Primary Vitreoretinal Lymphoma: Management of Isolated Ocular Disease

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Background: The prognosis for patients with primary vitreoretinal is dismal. The close association of primary vitreoretinal lymphoma with primary central nervous system lymphoma is responsible for high rates of mortality. Traditional treatments consist of systemic chemotherapy and whole-brain radiotherapy. The optimal approach for the treatment of isolated primary vitreoretinal lymphoma is unclear.

Methods: A review of the relevant medical and scientific literature was performed, focusing on the clinical features of primary vitreoretinal lymphoma and the progress made in the management of isolated ocular disease.

Results: Ocular treatment options for primary vitreoretinal lymphoma have recently expanded with the addition of intravitreal chemotherapeutic agents and localized radiation. Based on several retrospective reports, a general shift has been made toward local therapy (eg, orbital radiotherapy, intravitreal chemotherapy) for ocular disease. No prospective, randomized clinical trials yet exist to guide therapy.

Conclusions: Optimal treatment regimens for isolated primary vitreoretinal lymphoma continue to evolve. Further investigations into novel therapies and protocols are needed to decrease recurrence rates, reduce or prevent central nervous system involvement, and improve rates of overall survival.

Introduction

Primary vitreoretinal lymphoma (formerly known as primary intraocular lymphoma or reticulum cell sarcoma) continues to have a poor prognosis.1,2 Between 65% and 90% of patients with primary vitreoretinal lymphoma will develop primary central nervous system (CNS) lymphoma, a disease that ultimately results in a high rate of mortality.1,2 Several different treatment modalities can be used for these patients, each with varying degrees of success. Due to the rarity of primary vitreoretinal lymphoma, no prospective, randomized controlled trials exist to guide therapeutic decisions. Consequently, no consensus exists regarding the optimal treatment regimen.

Pathogenesis

Primary vitreoretinal lymphoma is most often (> 95% of the time) diffuse large B-cell lymphoma, which is a type of high-grade malignancy.3 The malignant cells are typically found in the vitreous, retina, or optic nerve head; however, the anatomical site of origin in many cases is unknown, as spillover into multiple compartments of the eye can occur early. Some have suggested a solitary, systemic, primary source of the malignant cells followed by intraocular metastases,4 whereas others have suggested that the malignancy has multiple, independent sites of origin (eg, eye, CNS) that can occasionally develop simultaneously.5 Infiltration of malignant lympho-
cytes into the eye or brain from the systemic circulation may be due to the ability of a malignant clone of cells, which expresses specific cell-surface molecules, to selectively home in to CNS tissue.\textsuperscript{6} Signaling molecules, such as chemokines, may direct these cells to the CNS.\textsuperscript{7} This theory is supported by evidence of tumor clones related to primary CNS lymphoma found in the blood and bone marrow of affected patients.\textsuperscript{8} The CNS may provide an attractive microenvironment for these cells to colonize.

Close association exists between primary vitreoretinal lymphoma and primary CNS lymphoma. Approximately 20\% of patients with primary CNS lymphoma develop lymphoma in the eye, and as many as 90\% of patients with primary vitreoretinal lymphoma develop CNS disease.\textsuperscript{6} The similarities between primary vitreoretinal lymphoma and primary CNS lymphoma include a unique affinity for CNS tissue (whereby this rarely appears outside the CNS), a worse prognosis than most extranodal types of non-Hodgkin lymphoma (NHL), and a high response rate to methotrexate.\textsuperscript{6} Historically, the treatment strategies for the 2 malignancies overlapped due to these similarities and the frequency with which they clinically coexisted.

Although they are pathologically similar in appearance, evidence suggests that primary vitreoretinal lymphoma differs from systemic diffuse large B-cell lymphoma in its origin from mature B cells due to differing frequency of expressed immunoglobulins.\textsuperscript{9}

### Diagnosis

Diagnosis can be difficult owing to its insidious onset, tendency to simulate other conditions, and its relative rarity.\textsuperscript{6,10} It is estimated that approximately 380 cases are diagnosed in the United States each year.\textsuperscript{6} The median age of diagnosis is 60 years and immunosuppression increases the risk of developing the condition.\textsuperscript{11,12} Delay in diagnosis, often confounded with prior diagnoses and treatments for uveitis, is common. In a large series, the median time to diagnosis was 6 months.\textsuperscript{10} However, delays in diagnosis as long as 24 months are not unusual.\textsuperscript{13,14} The diagnosis of primary vitreoretinal lymphoma is usually based on a cytological examination of a vitreous specimen on biopsy, supplemented with findings from immunohistochemistry, flow cytometry, gene rearrangement analysis, and assays for key cytokines.

### Clinical Examination

Primary vitreoretinal lymphoma may present as a collection of nonclumped vitreous cells visible upon slit lamp examination. The vitreous gel may appear hazy due to dispersed vitreous cells. When primary vitreoretinal lymphoma affects the retina, it can present with grey- to cream-colored retinal infiltrates (often found along retinal arterioles), sub-retinal pigment epithelium (RPE) lesions, or a combination of both. The sub-RPE lesions may appear as large RPE detachments with classic, creamy, or yellow colors. Others have described punctate or spiculated sub-RPE deposits, also referred to as a leopard-spot pattern of pigmentation.\textsuperscript{2} In more advanced cases, malignant cells can seed the anterior chamber, where they can settle in the angle or accumulate on the surface of the iris or lens. Less often, the tumor infiltrates the optic nerve head, where it presents as a mass lesion or results in ocular ischemia by interfering with the posterior circulation of the eye.

### Ocular Imaging

Findings on autofluorescent imaging will vary according to the location of the lesions. If lymphoma cells accumulate under the RPE, then the RPE may have hyperfluorescence. However, if the retinal deposits are anterior to the RPE, then they appear to have hypofluorescence due to blocking.

Spectral-domain optical coherence tomography can be used to demonstrate an intraretinal tumor, which may extend through the full-thickness retina, toward the RPE. Multiple, punctate, sub-RPE deposits have also been described.\textsuperscript{15}

Tumor deposits on fluorescein angiography will typically have hypofluorescence on early and late frames. However, leakage may be present from retinal veins and staining of retinal arterioles.\textsuperscript{15}

### Vitreous Biopsy

Definitive diagnosis of primary vitreoretinal lymphoma relies on vitreous biopsy. The decision to perform vitreous biopsy is often made after treatment for chronic progressive uveitis has failed. An anterior chamber tap for levels of interleukin (IL) 10 has been proposed to screen patients for vitreous biopsy.\textsuperscript{16}

However, this approach is controversial because the performance profile of the laboratory study (eg, positive and negative predictive probabilities, rates of sensitivity and specificity) is unclear.\textsuperscript{16} The findings of the vitreous samples of patients with primary vitreoretinal lymphoma often show evidence of apoptosis, cellular necrosis, scavenging macrophages, and reactive inflammatory cells.\textsuperscript{17} It is typically recommended that corticosteroids be withheld prior to vitreous biopsy because they may alter cellular morphology.\textsuperscript{18}

### Cytology

Although cytology (or histology) remains the gold standard of care, diagnostic sensitivity is not absolute due to sampling phenomenon, problems with cellular preservation, and difficulties with interpretation.\textsuperscript{39} Frequently, specimens are obtained with too few cells or cells that are poorly preserved. Under ideal circumstances, malignant B cells appear unambiguously ab-
normal with large, irregular nuclei, scanty cytoplasm, and prominent nucleoli (Figs 1 and 2).\textsuperscript{4,6}

Retinal, biopsy, choroidal biopsy, or both are less commonly performed than vitreous biopsy because this procedure has a higher risk of ocular and visual morbidity.

**Intraocular Cytokine Assay**

B-cell primary vitreoretinal lymphoma typically presents with elevated IL-10 levels in the eye.\textsuperscript{16} Lymphoma cells are thought to produce this cytokine, which acts as a growth factor. This is in contrast to IL-6, which is more commonly produced by inflammatory cells and is characteristic of uveitis.

Vitreous IL-10 levels, in combination with the IL-10:IL-6 ratio, have been used as a diagnostic test for lymphoma, although they do not have a 100% sensitivity rate.\textsuperscript{20} Additional studies have verified the high accuracy rate of cytokine profiling, but they have also confirmed that negative testing does not exclude the disease.\textsuperscript{19,21}

**Immunohistochemistry**

With samples of adequate size, immunohistochemistry studies for cluster designation\textsuperscript{20} and \(\kappa\) and \(\lambda\) light chain restriction can confirm B-cell monoclonality. However, demonstration of surface light chain on lymphocytes fixed in formalin can be technically challenging.

**Flow Cytometry**

Flow cytometry is well suited for the detection of cell-surface markers if the sample is sufficiently cellular. The ratio of \(\kappa:\lambda\) light chains may be useful to confirm a monoclonal expansion of lymphocytes.

**Polymerase Chain Reaction**

Monoclonal gene rearrangements in \(IGH\) (B-cell lymphoma) or \(TRG\) (T-cell lymphoma) are strongly inter-related with malignancy.\textsuperscript{21,22} A technique known as microdissection can be employed to obtain abnormal cells for analysis.\textsuperscript{21}

**Treatment**

No currently agreed upon therapeutic strategy exists for primary vitreoretinal lymphoma without CNS involvement (ie, isolated eye disease). Because no large comparative clinical series, or randomized, masked, clinical trials exist, the optimal treatment of primary vitreoretinal lymphoma relies on clinical judgment. Treatment regimens include local therapy, systemic therapy, or a combination of both. However, it is unclear whether any of the available treatments of isolated ocular primary vitreoretinal lymphoma increase rates of overall survival.\textsuperscript{23} Local therapy consists of intravitreal chemotherapy and ocular radiotherapy. Systemic therapy includes intravenous chemotherapy, intrathecal chemotherapy, whole-brain radiotherapy, and peripheral blood stem cell transplantation. Despite available treatments, which may produce adequate initial responses, recurrence is common, often involving the CNS.\textsuperscript{10} The goals of therapy include eradication of local disease with prevention of local and CNS recurrences as well as minimizing adverse events.

**Primary Central Nervous System Lymphoma**

Many of the current treatment strategies for primary vitreoretinal lymphoma are based on established treatments of primary CNS lymphoma due to their high coincidence and presumed shared pathogenesis. Several of the current treatments for primary vitreoretinal lym-
phoma first demonstrated their effectiveness in the treatment of primary CNS lymphoma.

Based on data from older studies in which the option of solely supportive care was more common, untreated primary CNS lymphoma was found to have an extremely poor prognosis (average survival rate < 3 months).12,24

The survival rate from primary CNS lymphoma is significantly worse in patients with AIDS.12 Initial success in the treatment of primary CNS lymphoma has been achieved through whole brain irradiation, but disease invariably recurs; the median survival rate is approximately 12 months and the local recurrence rate is nearly 90%.25 In 1 report, the 2-year survival rate was 28%.25

Treatment of NHL metastatic to the brain with high-dose methotrexate alone was introduced in 1977.26 The subsequent use of high-dose methotrexate alone in patients with primary CNS lymphoma produced a response rate between 38% and 74% and a median overall survival rate of about 2 years.27-29

Through the use of multiple chemotherapeutic agents, including methotrexate, response rates for primary CNS lymphoma have increased to 71%, with a median overall survival rate of 50 months.30

The success of these therapies in primary CNS lymphoma led to their application in primary vitreoretinal lymphoma.

**Systemic Chemotherapy**

Systemic therapy for primary vitreoretinal lymphoma without CNS involvement can include intravenous and intrathecal chemotherapy and whole-brain radiotherapy. The preferred strategy varies by clinical center.2

Systemic chemotherapy regimens for primary vitreoretinal lymphoma have included a single agent, multiple agents, and chemotherapeutic agents plus autologous stem cell transplantation (ASCT). Prior single-agent treatment regimens have included high-dose arabinofuranosyl cytidine, high-dose methotrexate, ifosfamide, and trofosfamide with varying degrees of success.31-33 Prior studies with intravenous high-dose methotrexate for the treatment of primary CNS lymphoma with concurrent primary vitreoretinal lymphoma achieved response rates that approached 100% in the brain, despite lower response rates of 78% in the eye.29,32 One trial with either ifosfamide or trofosfamide found a 100% response rate with a mean progression-free survival rate of 18 months and a median overall survival rate of 32 months.33

Comparing the efficacy of systemic chemotherapy alone for primary vitreoretinal lymphoma is confounded by the fact that many earlier studies included initial or simultaneous treatment with radiation; intravenous, intrathecal, and intravitreal chemotherapy; ASCT; or all therapies combined. One series of 14 study patients with primary CNS lymphoma or primary vitreoretinal lymphoma found a 100% response rate when patients were treated with intravenous methotrexate, vincristine, and thiopeta and intrathecal methotrexate and arabinofuranosyl cytidine in 21-day cycles without radiation.34 However, recurrence rates were high: 66% of cases recurred within 4.5 years.34

Experience with systemic chemotherapy and ASCT is limited.35 One trial demonstrated longer rates of progression-free survival and overall survival in patients with relapsed or refractory primary CNS lymphoma administered ASCT (in combination with high-dose chemotherapy) compared with those patients who did not receive it.36 Ten of the 43 study patients (23%) had intraocular involvement.36

Several challenges have arisen due to the direct application of these systemic treatments for primary CNS lymphoma to the management of primary vitreoretinal lymphoma. One in particular is the blood–ocular barrier, which limits access of systemically administered medication to the eye. Another is the vitreous: It is normally avascular and will limit chemical diffusion of specific agents depending on their physical properties. The vitreous is a prime tissue that harbors lymphoma.

When given systemically, high-dose methotrexate may achieve tumoricidal levels in the anterior chamber for up to 74 hours but at inadequate levels in the vitreous fluid.37,38

**Local Ocular Disease**

Local therapy for primary vitreoretinal lymphoma has included intravitreal chemotherapy and orbital radiotherapy. Often times, local treatment of ocular disease is initiated because health care professionals may be hesitant to treat a patient systemically unless evidence of CNS disease is present.2

Ocular lymphoma cells are highly sensitive to radiation.39 However, this treatment has not significantly increased the overall survival rate of these patients.40-42 Local response rates are generally high, but recurrence is common. When the tumor reappears, additional radiation is considered hazardous due to the cumulative effects of the radiation on the retina and optic nerve. The complications of orbital radiation include dry eyes, cataract, radiation retinopathy, and optic neuropathy. Although cataracts are surgically treatable, radiation injury to the retina and optic nerve is often permanent. Radiation to the orbits usually involves 35 to 40 Gy delivered in 14 to 15 separate doses, including both eyes in the treatment field.

Experience with intravitreal chemotherapy for primary vitreoretinal lymphoma has included methotrexate and rituximab. Intravitreal methotrexate for intraocular lymphoma is typically administered in a 400-µg dose in 0.1 uL, every 2 weeks as induction therapy, followed by consolidation and maintenance therapy.43,44
When administered intravitreally, this dose maintains therapeutic levels in the eye for at least 5 days. The adverse events of intravitreal methotrexate include epithelial keratopathy, cataract, retinopathy, and hypotony (ie, low intraocular pressure). Treated patients may also be at risk of tachyphylaxis with recurrent injections. Epithelial keratopathy, which has been reported in up to 58% of eyes, may be reduced by paracentesis before the injection.

No double-masked, randomized clinical trials exist for use of intravitreal methotrexate. The largest reported series consists of 44 eyes. In that series, remission was achieved after a mean of 6.4 injections (Table). The major shortcoming of intravitreal therapy is that it fails to prevent CNS relapse or disease in the contralateral eye.

Intravitreal rituximab has demonstrated efficacy and has the ability to penetrate full-thickness retina. It is typically administered on a weekly basis as 1 mg in a 0.1-mL dose. Experience with the medication has revealed a high response rate (≤ 100%), but it also has a high recurrence rate when treatment is discontinued (≤ 55% within 3 months). Recurrences typically occur within 3 months following treatment discontinuation. Additional courses of rituximab may cause disease remission; however, the effectiveness of the drug may diminish. Grossly visible retinal lesions may resolve with rituximab. Rituximab has been reported to cause clinical remission in some patients unresponsive to methotrexate. Adverse events of rituximab include vitritis, elevated intraocular pressure (60%), and iridocyclitis, with mutton-fat keratic precipitates (35%). Despite resolution of ocular lesions with rituximab, 69% of patients in a single trial developed CNS lymphoma.

Rituximab has a half-life of about 5 days in the eye and exerts tumoricidal effects for 3 to 4 weeks. Combination intravitreal methotrexate/rituximab has also been used with some benefit and may potentially decrease the adverse events seen with single-agent therapy.

A collaborative study of patients with primary vitreoretinal lymphoma without clinical or radiographic evidence of CNS involvement from 16 centers (including 9 study patients [11%] with lymphoma in the spinal fluid) found that local therapy did not increase the risk of brain relapse compared with systemic therapy. This retrospective series of 83 immunocompetent study patients with primary vitreoretinal lymphoma from 7 countries evaluated 16 different treatment regimens (3 local and 16 extensive). The median progression-free survival rate was 29.6 months and the overall median survival rate was 58 months; this rate was not impacted by the therapeutic regimen. Relapse rates were high (56%); the median time to relapse was 19 months. The site of relapse (eg, eyes, brain, other sites) was also not affected by the treatment regimen, with most (92%) patients experiencing relapse in the brain or eyes.

Another collaborative review lasting 20 years and covering 78 study patients with primary vitreoretinal lymphoma without signs of primary CNS lymphoma from 17 centers found that use of systemic chemotherapy was not associated with a reduced rate of CNS lym-

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<thead>
<tr>
<th>Study</th>
<th>Intravitreal Treatment</th>
<th>No. of Cases of Primary Vitreoretinal Lymphoma</th>
<th>No. of Cases of Primary Lymphoma of the CNS</th>
<th>No. of Eyes</th>
<th>Ocular Response, % (n)</th>
<th>No. of Injections Until Remission</th>
<th>No. of Eye Relapses</th>
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<td>3, followed by tachyphylaxis</td>
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<td>8.5 (median)</td>
<td>6/26 (23%)</td>
<td>18.5 (median)</td>
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CNS = central nervous system.
phoma, but it was associated with more severe adverse events compared with those seen with local treatment (ocular radiotherapy, ocular chemotherapy, or both).55

Combination Therapy
Combination therapy consists of local and systemic therapy. Some institutions recommend systemic treatment with high-dose methotrexate plus adjuvant local radiotherapy,56,57 whereas other centers prefer intravital chemotherapy with methotrexate or rituximab rather than radiotherapy.58

One retrospective series of 221 immunocompetent patients with primary CNS lymphoma and primary vitreoretinal lymphoma found that those who received dedicated ocular therapy in combination with systemic treatment had increased progression-free survival rates compared with those not receiving dedicated ocular therapy.58 However, no difference was seen in overall survival rates, and the study did not contain a control group and involved a variety of treatments.58 Those who did not receive dedicated ocular therapy were not at increased risk of developing ocular recurrence.58

Recommendations
No universally agreed-upon therapeutic strategy exists for primary vitreoretinal lymphoma without CNS involvement, although a common (but not standard) approach involves systemic therapy for patients with CNS disease and local therapy for those with primary vitreoretinal lymphoma confined to the eye.

Recommendations from the International Primary Central Nervous System Lymphoma Collaborative Group and the British Neuro-Oncology Society differ.5,18 For the treatment of ocular-only primary vitreoretinal lymphoma, the Primary Central Nervous System Lymphoma Collaborative Group recommends local therapy for unilateral disease and local therapy, systemic chemotherapy, or both for those with bilateral disease.6 Orbital radiotherapy may be the preferred local therapy in patients with bilateral disease, whereas intravitreal chemotherapy with or without orbital radiotherapy is preferred for unilateral disease.6 In patients with a prior history of radiotherapy, intravitreal chemotherapy is recommended.6

By contrast, the British Neuro-Oncology Society recommends systemic chemotherapy with high-dose methotrexate and ocular radiotherapy to both globes for isolated primary vitreoretinal lymphoma.18 The British Neuro-Oncology Society recognized that intravitreal methotrexate was an effective treatment option for isolated recurrences.18

Conclusions
The search for the optimal treatment for primary vitreoretinal lymphoma without central nervous system involvement presents a daunting challenge. At the crux of the dilemma is whether local treatment will be effective given the high risk of central nervous system disease and whether early systemic treatment has the potential to improve survival. The differential treatment response of primary vitreoretinal lymphoma may be related to different molecular genetic subtypes of the malignancy, which is a hypothesis that requires further study.3 Lack of a superior treatment strategy despite a decade of collective experience suggests that any major impact on reducing relapse rates in central nervous system and improving outcomes awaits future innovative therapeutic approaches.

References

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