Technol. 2019;8:9.
56. Sorger K. Recticulum cell sarcoma of the central nervous system. Can Med Assoc J. 1963;89:503–7.
57. Stacey AW, Pulido JS. The concept of minimal residual disease in the treatment and staging of vitreoretinal lymphoma. Retina. 2020;40:1213–14.
58. Stefanovic A, Davis J, Murray T, et al. Treatment of isolated primary intraocular lymphoma with high-dose methotrexate-based chemotherapy and binocular radiation therapy: a single-institution experience. Br J Haematol. 2010;151:103–6.
59. Taoka K, Yamamoto G, Kaburaki T, et al. Treatment of primary intraocular lymphoma with rituximab, high dose methotrexate, procarbazine, and vincristine chemotherapy, reduced whole-brain radiotherapy, and local ocular therapy. Br J Haematol. 2012;157:252–4.
60. Teckie S, Yahalom J. Primary intraocular lymphoma: treatment outcomes with ocular radiation therapy alone. Leuk Lymphoma. 2014;55:795–801.
61. Venkatesh P, Gogia V, Khanduja S, et al. Therapeutic vitrectomy for vitreal recurrence of intraocular lymphoma resistant to intravitreal methotrexate post systemic chemotherapy. J Cancer Res Ther. 2015;11:668.
62. Wallace DJ, Altemare CR, Shen DF, et al. Primary testicular and intraocular lymphomas: two case reports and a review of the literature. Surv Ophthalmol. 2006;51:41–50.
63. Wang CC, Carnevale J, Rubenstein JL. Progress in central nervous system lymphomas. Br J Haematol. 2014;166:311–25.
64. Zhou X, Zhou X, Shi H, et al. Reduced frequency of Intravitreal methotrexate injection lowers the risk of Keratopathy in Vitreoretinal lymphoma patients. BMC Ophthalmol. 2020;20:189.
65. Zhuang L, Lai J, Chen K, et al. Intraocular involvement is associated with a high risk of disease relapse in primary central nervous system lymphoma. Oncol Rep. 2019;41:397–404.