

## Research

## Original Investigation

# Treatment Strategies in Primary Vitreoretinal Lymphoma

## A 17-Center European Collaborative Study

Anjo Riemens, MD, PhD; Jacoline Bromberg, MD, PhD; Valerie Touitou, MD, PhD; Bianka Sobolewska, MD; Tom Missotten, MD; Seerp Baarsma, MD; Carel Hoyng, MD, PhD; Miguel Cordero-Coma, MD, PhD; Oren Tomkins-Netzer, MD, PhD; Anna Rozalski, MD; Ilknur Tugal-Tutkun, MD, PhD; Yan Guex-Crosier, MD, PhD; Leonoor I. Los, MD, PhD; Jan Geert Bollemeijer, MD; Andrew Nolan, MD, PhD; Joya Pawade, MD, PhD; Francois Willermain, MD, PhD; Bahram Bodaghi, MD, PhD; Ninette ten Dam-van Loon, MD; Andrew Dick, MD, PhD; Manfred Zierhut, MD, PhD; Susan Lightman, MD, PhD; Friederike Mackensen, MD, PhD; Alexandre Moulin, MD; Roel Erckens, MD, PhD; Barbara Wensing, MD, PhD; Phuc le Hoang, MD, PhD; Henk Lokhorst, MD, PhD; Aniki Rothova, MD, PhD

**IMPORTANCE** The best treatment option for primary vitreoretinal lymphoma (PVRL) without signs of central nervous system lymphoma (CNSL) involvement determined on magnetic resonance imaging or in cerebrospinal fluid is unknown.

**OBJECTIVE** To evaluate the outcomes of treatment regimens used for PVRL in the prevention of subsequent CNSL.

**DESIGN, SETTING, AND PARTICIPANTS** A retrospective cohort study was conducted at 17 referral ophthalmologic centers in Europe. We reviewed clinical, laboratory, and imaging data on 78 patients with PVRL who did not have CNSL on presentation between January 1, 1991, and December 31, 2012, with a focus on the incidence of CNS manifestations during the follow-up period.


**INTERVENTIONS** The term *extensive treatment* was used for various combinations of systemic and intrathecal chemotherapy, whole-brain radiotherapy, and peripheral blood stem cell transplantation. Therapy to prevent CNSL included ocular radiotherapy and/or ocular chemotherapy (group A, 31 patients), extensive systemic treatment (group B, 21 patients), and a combination of ocular and extensive treatment (group C, 23 patients); 3 patients did not receive treatment. A total of 40 patients received systemic chemotherapy.

**MAIN OUTCOMES AND MEASURES** Development of CNSL following the diagnosis of PVRL relative to the use or nonuse of systemic chemotherapy and other treatment regimens.

**RESULTS** Overall, CNSL developed in 28 of 78 patients (36%) at a median follow-up of 49 months. Specifically, CNSL developed in 10 of 31 (32%) in group A, 9 of 21 (43%) in group B, and 9 of 23 (39%) in group C. The 5-year cumulative survival rate was lower in patients with CNSL (35% [95% CI, 50% to 86%]) than in patients without CNSL (68% [95% CI, 19% to 51%];  $P = .003$ ) and was similar among all treatment groups ( $P = .10$ ). Adverse systemic effects occurred in 9 of 40 (23%) patients receiving systemic chemotherapy; the most common of these effects was acute renal failure.

**CONCLUSIONS AND RELEVANCE** In the present series of patients with isolated PVRL, the use of systemic chemotherapy was not proven to prevent CNSL and was associated with more severe adverse effects compared with local treatment.

*JAMA Ophthalmol.* doi:10.1001/jamaophthalmol.2014.4755  
Published online November 20, 2014.

 Supplemental content at [jamaophthalmology.com](http://jamaophthalmology.com)

**Author Affiliations:** Author affiliations are listed at the end of this article.

**Corresponding Author:** Anjo Riemens, MD, PhD, Department of Ophthalmology, University Medical Centre Utrecht, PO Box 85500, 3508 GA Utrecht, the Netherlands ([j.a.riemens@umcutrecht.nl](mailto:j.a.riemens@umcutrecht.nl)).

Opinions are divided on how to treat primary intraocular lymphoma in the absence of central nervous system lymphoma (CNSL). Primary intraocular lymphoma is an uncommon cancer, manifesting first in the retina and/or vitreous in 1 or both eyes and is classified as primary vitreoretinal lymphoma (PVRL).<sup>1,2</sup> Primary vitreoretinal lymphoma presents predominantly as diffuse, large B-cell lymphoma (DLBCL) and has a high association with CNS manifestations and occasionally with testicular manifestations.<sup>3-6</sup> Central nervous system lymphoma has been reported<sup>1</sup> to develop in approximately 65% to 90% of patients with PVRL and determines the survival of the PVRL-affected patients. The median overall survival of patients with PVRL is reported<sup>7</sup> to be 58 months.

The best therapeutic approach for patients with isolated PVRL without documented CNS manifestations has not achieved consensus, particularly because of a paucity of outcome data. There are 2 distinct approaches to therapy for patients with isolated PVRL. The first approach consists of aggressive treatment regimens, such as those used for CNSL, including high-dose methotrexate-based chemotherapy with or without intrathecal treatment and/or whole brain radiotherapy.<sup>8-13</sup> This treatment is aimed at both local control of PVRL and prevention of subsequent CNSL manifestations. The second approach consists of local ocular treatments. Systemic treatment, such as that used for CNSL, with intravenous and sometimes intrathecal chemotherapy may be associated with severe systemic adverse effects; local ocular treatment, such as ocular radiotherapy and intravitreal chemotherapy with methotrexate and/or rituximab, lacks systemic adverse effects. The aggressive first approach to treatment is based on the presumption that the patients already have developed subclinical lymphoma in the CNS, which cannot as yet be substantiated by magnetic resonance imaging or cerebrospinal fluid examination. The second approach, using local ocular therapy, is aimed at eradication of lymphoma cells in the eye but has no effect on possible subclinical manifestations elsewhere. Limited evidence is available on the efficacy of both approaches. We retrospectively evaluated the outcomes of diverse treatment regimens used for PVRL in 78 patients from 17 European referral ophthalmologic centers, with a focus on the incidence of CNS manifestations during the follow-up period.

## Methods

### Patients

The study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional ethical committee of the University Medical Center Utrecht, which concluded that the Dutch Medical Research Involving Human Subjects Act did not apply and written informed consent was not needed. This retrospective study included immunocompetent patients without human immunodeficiency virus with isolated PVRL (all classified as DLBCL) between January 1, 1991, and December 31, 2012, from all university medical centers as

well as the Rotterdam Eye Hospital in the Netherlands, Jules-Gonin Eye Hospital in Switzerland, and Bristol Eye Hospital and Moorfields Eye Hospital in England, as well as the departments of ophthalmology from Tübingen and Heidelberg University Hospitals in Germany, Istanbul University in Turkey, Pitié-Salpêtrière Hospital in France, University Hospital of León in Spain, and Centre Hospitalier Universitaire St-Pierre and Brugmann in Belgium. All data were reviewed for completeness and consistency.

For inclusion into the study, the minimal duration of follow-up needed to be at least 1 year after the patient's first presentation to an ophthalmologist. The last month of follow-up was July 2013. Patients with previous systemic lymphoma were excluded. Isolated PVRL was diagnosed by ocular tissue biopsy, whereas cerebrospinal fluid examination and imaging of the brain were used to exclude CNSL at the time of PVRL diagnosis or during the diagnostic process.

We collected clinical data on a total of 104 patients with PVRL; 26 of these patients were excluded (17 because the diagnosis of PVRL was confirmed when CNS manifestations had already developed and 9 because of insufficient data). The remaining 78 patients were included in our analysis (Table 1).

The following data were collected: age, sex, date of onset of ocular symptoms, date of diagnosis of PVRL, type and date of treatment, all relevant ocular and systemic treatment complications, date of PVRL relapse, date of manifestation of CNSL, survival (years), and cause of death. The term *extensive treatment* was used for various combinations of systemic and intrathecal chemotherapy, whole-brain radiotherapy, and peripheral blood stem cell transplantation.

### Statistical Analysis

The primary outcome of this retrospective study was the development of CNSL and its association with the type of PVRL treatment used. Secondary end points were relapse of PVRL, survival, and cause of death. The data were analyzed using SPSS, version 20 (SPSS Inc).

Differences in the distribution of individual features among treatment groups were analyzed by means of the  $\chi^2$  test or Fisher exact test for categorical variables and the Mann-Whitney test or Kruskal-Wallis test for continuous, nonparametric variables. Survival was defined as the time from first symptoms of PVRL to death or CNSL, or the time to the last follow-up assessment. Survival rates were calculated using the Kaplan-Meier method, and differences were compared with the use of the log-rank test.

## Results

### Patient Characteristics

The patient characteristics are reported in Table 1. The median age at the time of PVRL diagnosis was 58 years (range, 39-86 years) and 34 of 78 patients (44%) were male. At onset, PVRL was bilateral in 45 (58%) patients. The median duration from symptom onset to diagnosis of PVRL was 10 months (range, 0-63 months). The diagnosis of isolated PVRL was confirmed by ocular tissue biopsy in all 78 patients. The median

Table 1. Patient Demographics and Clinical Characteristics

Characteristic	All Cases (N = 78)	No Treatment (n = 3)	Group A <sup>a</sup> (n = 31)	Group B <sup>b</sup> (n = 21)	Group C <sup>c</sup> (n = 23)
Age, median (range), y	58 (39-86)	81 (55-83)	65 (41-86)	59 (43-73)	62 (39-83)
Male sex, No. (%)	34 (44)	2 (67)	12 (39)	8 (38)	12 (52)
Interval between onset of symptoms to diagnosis, median (range), mo	10 (0-63)	11 (9-19)	10 (1-42)	10 (2-41)	7 (0-63)
Bilateral PVRL, No. (%)	45 (58)	3 (100)	14 (45)	12 (57)	16 (70)
CNSL development, No. (%)	28 (36)	0	10 (32)	9 (43)	9 (39)
Interval between first manifestations of PVRL and CNSL, median (range), mo	29 (7-133)	Not available	28 (7-66)	29 (20-133)	46 (11-126)
Recurrence of vitreoretinal lymphoma during follow-up, No. (%)	17 (22)	0	4 (13)	6 (29)	7 (30)
Follow-up from first presentation to ophthalmologist, median (range), mo	49 (15-246)	34 (17-119)	48 (15-260)	44 (17-133)	78 (17-133)

Abbreviations: CNSL, central nervous system lymphoma; PVRL, primary vitreoretinal lymphoma.

<sup>a</sup> Included patients who received only ocular treatment; 2 patients also received CHOP (cyclophosphamide, hydroxydaunorubicin, Oncovin [vincristine], and prednisone), but this was not considered systemic treatment because it is not effective for CNSL.

<sup>b</sup> Included patients who received extensive systemic treatment.

<sup>c</sup> Included patients who received a combination of ocular and extensive treatment.

follow-up time after the first presentation to the ophthalmologist was 49 months (range, 15-246 months).

Of all 78 patients, 28 individuals (36%) subsequently developed CNSL and 23 (29%) patients died during the follow-up period. Patients with and those without CNSL manifestations were similar in male to female ratio and bilateral occurrence of PVRL ( $P = .34$  and  $P = .94$ , respectively). Age was similar between the patients who developed CNSL and those who did not develop CNSL (median age, 65 years; range, 41-86 years [95% CI, 60.1-65.6]; vs 59 years; range, 39-80 years [95% CI, 53.5-61.1];  $P = .15$ ). The follow-up time from first presentation to the ophthalmologist of patients with CNSL and those without CNSL was also similar (median 74 months; range, 9-122 months [95% CI, 49.3-76.5]; vs 42 months; range, 3-246 months [95% CI, 49.1-73.4];  $P = .34$ ). The CNSL manifestations were similar in patients included before 2005 compared with those included after 2005 ( $P = .28$ ).

### Therapeutic Approaches

Treatment regimens were principally classified into 3 categories: ocular radiotherapy and/or ocular chemotherapy (group A), extensive systemic treatment (group B), and a combination of ocular and extensive systemic treatment (group C). Three additional patients did not receive treatment (Table 2).

Ocular treatment included local radiotherapy and intravitreal application of methotrexate sodium and/or rituximab. Extensive treatment regimens are listed in Table 2 and consisted of combinations of different regimens of systemic and intrathecal chemotherapy (n = 40), whole-brain radiotherapy (n = 6), and peripheral blood stem cell transplantation (n = 4). Intrathecal treatment was always given in combination with intravenous treatment. CHOP (cyclophosphamide, hydroxydaunorubicin, Oncovin [vincristine], and prednisone) chemotherapy was not considered systemic treatment because it is not effective for CNSL (Table 2).<sup>15-17</sup>

The patient characteristics per treatment group are summarized in Table 1. Of the 78 included patients 31 individuals (40%) received only ocular treatment. These patients received radiotherapy (16 [52%]), intravitreal methotrexate and/or rituximab (12 [39%]), or a combination of radiotherapy and intravitreal chemotherapy (2 [6%]); 1 (3%) of the 31 affected eyes was enucleated. Additionally, 3 (4%) patients did not receive treatment initially for PVRL, owing to the preference of the patient (n = 2) or physician (n = 1).

### Patient Characteristics in Specific Treatment Groups

The 3 treatment groups were similar in diverse variables including sex ( $P = .54$ ), age ( $P = .07$ ), duration from the onset of symptoms to diagnosis of PVRL ( $P = .65$ ), interval from the first presentation of PVRL to the ophthalmologist to the onset of CNSL ( $P = .50$ ), and duration of follow-up ( $P = .24$ ). Furthermore, the duration of follow-up was similar for patients receiving ocular radiotherapy and chemotherapy ( $P = .18$ ).

### Effect of PVRL Treatment on CNSL Manifestations

Central nervous system lymphoma developed in 28 of 78 patients (36%): 10 (32%) patients in group A, 9 (43%) in group B, and 9 (39%) in group C ( $P = .76$ ) (Table 1). Similar rates of CNSL manifestations were observed when group A was compared with solely systemic chemotherapy and when group A was compared with group B ( $P = .53$  and  $P = .45$ , respectively). In addition, development of CNSL manifestations was similar in patients who received ocular chemotherapy and ocular radiotherapy ( $P = .23$ ). When patients receiving intrathecal therapy were not included in the extensive treatment group, the results of development of CNS manifestations did not change. Central nervous system lymphoma developed in 14 of 30 patients (47%) who received 6 courses of intravenous methotrexate and 4 of 14 (28%) patients receiving other extensive treatment modalities.

**Table 2. Types of Treatment Given for Primary Vitreoretinal Lymphoma in 78 Patients**

Type of Treatment	Patients, No. (%)
No treatment	3 (4)
Group A <sup>a</sup>	31 (40)
Ocular radiotherapy	16 (52)
Intravitreal methotrexate sodium and/or rituximab	12 (39)
Intravitreal methotrexate	9 (29)
Intravitreal rituximab	2 (6)
Intravitreal methotrexate and rituximab	1 (3)
Ocular radiotherapy and intravitreal chemotherapy	2 (6)
Enucleation	1 (3)
Group B <sup>b</sup>	21 (27)
Group C <sup>c</sup>	23 (29)
Intravitreal and intravenous chemotherapy	4 (17)
Intravitreal and intrathecal chemotherapy	1 (4)
Intravitreal and intravenous chemotherapy, cerebral radiotherapy	1 (4)
Intravitreal and intravenous chemotherapy, PBSCT	1 (4)
Ocular radiotherapy, intravenous chemotherapy	6 (26)
Ocular radiotherapy, intrathecal chemotherapy	3 (13)
Ocular and cerebral radiotherapy	2 (9)
Ocular radiotherapy, intravenous and intrathecal chemotherapy	2 (9)
Ocular and cerebral radiotherapy, intravenous chemotherapy	2 (9)
Ocular and cerebral radiotherapy, intravenous and intrathecal chemotherapy	1 (4)
Intravenous treatment	40 (51)
CHOP	2 (5)
High-dose methotrexate based	16 (40)
Cytarabine based	4 (10)
Methotrexate and cytarabine	5 (13)
Rituximab	1 (3)
Rituximab and cytarabine	2 (5)
Rituximab, methotrexate, and cytarabine	3 (8)
Rituximab, methotrexate, cytarabine, and PBSCT	4 (10)
COPADEM protocol <sup>d</sup>	3 (8)
Intrathecal treatment	10 (13)
Methotrexate	7 (70)
Methotrexate and cytarabine	3 (30)
Cerebral treatment	6 (8)
Radiotherapy	6 (100)

Abbreviations: CHOP, cyclophosphamide, hydroxydaunorubicin, Oncovin (vincristine), and prednisone; CNS, central nervous system; COPADEM, cyclophosphamide, vincristine, prednisolone, doxorubicin, hydrocortisone, folic acid, and methotrexate; PBSCT, peripheral blood stem cell transplantation.

<sup>a</sup> The ocular treatment group included 2 patients who also received CHOP and were considered as not receiving systemic treatment.

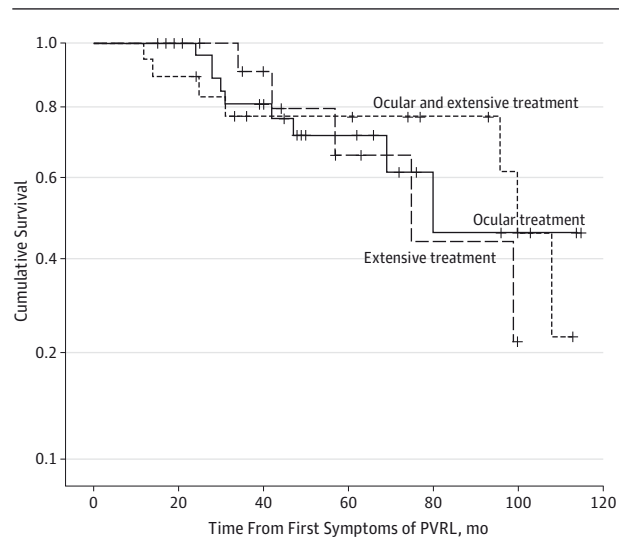
<sup>b</sup> Extensive treatment only.

<sup>c</sup> Combination of ocular and extensive treatment.

<sup>d</sup> Reported in the study of Blay et al.<sup>14</sup>

Kaplan-Meier 10-year survival curves (calculated from the first presentation with PVRL symptoms to the ophthalmologist to the development of CNS manifestations) were similar when the 3 treatment groups were compared ( $P = .91$ ) (Figure 1).

**Figure 1. Kaplan-Meier 10-Year Survival Estimates in 78 Patients With Primary Vitreoretinal Lymphoma (PVRL)**



Central nervous system lymphoma was the outcome. Survival estimates did not differ significantly between the treatment groups ( $P = .91$ ).

Similar outcomes were observed between the specific treatment groups (ocular treatment only vs extensive treatment only,  $P = .96$ ; ocular treatment only vs a combination of extensive and ocular treatment,  $P = .56$ ; and extensive treatment only vs a combination of systemic chemotherapy and ocular treatment,  $P = .80$ ).

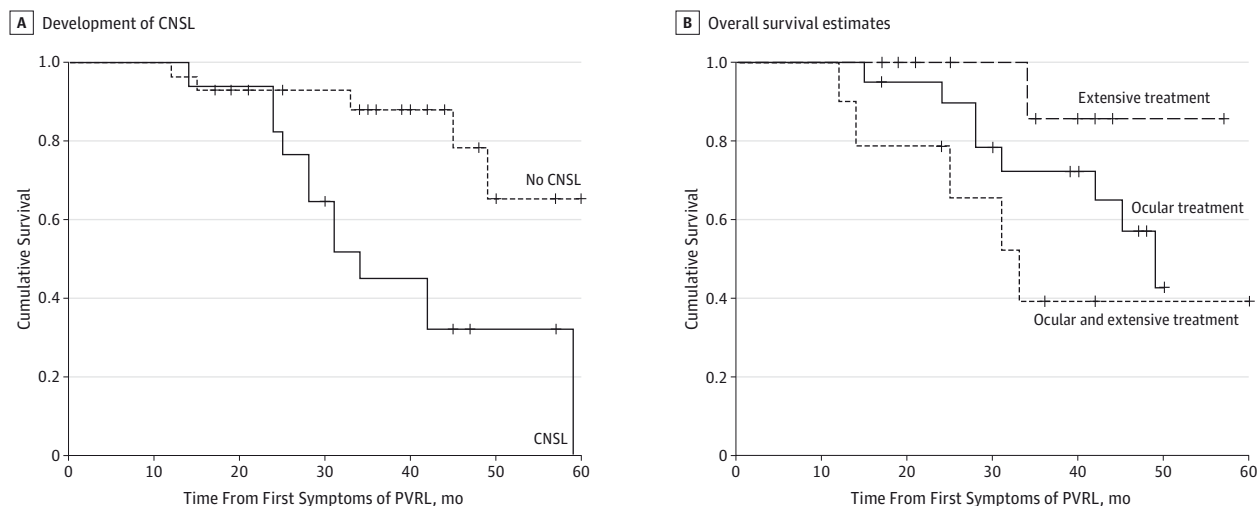
### Ocular Relapse of PVRL

Ocular relapse of PVRL occurred in 17 of 78 patients (22%) within 12 to 131 months after the first symptoms of PVRL (95% CI, 24.9 to 66.7; median, 28 months). The risk of ocular relapse was similar among the specific treatment groups ( $P = .53$ ). The incidence of ocular relapse in patients in group A was not significantly different from that in patients who received only systemic chemotherapy ( $P = .31$ ). A similar incidence of ocular relapse also was observed between patients who received solely ocular chemotherapy and those who underwent ocular radiotherapy ( $P = .60$ ).

### Treatment Complications

Systemic chemotherapy was used in 40 patients (51%) (23 who were given extensive treatment only and 17 who received a combination of ocular and extensive treatment). One or more complications developed in 9 of 40 (23%) patients who received systemic chemotherapy (eTable 1 in the Supplement) with acute renal failure being the most common (4 [10%]). Ocular radiotherapy was administered in 34 eyes. One or more complications occurred in 10 of these patients (29%) (eTable 1 in the Supplement). Intravitreal chemotherapy was given to 19 patients and complications developed in 5 of these individuals (26%) (eTable 1 in the Supplement). Radiotherapy-associated encephalopathy did not develop in patients who received treatment for PVRL with whole-brain radiotherapy ( $n = 6$ ) during a median follow-up time of 46 months (range, 3-134 months).

Figure 2. Kaplan-Meier 5-Year Overall Survival for Primary Vitreoretinal Lymphoma (PVRL)



A, Patients who developed central nervous system lymphoma (CNSL) and patients who did not develop CNSL ( $P = .003$ ). B, Overall survival estimates following treatment for PVRL by treatment group ( $P = .10$ ).

### Cause of Death

Of 78 patients, 23 individuals (29%) died; 7 (30%) patients from CNSL, 3 (13%) from indirect complications of CNSL, including complications of treatment, and 3 (13%) patients died of lymphoma-unrelated causes. Data were not available on 10 patients. The death rates between the 3 treatment groups (untreated patients were not included) were similar ( $P = .07$ ). Central nervous system lymphoma was highly associated with death (14 of 28 patients [50%] who developed CNSL vs 9 of 50 patients [18%] who did not develop CNSL;  $P = .003$ ). The causes of death per treatment group are displayed in eTable 2 in the Supplement.

### Overall Survival and Progression-Free Survival

The median overall survival from presentation to the ophthalmologist with PVRL until death was 44 months (range, 11-113 months) in patients who did not develop CNSL and 34 months (range, 12-131 months) in patients who developed CNSL (95% CI, -32.9 to 58.7;  $P = .43$ ). The 5-year cumulative survival rate was lower in patients with CNSL (35% [95% CI, 50% to 86%]) than in patients without CNSL (68% [95% CI, 19% to 51%];  $P = .003$ ) (Figure 2A) and was similar among all treatment groups ( $P = .10$ ) (Figure 2B). The median CNSL-free survival was 47 months (95% CI, 46.8 to 61.8; range, 7-152 months) in all patients who received treatment. Overall and progression-free survival were similar among the 3 treatment groups ( $P = .74$  and  $P = .15$ , respectively).

## Discussion

Our study illustrates the lack of a consistent treatment approach for patients with PVRL, and the data provide current outcomes of a similar prevalence of CNSL manifestations among patients with PVRL treated with various ocular and ex-

tensive treatment regimens. In our retrospective study the benefit of extensive treatment strategies in patients with PVRL without CNS involvement could not be substantiated in a median follow-up duration of 49 months.

To our knowledge, the present study represents one of the largest contemporary series on PVRL outcomes and is particularly pertinent because it presents a homogeneous group of patients with PVRL without signs of CNS involvement. The previously reported<sup>1</sup> prevalence of CNSL (60%-95%) secondary to PVRL appears to be higher than that in the present series, which might in part be explained by the fact that our study excluded all patients with positive cerebrospinal fluid findings as well as patients in whom the diagnosis of PVRL was confirmed after CNSL had developed. Inclusion of these patients would have biased the study toward a higher frequency of CNSL. Grimm et al<sup>7</sup> conducted a retrospective study including 83 patients with PVRL from 16 centers in 7 countries. In contrast to our study, the classification of PVRL in their series included 11 patients with cerebrospinal fluid that contained lymphoma cells. Furthermore, the median follow-up in the study by Grimm et al was 32 months and no minimal duration of follow-up was used as an inclusion criterion. In line with our findings, initial treatment regimens in the study by Grimm et al varied widely and consisted of local therapy in 28% of the patients (which included ocular radiotherapy and chemotherapy), extensive therapy in 64% of the patients (systemic chemotherapy and whole brain radiotherapy), and no treatment in 7% of the patients. Central nervous system lymphoma developed in 47% of all included patients in the Grimm et al series and local therapy without systemic treatment or brain radiotherapy did not increase the risk of brain relapse compared with an intensive treatment regimen ( $P = .4$ ). These results are in accordance with our findings and indicate that ocular treatment of PVRL was not associated with an excess of CNS manifestations compared with more aggressive (sys-



temic) treatment regimens. Furthermore, our patients were selected from ophthalmology departments rather than neuro-oncology departments as in the series by Grimm et al, eliminating possible selection bias in favor of CNSL development. Most published studies<sup>8,18,19</sup> on local PVRL treatment focus on its effect on PVRL and do not have sufficient follow-up data to report on the incidence of subsequent CNS manifestations.

Of the patients in the present study who received only ocular radiotherapy, 29% developed adverse effects. However, our series included patients from 1991 onward. In the early 1990s radiotherapy treatment regimens differed in intensity compared with more recent strategies.<sup>20</sup> At present, radiotherapy is of lower intensity (36 Gy), therapy is fractionated, and although dry eyes during treatment and cataract after radiotherapy develop regularly, retinopathy is uncommon.<sup>20,21</sup> Teckie and Yahalom<sup>19</sup> indicated in their series that no serious adverse effects of radiotherapy developed and countered the claim that permanent visual loss might occur.

More recently, intraocular chemotherapy has gained popularity and includes diverse regimens of methotrexate and rituximab. Adverse effects of administration of these agents occur only within the eye and include hyperemia, keratopathy, cataract, glaucoma, iridocyclitis, vitreous hemorrhage, retinal detachment, maculopathy, and endophthalmitis.<sup>22-25</sup> Proof of superiority of intraocular chemotherapy vs radiotherapy is lacking because no comparative studies have been performed. The advantages of local chemotherapy over intravenous treatment are higher levels of chemotherapeutic agents in the eye and the lack of systemic, possibly life-threatening, adverse effects.

To date, the pathogenesis of VRL with CNSL is not known and the mechanism of its origin and subsequent metastasis has not been elucidated. It is not known whether CNS and ocular manifestations occur independently or whether this type of lymphoma originates at one site, subsequently spreading to other sites. Our results, as well as the frequent bilateral involvement in VRL and the long intervals between manifestations of large B-cell lymphoma at different immune-privileged sites, favor the possibility of a multifocal origin.<sup>26</sup> In addition, spreading from one site to others might concurrently develop. The multifocal origin of lymphoma at various immune-privileged sites has been ascribed<sup>27</sup> to an ineffective immune response to lymphoma cells at these protected sites. Booman et al<sup>28</sup> studied the genomic alteration of DLBCL of the

testes and CNSL and showed that DLBCL in these 2 locations exhibits both shared and site-specific genetic alterations. They concluded that these findings underline the concept of immune-privileged site lymphoma but that CNS and testes lymphoma do not form a single entity.

Our study has the shortcomings of a retrospective design. The reasoning for the choice of treatment in individual patients could not be determined. However the different hospitals tended to use the same treatment modalities for all of their patients. Because the patient characteristics did not differ significantly between treatment groups and the choice of treatment was based primarily on which treatment option was conventional per treatment center, the bias seems to be limited. Survival analysis of the 3 treatment subgroups showed a possible trend in favor of patients who received extensive treatment and an analysis using a larger series may disclose conclusions that differ from the current data. The log-rank of this Kaplan-Meier 10-year survival curve was similar when the 3 treatment groups were compared; however, the proportional hazard assumption was not met, and therefore the log-rank was biased. In our study, the rate of local recurrences was similar for local and systemic treatment regimens. The intravenous chemotherapy regimens differed widely and illustrate the lack of a systematic approach even within this treatment approach. Peripheral blood stem cell transplantation has shown promising results,<sup>29-31</sup> but the number of patients in our study was too limited to evaluate this treatment. Our results relate to the group as a whole and do not exclude a possible beneficial effect of a specific treatment strategy, which emphasizes the need for international cooperation and prospective studies.

## Conclusions

The development of CNS manifestations after PVRL in our study was similar in patients with PVRL who received local ocular treatments compared with patients who received systemic treatments. Specific regimens, such as peripheral blood stem cell transplantation and novel chemotherapies, should be systematically analyzed because these regimens might have greater value than local treatment. In the present series, the additional benefit of systemic chemotherapy could not be proven and was associated with a greater number of and more severe adverse effects compared with local therapy.

### ARTICLE INFORMATION

**Submitted for Publication:** July 3, 2014; final revision received September 29, 2014; accepted October 2, 2014.

**Published Online:** November 20, 2014.  
doi:10.1001/jamaophthalmol.2014.4755.

**Author Affiliations:** Department of Ophthalmology, University Medical Centre Utrecht, Utrecht, the Netherlands (Riemens, ten Dam-van Loon); Department of Neuro-Oncology, Erasmus Medical Centre, Rotterdam, the Netherlands (Bromberg); Department of Ophthalmology, Pitié-Salpêtrière Hospital, Paris, France (Touitou,

Bodaghi, le Hoang); Department of Ophthalmology, Tübingen University Hospital, Tübingen, Germany (Sobolewska, Zierhut); Rotterdam Eye Hospital, Rotterdam, the Netherlands (Missotten, Baarsma); Department of Ophthalmology, Radboud Medical Centre, Nijmegen, the Netherlands (Hoyng); Department of Ophthalmology, Uveitis Unit, University Hospital of León, León, Spain (Cordero-Coma); Moorfields Eye Hospital, London, England (Tomkins-Netzer, Lightman); Department of Ophthalmology, Heidelberg University Hospital, Heidelberg, Germany (Rozalski, Mackensen); Department of Ophthalmology, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey

(Tugal-Tutkun); Department of Ophthalmology, University of Lausanne, Jules-Gonin Eye Hospital, Lausanne, Switzerland (Guex-Crosier, Moulin); Department of Ophthalmology, University Medical Center, Groningen, the Netherlands (Los); W. J. Kolff Institute, Graduate School of Medical Sciences, University of Groningen, Groningen, the Netherlands (Los); Department of Ophthalmology, Leiden University Medical Centre, Leiden, the Netherlands (Bollemeyer); Bristol Eye Hospital, Bristol, England (Nolan, Pawade, Dick); Department of Ophthalmology, Centre Hospitalier Universitaire St-Pierre and Brugmann, Université Libre de Bruxelles, Bruxelles, Belgium (Willermain);

Department of Ophthalmology, University Medical Centre, Maastricht, the Netherlands (Erckens); Department of Ophthalmology, Amsterdam Medical Centre, Amsterdam, the Netherlands (Wensing); Department of Hematology, University Medical Centre Utrecht, Utrecht, the Netherlands (Lokhorst); Department of Ophthalmology, Erasmus Medical Centre, Rotterdam, the Netherlands (Rothova).

**Author Contributions:** Dr Riemens had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Riemens, Bromberg, Baarsma, Cordero-Coma, Wensing, Lokhorst.

**Acquisition, analysis, or interpretation of data:** All authors.

**Drafting of the manuscript:** Riemens, Bromberg, Willermain, Erckens.

**Critical revision of the manuscript for important intellectual content:** Bromberg, Touitou, Sobolewska, Missotten, Baarsma, Hoyng, Cordero-Coma, Tomkins-Netzer, Rozalski, Tugal-Tutkun, Guex-Crosier, Los, Bollemeijer, Nolan, Pawade, Bodaghi, ten Dam-van Loon, Dick, Zierhut, Lightman, Mackensen, Moulin, Wensing, le Hoang, Lokhorst.

**Statistical analysis:** Riemens, Tomkins-Netzer.

**Obtained funding:** Riemens.

**Administrative, technical, or material support:** Touitou, Sobolewska, Baarsma, Cordero-Coma, Bollemeijer, Pawade, ten Dam-van Loon, Dick, Erckens, Wensing.

**Study supervision:** Missotten, Hoyng, Guex-Crosier, Moulin, Lokhorst.

**Conflict of Interest Disclosures:** All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

**Funding/Support:** Funding was provided by Dr PF Fischer Stichting, Landelijke stichting voor Blinden en Slechtzienden, Stichting Nederlands Oogheelkundig Onderzoek, Stichting Blindenpenning, Gelderse Blinden Stichting, the Netherlands.

**Role of the Funder/Sponsor:** The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

**Additional Contributions:** Alfredo Adán, MD, PhD (Hospital Clinic, Barcelona, Spain), Carme Macià, MD (Hospital Vall d'Hebrón, Barcelona, Spain), Manuel Díaz-Llopis, MD, PhD (Hospital La Fe, Valencia, Spain), and José Luis Olea, MD, PhD (Hospital Son Espases, Mallorca, Spain), contributed data on the Spanish cohort of patients of this study. They did not receive financial compensation.

## REFERENCES

- Chan C-C, 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(11):1589-1599.
- Coupland SE. Molecular pathology of lymphoma. *Eye (Lond)*. 2013;27(2):180-189.
- Davis JW, Moriarty RP, Schlossberg SM, Schellhammer PF. Bilateral testicular lymphoma treated with chemotherapy and radiation without orchiectomy: complete response relapsed at 52 months in the vitreous humor. *Urology*. 2001;57(3):555.
- Pe'er J, Rowe JM, Frenkel S, Dann EJ. Testicular lymphoma, intraocular (vitreoretinal) lymphoma, and brain lymphoma: involvement of three immunoprivileged sites in one patient. *Am J Hematol*. 2010;85(8):631-633.
- Aliferis K, Chan CC, Donati G, Baglivo E. Intraocular lymphoma following a primary testicular lymphoma in remission for 10 years. *Int Ophthalmol*. 2008;28(6):439-440.
- 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(1):41-50.
- 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(11):1851-1855.
- Hormigo A, Abrey L, Heinemann M-H, DeAngelis LM. Ocular presentation of primary central nervous system lymphoma: diagnosis and treatment. *Br J Haematol*. 2004;126(2):202-208.
- Batchelor TT, Kolak G, Ciordia R, Foster CS, Henson JW. High-dose methotrexate for intraocular lymphoma. *Clin Cancer Res*. 2003;9(2):711-715.
- Jahnke K, Thiel E, Abrey LE, Neuwelt EA, Korfel A. Diagnosis and management of primary intraocular lymphoma: an update. *Clin Ophthalmol*. 2007;1(3):247-258.
- 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(6):663-669.
- Vosganian GS, Boisot S, Hartmann KI, et al. Primary intraocular lymphoma: a review. *J Neurooncol*. 2011;105(2):127-134.
- Plowman PN, Taylor A, Jackson AS, Lightman S, Pavesio C. Optimal therapy of primary ocular lymphoma. *Clin Oncol (R Coll Radiol)*. 2002;14(6):521.
- Blay JY, Bouhour D, Carrie C, et al. The C5R protocol: a regimen of high-dose chemotherapy and radiotherapy in primary cerebral non-Hodgkin's lymphoma of patients with no known cause of immunosuppression. *Blood*. 1995;86(8):2922-2929.
- Mead GM, Bleeher NM, Gregor A, et al. A medical research council randomized trial in patients with primary cerebral non-Hodgkin lymphoma: cerebral radiotherapy with and without cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy. *Cancer*. 2000;89(6):1359-1370.
- Deckert M, Engert A, Brück W, et al. Modern concepts in the biology, diagnosis, differential diagnosis and treatment of primary central nervous system lymphoma. *Leukemia*. 2011;25(12):1797-1807.
- Ferreri AJM. How I treat primary CNS lymphoma. *Blood*. 2011;118(3):510-522.
- Berenbom A, Davila RM, Lin HS, Harbour JW. Treatment outcomes for primary intraocular lymphoma: implications for external beam radiotherapy. *Eye (Lond)*. 2007;21(9):1198-1201.
- Teckie S, Yahalom J. Primary intraocular lymphoma: treatment outcomes with ocular radiation therapy alone. *Leuk Lymphoma*. 2014;55(4):795-801.
- Durkin SR, Roos D, Higgs B, Casson RJ, Selva D. Ophthalmic and adnexal complications of radiotherapy. *Acta Ophthalmol Scand*. 2007;85(3):240-250.
- Monroe AT, Bhandare N, Morris CG, Mendenhall WM. Preventing radiation retinopathy with hyperfractionation. *Int J Radiat Oncol Biol Phys*. 2005;61(3):856-864.
- 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.
- Levy-Clarke GA, Chan CC, Nussenblatt RB. Diagnosis and management of primary intraocular lymphoma. *Hematol Oncol Clin North Am*. 2005;19(4):739-749.
- 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(9):1709-1716.
- Frenkel S, Hendlar K, Siegal T, Shalom E, Pe'er J. Intravitreal methotrexate for treating vitreoretinal lymphoma: 10 years of experience. *Br J Ophthalmol*. 2008;92(3):383-388.
- Riemens A, Missotten T, Baarsma S, et al. Diffuse large B-cell lymphoma in immunoprivileged sites: association of vitreoretinal, testicular and central nervous system lymphoma. *Acta Ophthalmol*. 2014;92(2):e159-e160. doi:10.1111/aos.12236.
- Riemersma SA, Jordanova ES, Schop RF, et al. Extensive genetic alterations of the HLA region, including homozygous deletions of HLA class II genes in B-cell lymphomas arising in immune-privileged sites. *Blood*. 2000;96(10):3569-3577.
- Booman M, Suzhaki K, Rosenwald A, et al. Genomic alterations and gene expression in primary diffuse large B-cell lymphomas of immune-privileged sites: the importance of apoptosis and immunomodulatory pathways. *J Pathol*. 2008;216(2):209-217.
- Soussain C, Hoang-Xuan K, Levy V. Results of intensive chemotherapy followed by hematopoietic stem-cell rescue in 22 patients with refractory or recurrent primary CNS lymphoma or intraocular lymphoma [in French]. *Bull Cancer*. 2004;91(2):189-192.
- Soussain C, Choquet S, Fourme E, et al. Intensive chemotherapy with thiotepa, busulfan and cyclophosphamide and hematopoietic stem cell rescue in relapsed or refractory primary central nervous system lymphoma and intraocular lymphoma: a retrospective study of 79 cases. *Haematologica*. 2012;97(11):1751-1756.
- Abrey LE, Moskowitz CH, Mason WP, et al. Intensive methotrexate and cytarabine followed by high-dose chemotherapy with autologous stem-cell rescue in patients with newly diagnosed primary CNS lymphoma: an intent-to-treat analysis. *J Clin Oncol*. 2003;21(22):4151-4156.