AMERICAN ACADEMY OF OPHTHALMOLOGY®

Presentation, Diagnostic Testing and Initial Treatment of Vitreoretinal Lymphoma

*The International Vitreoretinal B-Cell Lymphoma Registry Investigator Group**

Purpose: Vitreoretinal lymphoma is a malignancy with high mortality. Incidence is rare, and there is a lack of medical evidence to direct management. This work describes presentation, diagnostic testing, and first treatment approaches in a recently diagnosed and treated patient cohort.

Design: Clinical registry-based observational study.

Subjects: Forty-eight women and 32 men (age range, 32–91 years; median age, 64 years) diagnosed with vitreoretinal lymphoma.

Methods: An international network of ophthalmologists reported clinical features and management of patients presenting with vitreoretinal lymphoma between January 1, 2020 and December 31, 2022 via an electronic platform.

Main Outcome Measures: Visual acuity at presentation (logarithm of the minimum angle of resolution [logMAR]); basis for diagnosis; first treatment.

Results: Vitreoretinal lymphoma was bilateral at presentation in 65% of patients (n = 52) and an initial site of lymphoma in 78% (n = 62). Of 127 eyes with lymphoma at presentation, vitreous was involved in 89% (n = 113) and was the only involved eye tissue in 40% (n = 51), and retina was involved in 46% (n = 59) and was the only involved eye tissue in 9% (n = 11). Median logMAR visual acuity of the worse-seeing eye was 0.50. The lymphoma was diagnosed from ocular specimens in 80% of patients (64/80), usually vitreous (57/64 patients [89%]), and on other clinical information in 20% of patients (16/80). Cellular studies were performed on ocular specimens from 59 of 64 patients (92%), most often cytology. Tumor gene analysis was used in 21 of 64 patients (33%), and cytokine assays were used in 13 of 64 patients (20%). For 76 patients (95%), treatment was initiated within 6 months of diagnosis and included ocular (38/76 [48%]), extraocular (17/76 [21%]), and ocular plus extraocular (21/76 [26%]) approaches. Intravitreal methotrexate was the most common ocular treatment (83/87 eyes [95%]).

Conclusions: Using data collected from 80 patients diagnosed with vitreoretinal lymphoma since 2020, we show that visual impairment is common, and that management often involves diagnosis by cellular tests and treatment with intravitreal chemotherapy.

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Vitreoretinal non-Hodgkin B-cell lymphoma is a rare, intraocular, malignant tumor that is categorized as a subset of primary central nervous system (CNS) lymphoma.[1,2] Based on data from the United States National Cancer Institute Surveillance, Epidemiology, and End Results Database, and the Australian Cancer Database, 5-year survival has been estimated at 41% and 30%, with median survival of 3.2 and 2.1 years, respectively.[3,4] The usual cause of cancer-related death is progression of established or secondary brain involvement. Multiple factors contribute to the poor survival outcome of vitreoretinal lymphoma,[5] including delays in diagnosis due to the similarity in appearance to uveitis, plus diagnostic and treatment challenges.[6,7] Critically, there is a limited body of medical evidence on which to base the management approach.[8]

A major reason for the paucity of medical evidence around managing vitreoretinal lymphoma is the low incidence of the cancer, estimated at 1 per 2 million person-years across studies from different countries.[9] The largest patient series from single institutions or small groups of centers have been collected over several decades.[10–12] Across this time period, treatments for primary CNS lymphoma have changed substantially, including the introduction of targeted chemotherapeutic and immunotherapeutic drugs, innovations that reduce irradiation dosing, and the use of autologous stem-cell transplantation as consolidation treatment.[13–15]

Independent groups have advocated for a clinical registry to improve outcomes of vitreoretinal lymphoma.[8,16,17] Apart from the potential to provide current information about a large number of patients, registry data reflect the total patient population with diverse demographics,

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comorbidities, and drug use, as well as health care systems and providers.[18] In response to this call, we recently launched an international clinical registry for vitreoretinal B-cell lymphoma.[19] Drawing from the registry, this report describes the presentation, and diagnostic and initial treatment approaches, in a group of 80 patients diagnosed with vitreoretinal lymphoma from 2020 onward.

Methods

An international network of ophthalmologists provided data on the clinical features and management of adult patients (aged ≥ 18 years), who had presented with new-onset or recurrent vitreoretinal B-cell lymphoma between January 1, 2020, and December 31, 2022, via an internet-based platform (date of censor: April 12, 2023). This was an observational study of current clinical practice. Patients were identified by their ophthalmologists using processes appropriate to the individual ophthalmologist's clinical record keeping. Data were entered retrospectively. All clinical decisions were at the discretion of the treating ophthalmologist, including form of diagnostic test and methods, and type of treatment and combinations. The study, termed the International Vitreoretinal B-Cell Lymphoma Registry,[19] was approved in Australia by the Human Research Ethics Committee of the Royal Australian and New Zealand College of Ophthalmologists (protocol number: 109.20). The approval included a waiver of consent to collect non-identifiable patient data. In other countries, an equivalent research ethics body reviewed the study protocol and approved participation, including any consent process, in accordance with local regulations and requirements. The research adhered to the tenets of the Declaration of Helsinki.

The clinical data collected for this report were: demographics including gender, age at diagnosis, and human immunodeficiency virus infection status; mode of presentation, presenting ocular tissue involvement, and initial site of lymphoma; visual acuity at presentation; diagnostic tissue sampling and testing; and initial ocular and extraocular treatment, defined as the first treatment given during the first 6 months after diagnosis. Age at diagnosis was dichotomized as < 60 years, or ≥ 60 years, consistent with the typical median onset age of 60 years for vitreoretinal lymphoma,[1] and because age ≥ 60 years is a negative prognostic factor for non-Hodgkin's lymphoma, including within the CNS.[20,21]

Visual acuity was entered in one of 4 formats (i.e., Snellen feet, Snellen meter, Snellen decimal, and logarithm of the minimum angle of resolution [logMAR]) to limit stenographic errors,[22] and was converted to logMAR for reporting. For logMAR visual acuity > 1.00, a value of 1.20 was assigned for the purpose of calculations. Visual acuity categories of impairment (by eye) and burden (by patient) followed the recommendations of others.[23–25] Visual impairment of an involved eye was categorized in logMAR as: none (≤ 0.30); mild to severe (≥ 0.40); moderate to severe (≥ 0.60); and severe (≥ 1.00). Visual burden to the individual was categorized in logMAR as: functional (≤ 0.30); mild (0.40−0.50); moderate (0.60−0.90); and severe (≥ 1.00). For bilateral vitreoretinal lymphoma, visual burden was judged on the basis of visual acuity in the worse-seeing eye.

The data were exported from the online platform in Microsoft .xlsx file format and prepared and analyzed using IBM SPSS Statistics (version 28), Microsoft Excel (version 23), and GraphPad Prism (version 7). Continuous variables were expressed as the median (quartile range), and categorical data were expressed as frequencies and percentages of the cohort. Age-dichotomized categorical observations were assessed for independence using the Pearson chi-square test with Yates continuity correction. A P value ≤ 0.05 was taken to indicate a statistically significant difference between groups.

Results

Clinical data from 80 persons (132 eyes) with vitreoretinal lymphoma were reported by ophthalmologists from 11 countries. For the majority of patients (n = 68 [85%]), this represented their first presentation with vitreoretinal lymphoma. Demographics and characteristics of the cohort are presented in Table 1. Women were represented slightly more than men (men:women = 1:1.5). Patient age at diagnosis ranged from 32 to 91 years, with most (n = 55 [69%]) aged ≥ 60 years.

In approximately two thirds of patients (n = 52 [65%]), the vitreoretinal lymphoma presented bilaterally, and this was similar for those aged < 60 years and those aged ≥ 60 years (P > 0.05). The tumor was bilateral in 62% (n = 42) of the 68 patients with new-onset disease and in 83% (n = 10) of the 12 patients with recurrent disease. Within the latter group, 5 patients had a recurrence in a single eye or delayed involvement of their second eye; thus, of 132 involved eyes, 127 eyes (96%) had active vitreoretinal lymphoma at presentation, and 5 eyes (4%) had a history of vitreoretinal lymphoma that was in remission at presentation. The eye was one of the initial sites of lymphoma in 78% (62/80) of patients and was the sole initial site of lymphoma in 69% (n = 55). This pattern of involvement did not differ between the 2 age groups (P > 0.05). Before the onset of vitreoretinal lymphoma, 18% (n = 14) and 5% (n = 4) of the group had been diagnosed with extraocular CNS and systemic lymphoma, respectively. Overall, at presentation to the ophthalmologist, 40% of patients (n = 32) had concurrent extraocular lymphoma or lymphoma in remission, most commonly at another site within the CNS (n = 28 [35%]) and particularly the brain (n = 26 [33%]), but also outside the CNS (n = 5 [6%]), including ovary, breast, skin, and retroperitoneum.

Patterns of ocular tissue involvement with lymphoma are shown in Figure 1. Ninety percent of the 80 patients (n = 72) presented with lymphoma in the vitreous, and this was bilateral in 41 (51%). Approximately one half of the cohort (n = 43 [54%]) had lymphoma in the retina, involving both eyes in 16 (20%). In the 127 eyes with active disease, vitreous was the most common site (n = 113 [89%]) and the single involved site in 40% (n = 51). It was uncommon for retina to be the only site (n = 11 [9%]), and optic nerve and/or anterior segment involvement was always associated with lymphoma at another site. Approximately one half of the 113 eyes (n = 62 [55%]) with vitreous involvement had lymphoma in ≥ 1 other site, most often the retina (total: n = 45 [40%]; retina alone: n = 26 [23%]). The prevalence of eyes with single versus multiple ocular tissue involvements was the same dichotomized by age group (P > 0.05).

Visual acuities at presentation were used to quantify visual impairment by eye and visual burden by individual, as presented in Table 2. Across all involved eyes (n = 132), median visual acuity was 0.30, with the quartile range spanning none to moderate visual impairment, and 24% of eyes having severe visual impairment. Median visual acuity of the worse-seeing eye of each patient was

Table 1. Characteristics of Patients with Vitreoretinal Lymphona

Characteristic	Number (%)* or Median (Quartile Range)
Gender	
Man	32 (40%)
Woman	48 (60%)
HIV status	
Negative	64 (80%)
Positive	1 (1%)
Unknown	15 (19%)
Age at diagnosis, yrs	
All ages	64 (56–71)
< 60	25 (31%)
≥ 60	55 (69%)
Presentation	
New onset	68 (85%)
Unilateral	26 (33%)
Bilateral	42 (53%)
Recurrent	12 (15%)
Unilateral − same eye	2 (3%)
Bilateral − 1 eye	5 (6%)
Bilateral − both eyes	5 (6%)
Status at presentation (N = 132 eyes)	
Active disease	127 (96%)
In remission	5 (4%)
Initial site of lymphoma	
Eye	55 (69%)
Eye + brain	6 (8%)
Eye + leptomeninges (including CSF) + non-CNS site	1 (1%)
Brain	14 (18%)
Non-CNS site	4 (5%)
Nonocular CNS lymphoma and/or non-CNS lymphoma at presentation†	32 (40%)
Nonocular CNS lymphoma	28 (35%)
Active disease	20 (25%)
Brain	14 (18%)
Brain + leptomeninges (including CSF)	3 (4%)
Brain + spinal cord	1 (1%)
Leptomeninges (including CSF)	2 (3%)
In remission	8 (10%)
Brain	8 (10%)
Non-CNS lymphoma	5 (6%)
Active disease	3 (4%)
In remission	2 (3%)

CNS = central nervous system; CSF = cerebrospinal fluid; HIV = human immunodeficiency virus; N = number.
N = 80 persons unless otherwise specified.
*Percentages have been rounded and may not equal 100.
†One patient had both nonocular CNS lymphoma and non-CNS lymphoma at presentation.

0.50, with 39 persons (49%) having moderate or severe visual burden. For the 52 people with bilateral involvement, 42 (81%) had no visual impairment in 1 eye, and 23 (44%) had none in both eyes. The proportion of patients classified as having functional vision was 92% and 77% for those aged < 60 years and ≥ 60 years, respectively.

The basis for diagnosing vitreoretinal lymphoma is reported in Table 3 and Figure 2. For the majority of patients (n = 64/80 [80%]), diagnostic investigations were performed on ocular specimens, usually a single tissue (n = 55/64 [86%]). Vitreous was the most analyzed tissue (n = 57/64 [89%]) and was the sole tissue tested for 84% of this subgroup (n = 48/57). Retinochoroidal tissue alone was evaluated in 7 patients and was combined with vitreous in another 2 patients (n = 9/64 [14%]). Aqueous was tested in parallel with vitreous in 7 patients (11% of 64). In the remainder of the patient cohort (n = 16 [20%]), other clinical information was used to reach the diagnosis, including a history of CNS lymphoma, and brain biopsy and imaging.

Overall, 126 tests were performed across the 64 patients whose vitreoretinal lymphoma was diagnosed by ocular tissue analysis. In 59 patients (92% of 64), the lymphoma was diagnosed by cellular studies. Cytological assessment of the vitreous was most common (n = 43/59 [73%]), representing 34% of all ocular tissue tests (n = 43/126), and commonly combined with flow cytometry (n = 16/43 [37%]). Assessment of retinochoroidal tissue was far less common (n = 9/59 patients [15%]) and was conducted largely by histopathology (n = 8/9 [89%]). Tumor gene analysis was used in 21 patients (33% of 64). Polymerase chain reaction for the *IGH* gene rearrangement and for the *MYD88* gene mutation were performed individually or in combination, approximately equally,

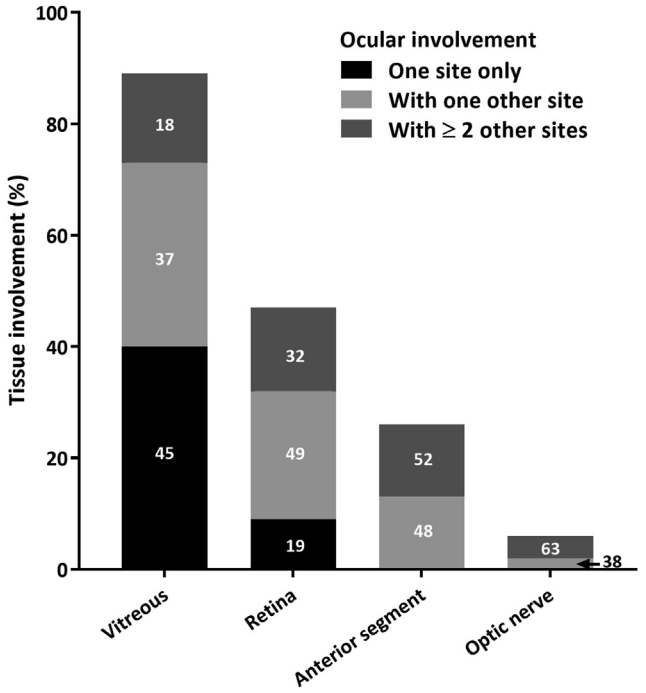

Figure 1. Ocular involvement at presentation as percent of all eyes with vitreoretinal lymphoma (n = 127) in the vitreous (n = 113), retina (n = 59), anterior segment (n = 33), and optic nerve (n = 8). Black = single site; light gray = in association with one other site; dark gray = in association with ≥ 2 other sites (annotated as percent for each site).

representing 21% of all ocular tissue tests (n = 27/126), and often on vitreous (n = 22/27 [81%]). Cytokine assays were performed for 13 patients (20% of 64), usually measuring the interleukin-10:interleukin-6 ratio (n = 12/13 [92%]) and mostly for vitreous samples (n = 10/13 [77%]).

Two thirds of the 64 patients (n = 41 [64%]) had ≥ 2 diagnostic investigations on ocular tissue, which did not differ by the age groups dichotomized at 60 years ($P > 0.05$). For the 23 patients (36% of 64) diagnosed on the basis of a single ocular tissue test, most tests were performed on vitreous (n = 19/23 [83%]), with cytology being the most common test (n = 12 [52%]), followed by flow cytometry (n = 6 [26%]), and tumor gene analysis (n = 2 [9%]). Three people (13% of 23) were diagnosed with lymphoma based on histopathology of a retinochoroidal tissue biopsy alone.

A large majority of patients (n = 76 [95%]) began treatment within 6 months of diagnosis with vitreoretinal lymphoma, as presented in Table 4. The 4 patients (5%) who did not receive treatment were all aged ≥ 60 years with new-onset vitreoretinal lymphoma, and they were not treated because they had not continued in follow-up, declined treatment, or remained under observation after clinical improvement following vitrectomy.

Most patients (n = 59/76 [78%]) were treated initially with ocular therapies, and the proportion of treated individuals was similar between groups dichotomized by age group (76% of persons aged < 60 years, 78% of persons aged ≥ 60 years; $P > 0.05$). Totals of 22 patients (79% of 28) with unilateral lymphoma and 37 patients (71% of 52) with bilateral lymphoma had ocular treatments; among the 52 patients with bilateral disease, 9 (17%) had unilateral treatment and 28 (54%) had bilateral treatment. Overall, 87 eyes received ocular-directed treatment, most commonly intravitreal chemotherapy (n = 83/87 [95%]). Methotrexate (400 μg as standard) was administered to all 83 eyes (100%), and rituximab (1 mg as standard) was coadministered to 5 eyes (6%). Four eyes (5% of 87) had ocular radiotherapy as the sole local therapy.

One half of the patients (n = 38/76 [50%]) received initial extraocular treatment, of whom 21 (55% of 38) also received ocular therapies. There was no difference between those aged < 60 years and those aged ≥ 60 years ($P > 0.05$). The group included 11 patients (29% of 38) with unilateral disease and 27 patients (71% of 38) with bilateral disease. The most common extraocular treatment was systemic chemotherapy, given to 97% of these patients (n = 37/38) and usually not combined with other therapies (n = 29/37 [78%]).

Discussion

The rare incidence of vitreoretinal B-cell lymphoma has been a major challenge for clinical studies. To date, large data sets have taken multiple decades to generate. To address the problem, we established an international registry, allowing us to report clinical characteristics at presentation, and diagnostic and initial treatment approaches in a sizable group of 80 patients, who have presented with active new-onset or recurrent cancer within the past 3 years. This patient cohort presented expected demographics: a slight predominance of women (1.5-fold higher prevalence than men), and almost 70% aged ≥ 60 years. In keeping with the ophthalmological perspective of this research, the initial site of the lymphoma was the eye in the majority of patients, with other CNS sites involved in one third at presentation or previously. In less than 10% of patients there was an associated systemic lymphoma, which has been reported by other groups.[26,27] Vitreoretinal lymphoma was bilateral in around two thirds of patients. The posterior segment was always involved, and the most common patterns of ocular tissue involvement were vitreous alone, and vitreous plus retina, accounting for approximately 40% and 35% of presentations, respectively.

There is a common perception that visual acuity is maintained in patients with vitreoretinal lymphoma; indeed, a visual acuity better than would be expected for the severity of vitreous cellular infiltration and haze is said to be a clue to this diagnosis.[2] Although the data are limited, comprehensive descriptions of visual acuity suggest otherwise. One study conducted across 2 ophthalmology services in Israel, involving patients who were targeted for intravitreal methotrexate over a 20-year period, provided a detailed description of logMAR visual acuity in 86 involved eyes:[10] at presentation, 20% had visual acuity of < 0.3; 56% had visual acuity between 0.3 and 1.0; and 24% had visual acuity > 1.0. Visual impairment was also evident in our patient cohort. Approximately one half of eyes had visual acuities measuring ≥ 0.40, and one quarter had vision of ≥ 1.00. Overall, 60% had some degree of visual burden, defined on impairment in 1 eye, and 20% had visual burden defined on impairment in both eyes. Because patients with vitreoretinal lymphoma are mostly older

Table 2. Vision at Presentation with Vitreoretinal Lymphoma

Variable	Number (%)* or Median (Quartile Range)
All eyes with lymphoma	132
Visual acuity (logMAR)†	0.30 (0.10–0.90)
Visual impairment (logMAR)	
None (≤ 0.30)	74 (56%)
Mild to severe (≥ 0.40)	58 (44%)
Moderate to severe (≥ 0.60)	44 (33%)
Severe (≥ 1.00)	32 (24%)
All patients	80
Visual acuity: worse-seeing eye (logMAR)†	0.50 (0.20–1.00)
Visual burden: worse-seeing eye (logMAR)†	
Functional (≤ 0.30)	32 (40%)
Mild (0.40–0.50)	9 (11%)
Moderate (0.60–0.90)	10 (13%)
Severe (≥ 1.00)	29 (36%)
Patients with bilateral lymphoma	52
Visual burden: better-seeing eye/worse-seeing eye (logMAR)	
Better-seeing eye functional (≤ 0.30)	
Functional/functional	23 (44%)
Functional/mild	4 (8%)
Functional/moderate	2 (4%)
Functional/severe	13 (25%)
Better-seeing eye mild (0.40–0.50)	
Mild/mild	1 (2%)
Mild/moderate	3 (6%)
Mild/severe	1 (2%)
Better-seeing eye moderate (0.60–0.90)	
Moderate/moderate	1 (2%)
Moderate/severe	1 (2%)
Better-seeing eye severe (≥ 1.00)	
Severe/severe	3 (6%)

logMAR = logarithm of the minimum angle of resolution.
N = 80 persons, unless otherwise specified.
*Percentages have been rounded and may not equal 100.
†Eyes without vitreoretinal lymphoma are not included.

Table 3. Basis for Diagnosis of Vitreoretinal Lymphoma

Variable	Number (%)*
Ocular specimen	64 (80%)
One tissue	55 (69%)
Vitreous	48 (60%)
Retina-choroid	7 (9%)
Two tissues	9 (11%)
Vitreous + aqueous	7 (9%)
Vitreous + retina-choroid	2 (3%)
Diagnostic test†	
Vitreous	57 (71%)
Cytology	43 (54%)
Flow cytometry	25 (31%)
Tumor gene PCR	16 (20%)
Cytokine analysis	11 (14%)
NGS	3 (4%)
Retina-choroid‡	9 (11%)
Histopathology	8 (10%)
Immunohistochemistry	3 (4%)
Tumor gene PCR	1 (1%)
Cytology	1 (1%)
Aqueous	7 (9%)
Tumor gene PCR	4 (5%)
Cytokine analysis	3 (4%)
Indirect evidence§	16 (20%)
CNS specimen	3 (4%)
CNS specimen + brain MRI	3 (4%)
Brain MRI	5 (6%)
History of CNS lymphoma	3 (4%)
Other	2 (3%)

CNS = central nervous system; MRI = magnetic resonance imaging; NGS = next generation sequencing; PCR = polymerase chain reaction.
N = 80 persons.
*Percentages have been rounded and may not equal 100.
†Tumor gene PCR refers to *IGH* gene arrangements and *MYD88* gene mutation. Cytokine analysis refers to interleukin (IL)-10 level and IL-10:IL-6 ratio.
‡Retina-choroid includes subretinal fluid specimen, tested by cytology and PCR.
§CNS specimen includes brain and/or cerebrospinal fluid.

adults, ocular comorbidities are likely to compound any visual disability.[28]

The potential pitfalls in establishing a diagnosis of vitreoretinal lymphoma are multi-fold. The gold standard for diagnosis is cytopathological identification of malignant lymphocytes.[29] Within the vitreous, viable tumor cells are fragile and often scant, and the thick consistency of the vitreous can interfere with processing. Specialist cytopathology assessment, not available in many ophthalmology centers, is another hurdle. Recent consensus guidelines have encouraged the use of molecular analyses as adjunctive diagnostic investigations,[30,31] and there have been calls to move beyond cytology to ensure patients are treated in a timely fashion.[32,33] For most patients, the malignancy was diagnosed by analysis of ocular fluid specimens, which involved cellular studies in the large majority; however, tumor genetic analysis was used to achieve a diagnosis for one third. The latter included polymerase chain reaction tests for the *IGH* gene rearrangement and for the *MYD88* gene mutation. Detection of the *MYD88* gene mutation is possible with relatively small amounts of tumor DNA, meaning it may be identified in aqueous.[34,35] Several patients were diagnosed through next generation sequencing, recently described for this cancer.[36] Ophthalmic imaging, particularly optical coherence tomography, is providing options for more confident clinical assessment.[37] We did not systematically collect information in this area.

Decision-making around treatment of vitreoretinal lymphoma is not straightforward. There are numerous treatment approaches described in the literature and these have changed over time, including local ocular, and extraocular which is sometimes referred to as "extensive:" the report of 78 patients treated at 17 European centers over a period of 22 years described over 25 different treatment regimens.[11] Several issues continue to be discussed without resolution. There is debate over the impact of locally focused versus systemically directed therapeutics, and the combination, on survival outcomes.[6,38,39] Local treatment options

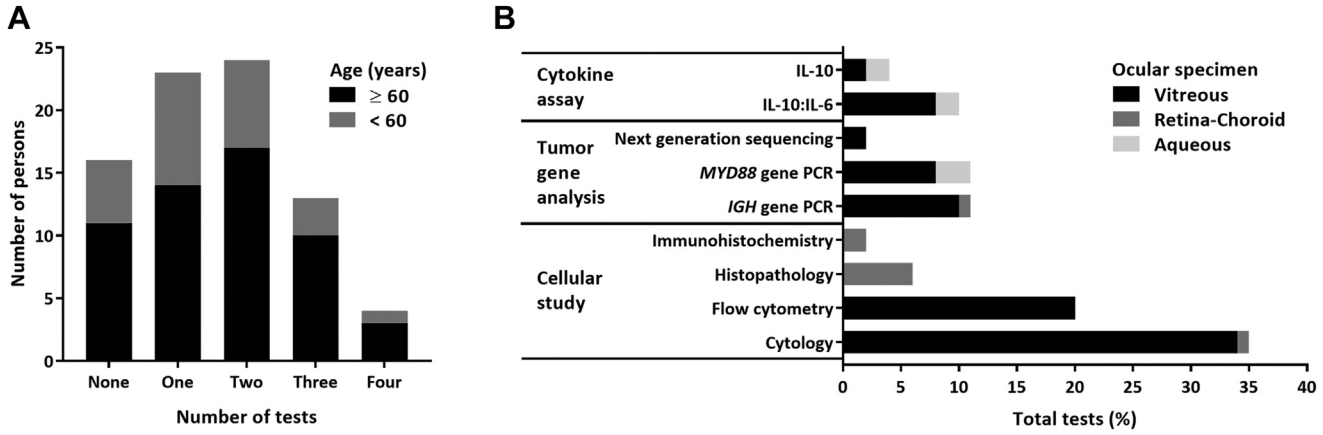

Figure 2. Tests used to diagnose vitreoretinal lymphoma. **A,** Number of diagnostic tests performed in each patient: none (clinical evidence, n = 16), 1 (n = 23), 2 (n = 24), 3 (n = 13), and 4 (n = 4), dichotomized by age group. Black ≥ 60 years; dark gray < 60 years. **B,** Tissue tests as a percent of all tests (n = 126 tests; n = 64 persons). Black = vitreous; dark gray = retinochoroidal sample; light gray = aqueous. IL = interleukin; PCR = polymerase chain reaction.

include intravitreal chemotherapy and radiotherapy, with proponents of each.[40,41] Our data show a spectrum of treatment approaches, but indicate that approximately 50% patients are treated initially with ocular therapy only, another 30% treated with ocular and extraocular therapy, and 20% treated with extraocular therapy only. Although some recent reports that span multiple decades describe the common use of ocular irradiation,[11,42] our data suggest intravitreal chemotherapy is the standard first local approach today: 95% of eyes were treated with intravitreal methotrexate, occasionally combined with intravitreal rituximab, and just 5% of eyes were irradiated. Melphalan has also been reported as another option for intravitreal chemotherapy,[43] but was not used in this patient cohort.

Oncology practice differs between countries, related to considerations that include national health care systems, and general availability of diagnostic modalities and therapeutics.[44] Even within a country, management approaches may vary substantially.[45] Although our data were collected at ophthalmology practices in countries of Asia, Oceania, Europe, North America and the Middle East, the number of patients in our study is insufficient for meaningful

Table 4. Initial Treatment for Vitreoretinal Lymphoma

Variable	Total, Number (%)*	Age (yrs), Number (%)*	
		< 60	≥ 60
Treatment approach	80	25	55
Ocular	38 (48%)	12 (48%)	26 (47%)
Extraocular	17 (21%)	6 (24%)	11 (20%)
Ocular plus extraocular	21 (26%)	7 (28%)	14 (25%)
None	4 (5%)	0 (0%)	4 (7%)
Ocular treatment			
Persons	59	19	40
Unilateral	31 (53%)	13 (68%)	18 (45%)
Bilateral	28 (47%)	6 (32%)	22 (55%)
Eyes	87	25	62
Intravitreal drug	83 (95%)	24 (96%)	59 (95%)
Methotrexate	78 (90%)	21 (84%)	57 (62%)
Methotrexate + rituximab	5 (6%)	3 (12%)	2 (3%)
Ocular irradiation	4 (5%)	1 (4%)	3 (5%)
Extraocular treatment	38	13	25
Systemic chemotherapy	37 (97%)	13 (100%)	24 (96%)
Alone	29 (78%)	8 (62%)	21 (84%)
+ Intrathecal chemotherapy	6 (17%)	4 (31%)	2 (8%)
+ Brain irradiation	2 (6%)	1 (8%)	1 (4%)
CAR T-cell therapy	1 (3%)	0 (0%)	1 (4%)

CAR = chimeric antigen receptor.
N = 80 persons unless otherwise specified.
*Percentages have been rounded and may not equal 100.

regional comparisons. A larger patient cohort could illuminate differences in the management of vitreoretinal lymphoma in different parts of the world.

As with any clinical registry, the major limitation of this work is the potential for selection bias.[46] Nonetheless, for a rare disease, a registry is also the most feasible approach for collecting sufficient clinical data to draw meaningful conclusions. With this approach we have been able to collect quality data from a large number of patients over a short timeframe, i.e., from 2020, allowing us to report the visual acuity impact of vitreoretinal lymphoma and highlight current trends in management. One key finding is the majority use of cellular tests to make the diagnosis, with some reliance on molecular investigations. Another key finding is the common use of ocular therapies, with strong bias toward intravitreal chemotherapy with methotrexate. Given the short-term nature of the data reported in this article, it is not possible to comment on outcomes of different management approaches. Ongoing data collection over multiple years should provide the opportunity to evaluate diagnostic and therapeutic approaches for preservation of visual acuity, and for survival outcomes, including overall and progression-free survival rates.

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Appendix 1

The International Vitreoretinal B-Cell Lymphoma Registry Investigator Group

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No animal subjects were used in this study.

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CNS = central nervous system; **logMAR** = logarithm of the minimum angle of resolution.

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