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Intraocular Chemotherapy for Vitreoretinal Lymphoma

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Abstract

Vitreoretinal lymphomas are rare ocular cancers, and the subset of primary central nervous system lymphomas that are based in the posterior eye. These tumours are challenging to treat, and today management generally involves a multispecialty team coordinating a treatment protocol that may include intraocular chemotherapy, ocular irradiation, systemic chemotherapy and/or autologous stem cell transplantation. The ophthalmologist has specific responsibility for the intraocular chemotherapy, which is delivered to the eye by intravitreal injection. The most commonly injected drugs are methotrexate – an anti-metabolite – and rituximab – an anti-human B cell monoclonal antibody. A range of intraocular chemotherapy treatment schedules have been described in the medical literature, although to date there have been no randomised clinical trials of these schedules. In this article, we review the development and current status of intraocular chemotherapy for vitreoretinal lymphoma.

Keywords
lymphoma; eye; retina; drug therapy
Introduction

Vitreoretinal lymphoma (VRL) is a subgroup of primary central nervous system lymphoma (PCNSL) that is based in the posterior segment of the eye.\textsuperscript{1,2} Most cases of this tumour represent an aggressive form of diffuse large B cell lymphoma, but T cell intraocular lymphoma also has been described.\textsuperscript{3} Vitreoretinal lymphoma is rare: a relatively recent estimate calculated from North American data indicates an incidence of 0.048 cases per 100 000 people each year.\textsuperscript{4} When PCNSL first presents in the eye, VRL is termed ‘primary’. However, for a majority of patients, if not at presentation, VRL ultimately also involves the intracranial CNS, which is associated with considerable morbidity and high mortality.\textsuperscript{5}

The majority of persons who present with VRL are over 50 years of age, and there is no clear sex predilection.\textsuperscript{1,2} Typically, the patient is first diagnosed with intermediate and/or posterior uveitis, manifest as vitritis and/or subretinal infiltrates.\textsuperscript{1,2} Less commonly there is optic nerve or anterior segment infiltration. The patient is often troubled by floaters, but has visual acuities that are unexpectedly good. A diagnosis of VRL is made when cytology and flow cytometry of ocular samples identify a monoclonal neoplastic B lymphocyte population; ancillary testing may detect elevated interleukin-10 in intraocular fluid and/or demonstrate of clonal immunoglobulin heavy-chain gene rearrangements or mutation in the myeloid differentiation primary response gene 88 (\textit{MYD88}) in tumour cells.\textsuperscript{6} Several ocular biopsy procedures may be required to make this diagnosis, since in many cases, tumour cells are fragile and sparse.\textsuperscript{7} Corticosteroid drugs are lymphotoxic, and it is recommended that sampling be postponed for a few weeks if the patient has been taking local and/or systemic corticosteroids, in order to maximise the yield of malignant cells.\textsuperscript{8}
There is a limited evidence-base to guide the management of VRL. There have been no randomised clinical trials directed at the management of VRL specifically, although some clinical trials of treatments for PCNSL have included patients with VRL, allowing limited subset analyses. Therapeutic choices therefore depend in part on the expertise of a multispecialty medical team that may involve ophthalmologists, neurologists, oncologists and/or radiotherapists. Treatment regimens include one or more of the following options: intraocular chemotherapy, ocular irradiation that may be combined with whole brain radiotherapy, a number of systemic chemotherapy protocols (which may be directed to the CNS with hyper-osmotic blood-brain barrier disruption), and following chemotherapy, autologous stem cell transplantation; intrathecal chemotherapy is not widely used today after recent clinical trials showed no benefit over systemically delivered drugs in patients with PCNSL. The ophthalmologist is expert in the use of intraocular chemotherapy in particular. In this article, we review developments in and the current status of intraocular chemotherapy for VRL.

Overview of intraocular chemotherapy for vitreoretinal lymphoma

Intraocular chemotherapy for VRL involves the delivery of drugs to the posterior eye by intravitreal injection. There are several possible indications for this intervention, and it may be given as the primary therapy, or as adjunctive therapy to more extensive treatments. Resolution of the tumour improves bothersome floaters and blurred vision, and limits the potential for retinal or retinal pigment epithelial damage, related to infiltration with tumour sheets. Local delivery also avoids the potentially serious systemic toxicity of the chemotherapeutic agent. However, treatment may be given for the express goal of improving overall survival from PCNSL. Macular oedema is an unusual presenting sign of primary VRL, and occurs more often as a complication of
medical or surgical interventions. Thus, macular oedema in particular may not be an indication for intraocular chemotherapy.

A range of drugs have been used in intraocular chemotherapy. The majority of published literature in this field focuses on the use of methotrexate. Intraocular methotrexate – an anti-metabolite – was first administered to a patient with VRL approximately 25 years ago, as reported by De Smet et al of the National Eye Institute of the National Institutes of Health (NEI/NIH, Bethesda, MD) at the American Academy of Ophthalmology annual meeting. The group had observed that methotrexate achieved tumouricidal concentrations within the eye for 3 days when administered at high dose intravenously. They subsequently described the pharmacokinetics of a single intraocular injection of methotrexate in the blind eye of a patient with recurrent VRL: an intravitreal injection of 400 µg injected intravitreally resulted in concentrations that were lymphocytotoxic for 5 days. Importantly, this treatment was administered without ocular complications. Although originally developed at the NEI/NIH, intraocular chemotherapy with methotrexate is now used widely internationally.

While usually highly effective in inducing remission, the need for frequent injections of this drug and reports of tumour recurrence after the course of methotrexate treatment led to an interest in other chemotherapeutic agents. Just over one decade ago, the first reports of treating VRL with the anti-B cell chimaeric mouse/human monoclonal antibody – rituximab – were published. The observation that intrathecal rituximab resulted in a reduction in tumour load in VRL was soon followed by use of the drug intravitreally in patients with VRL. Initial studies in rabbits showed pan-retinal penetration and an absence of retinal and optic nerve pathology following intravitreal
administration of rituximab, and provided pharmacokinetic evidence that the drug would achieve detectable levels within the eye for several months after an injection.\textsuperscript{17-19}

Kitzmann et al from the Mayo Clinic (Rochester, MN)\textsuperscript{18} described the first experience in humans after treating 5 eyes of three patients without complications. Since the first descriptions, a number of groups have combined rituximab with methotrexate in their treatment protocols, which also is consistent with the treatment of other forms of diffuse large B cell lymphoma.\textsuperscript{20}

Additional drugs have also been used in intraocular chemotherapy protocols for VRL, albeit less often, including thiotepa,\textsuperscript{15} melphalan\textsuperscript{21} and corticosteroid.\textsuperscript{22} Here we describe the technique of intravitreal injection, ahead of summarising clinical studies of the different chemotherapeutic drugs delivered into the eye (Table 1), and considering the role of intraocular chemotherapy in the management of PVRL.

\textbf{Technique of intravitreal injection}

Intravitreal injection is widely used for delivery of multiple classes of drugs to the eye, and has been shown to be safe and well tolerated in large patient cohorts. Ocular irritation, conjunctival hyperaemia and limited subconjunctival haemorrhage are common following the procedure, but usually resolve promptly. The most serious complication is endophthalmitis, which has an estimated rate of 0.05\% in a meta-analysis of 105,536 cases injections of antibody against vascular endothelial growth factor.\textsuperscript{23} Intraocular haemorrhage and retinal detachment are other visually significant complications, which are reported at rates of 0.06\% (in a series of 7113 injections)\textsuperscript{24} and 0.01\% (in a series of 35,942 injections),\textsuperscript{25} respectively. Raised intraocular pressure is also possible, but is readily monitored and addressed by anterior chamber paracentesis if necessary.\textsuperscript{26}
Table 1. Summary of clinical studies of intravitreal chemotherapy for vitreoretinal lymphoma, identified by first author last name and reference number. Individual case reports have not been included.

<table>
<thead>
<tr>
<th>Drug*</th>
<th>Report (number of eyes/patients)</th>
</tr>
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<tbody>
<tr>
<td>Methotrexate</td>
<td>Fishburne et al\textsuperscript{29} (7/4); Smith et al\textsuperscript{30} (26/16); Frenkel et al\textsuperscript{34} (44/26); Sou et al\textsuperscript{35} (10/6); Akiyama et al\textsuperscript{36} (17/10); Ma et al\textsuperscript{37} (29/19); Kaburaki et al\textsuperscript{38} (27/17); Klimova et al\textsuperscript{39} (34/20); Cho et al\textsuperscript{40} (NS/16); Smith et al\textsuperscript{50} (122/74)</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Kitzmann et al\textsuperscript{18} (5/3); Ohguro et al\textsuperscript{55} (3/2); Hashida et al\textsuperscript{56} (20/13); Cicinelli et al\textsuperscript{59} (18/9)</td>
</tr>
<tr>
<td>Rituxumab ± Methotrexate</td>
<td>Larkin et al\textsuperscript{20} (48/34)</td>
</tr>
<tr>
<td>Melphalan</td>
<td>Shields et al\textsuperscript{21} (3/2)</td>
</tr>
<tr>
<td>Drug not specified and/or outcome not reported separately from outcomes of other treatments</td>
<td>Levasseur et al\textsuperscript{4} (NS/NS); Castellino et al\textsuperscript{22} (NS/24); Turaka et al\textsuperscript{46} (6/3); Abu Samra et al\textsuperscript{47} (NS/26); Dalvin et al\textsuperscript{48} (NS/NS); Grimm et al\textsuperscript{66} (NS/11); Grimm et al\textsuperscript{67} (NS/23); Riemens et al\textsuperscript{68} (NS/21)</td>
</tr>
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Abbreviation: NS = not specified

*In addition to the treatments listed, intravitreal chemotherapy with thiotepa has been reported in 1 patient\textsuperscript{15} and in one study listed under “drug not specified and/or outcome not reported separately from outcomes of other treatments”, corticosteroid was included in the intravitreal chemotherapy\textsuperscript{22}.
For the benefit of readers who are not ophthalmic surgeons, we describe a typical injection procedure (used by co-author, SRL), recognising that there are multiple minor variations on this technique. Two eyedrops of 0.5% amethocaine hydrochloride are administered to the eye, spaced 1 minute apart. After 2 minutes, the site is prepared with 5% povidone-iodine solution, and a speculum is used to separate the eyelids and clear the field of eyelashes. A volume of 0.2 mL of 2% lignocaine is injected subconjunctivally in the superotemporal region of the eye with a 30 G needle to produce a small conjunctival bleb. The intravitreal injection is given with a new 30 G needle through the anaesthetised area, 3.5 or 4 mm behind the limbus in patients with an intraocular lens or their natural lens, respectively, and directed towards the centre of the vitreous cavity. Following the injection, the speculum is removed, and the eye is irrigated with 0.9% normal saline to minimise late ocular irritation. No eye pad, antibiotics, sedatives or pain relief are given.

**Intraocular methotrexate therapy**

Methotrexate is an anti-metabolite that acts by competitive inhibition of the enzyme, dihydrofolate reductase, ultimately resulting in reduced synthesis of thymine, which is an essential nucleobase in DNA. This drug became a cornerstone of the treatment of non-Hodgkin lymphoma in the 1970s. Twenty years later, in the mid-1990s, the first small cohort of patients was treated with intraocular methotrexate for VRL: at Oregon Health & Science University (OHSU, Portland, OR), Fishburne et al managed 7 eyes of 4 patients – tested negative for the human immune-deficiency virus (HIV) – with a 14-month course of intravitreal methotrexate injections, in conjunction with systemic chemotherapy delivered by hyper-osmotic blood-brain barrier disruption. All eyes demonstrated remission of the tumour after a median of 6 injections and a maximum of
11 injections per eye. The authors reported “no serious ocular toxic reaction” in any eye, and stable visual acuity in 6 of 7 eyes after a median of 14 months follow-up.

In 2002, the OHSU group teamed up with ocular oncologists at Hadassah University (Jerusalem, Israel) to publish a report detailing outcomes in a larger group of 16 HIV-negative patients with VRL treated by intraocular methotrexate, with slight modifications on the injection schedule: Smith et al\textsuperscript{30} reported the use of intravitreally injected methotrexate in 3 phases: induction (ie. twice weekly for 1 month), consolidation (ie. weekly for 1-2 months) and maintenance (ie. monthly for 9-12 months). Remission was achieved in all 26 eyes of 16 patients after a median of 8.5 injections and maximum of 12 injections per eye. In general, the intraocular chemotherapy was combined with systemic chemotherapy, which involved quite diverse protocols. However, two patients with isolated bilateral primary VRL were given local chemotherapy as sole treatment. Six of 16 patients died in follow-up, as a result of progressive intracranial tumour, but without clinical ocular involvement on the final eye examination. Notably, for 3 patients whose VRL recurred in follow-up (median of 18 months), the tumour was again put into remission with a second course of intravitreal methotrexate injections.

The report by Smith et al\textsuperscript{30} also provided a detailed description of the potential adverse events associated with intraocular methotrexate therapy, noting the possibility that some of these might be related to the vitrectomy required to make the diagnosis, the systemic therapy that was co-administered and/or the tumour itself. In particular, hyper-osmotic blood-brain barrier disruption is associated with a maculopathy,\textsuperscript{31,32} and VRL may produce retinal pigment epithelial detachments that result in atrophy, pigmentary changes and disciform scars.\textsuperscript{33} Complications that occurred in injected eyes during the treatment period were: progression of cataract (73\%), corneal epitheliopathy (58\%),
maculopathy (42%), vitreous haemorrhage (8%), optic atrophy (4%) and sterile endophthalmitis (4%). Corneal epitheliopathy is avoided by taking care to avoid spillage of drug onto the ocular surface during the procedure, with washing if necessary, and treated with the use of folinic acid 0.003% eye drops 4 times daily. No patient suffered loss of vision that could be definitely attributed to the treatment.

Subsequent to the original clinical case series, medical centres in North America, Europe, the Middle East and Asia also have reported their experience in treating groups totalling at least 177 eyes of 114 patients with VRL, as well as multiple individual patients, using intravitreal methotrexate injections. Additional reports have described groups of patients suffering from VRL, who received a range of treatments that included methotrexate and/or rituximab intravitreal injections (see below). Outcomes reported for the 114 patients were consistent with those previously reported by the OHSU and Hadassah University investigators. In summary, the treatment appeared to be highly effective at inducing ocular remission of the VRL, and was also used successfully to re-induce remission in cases of recurrent tumour. As in the original reports, many patients received concurrent systemic treatments for PCNSL, making it difficult to dissect the therapeutic benefit of intravitreal methotrexate specifically, but those patients treated with the local therapy alone also experienced disease remission. The majority of patients whose data were reported in these studies did not experience loss of vision. Corneal epitheliopathy was identified as the most common complication, and in addition to the other side effects originally described, glaucoma also was observed to complicate treatment. Although infrequent, cases of neovascular glaucoma have been described.

Today, the largest experience with intravitreal methotrexate therapy for VRL has occurred at Hadassah University. At the 2018 Association for Research in Vision and
Ophthalmology and Champalimaud Foundation Oncogenesis and Oncology
Conference, Professor Jacob Pe’er lectured about the team’s experience dating back more than 20 years, as summarised in the meeting proceedings. In total, the group has treated 122 eyes of 74 patients with VRL, and have observed remission of the tumour in all cases after a range of 2 to 16 intravitreal methotrexate injections. A small number of recurrent cases have been successfully re-treated, and side effects are described as “mostly superficial and temporary”.

Intraocular methotrexate therapy also has been used to treat those cases of VRL which occur as T cell lymphomas. In 2016, a multinational group based across the United States and Europe reported the clinical data from 7 patients with this very rare cancer, of whom three women and one man were treated with intravitreal injections of methotrexate, along with systemic chemotherapy and in one case, local radiotherapy. For three patients, tumour remission was achieved, although this recurred immediately on cessation of the intraocular chemotherapy in one individual. The fourth patient developed treatment-limiting keratopathy while the tumour was still clinically present.

There are some differences in practice between institutions when using intravitreal methotrexate monotherapy to treat VRL. The vast majority of treating ophthalmologists inject methotrexate at a dose of 400 μg (in 0.1 mL). However, the number of injections varies quite widely. There are generally three phases of treatment – an intensive frequency induction phase; a reduced frequency consolidation phase; and a low frequency maintenance phase – and the total course is completed over approximately one year. While the Hadassah University protocol involves 25 injections, other reported protocols have involved considerably less. For example, Karimi et al published the description of a young adult man, whose isolated, bilateral VRL was put into extended remission with three right eye injections and two left eye injections of intravitreal.
methotrexate over a 6-month period following pars plana vitrectomy. Klimova et al,\textsuperscript{39} who reported on the treatment for 34 eyes of 20 patients with VRL, also preferred a less intensive injection schedule, treating "according to the clinical behaviour of the lymphoma".

Resistance during intraocular methotrexate therapy is unusual, but has been reported. Sen et al\textsuperscript{42} used intravitreal injections of methotrexate to treat a 57-year-old woman with isolated, unilateral VRL. This treatment initially was highly effective, inducing tumour remission, but subsequently the disease became resistant to the cytotoxic effect of the drug. In comparison to malignant lymphocytes taken from the eye of a patient whose tumour responded well to intravitreal methotrexate, intraocular lymphocytes from this patient exhibited decreased expression of drug influx proteins, and increased expression of drug efflux proteins. The finding suggested to the authors that their patient’s tumour had acquired the ability to reduce intracellular accumulation and metabolism of the methotrexate. Ocular radiotherapy was substituted for the intraocular chemotherapy, and fortunately effected a lasting remission of the VRL.

**Intraocular rituximab therapy**

Rituximab is a chimaeric mouse-human monoclonal antibody specifically targeted to human cluster of differentiation 20 (CD20). CD20 is a protein that participates in the generation of T lymphocyte-independent antibody responses; it is present on the surface of B lymphocytes from pre-B cell through mature B cell, and lost when the cells terminally differentiate into plasma cells.\textsuperscript{52} Thus, CD20 is also present on lymphomatous cells in most cases of PCNSL and VRL. In targeting B lymphocytes, rituximab effects depletion of the B lymphocytes by multiple mechanisms that include antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity and
lymphocyte apoptosis. The drug is used systemically in the treatment of a range of B lymphocyte-mediated diseases: autoimmune diseases, including some forms of uveitis; and B cell lymphomas, including PCNSL. The first reported uses of intraocular rituximab therapy for VRL were in 2007, by Kitzmann et al from Mayo Clinic (Rochester, MN) and Ohgura et al from Osaka University Medical School (Osaka, Japan): a total of 8 eyes of 5 patients were treated with up to 4 intravitreal injections of rituximab. The follow-up intervals were short, but all injected eyes showed partial or complete remission of VRL following the treatment, which also was well tolerated. Treatment with intraocular rituximab therapy in larger groups of patients with VRL followed for longer intervals were published a few years after the initial reports. Hashida et al provided an update on the experience at Osaka University Medical School by describing the treatment of 20 eyes of 13 patients who were followed for at least one year. The indication for rituximab in all patients was methotrexate treatment-limiting corneal epitheliopathy. Intravitreal injections of rituximab were given weekly for 4 weeks, resulting in remission of VRL in all eyes; tumours recurred in 55% of eyes, and these recurrences were managed with additional courses of treatment. Case reports and small series have detailed consistent experiences with intraocular rituximab therapy at ophthalmology centres in other countries, including Puerto Rico, Spain and Italy. In addition, a number of North American eye clinics have published outcomes of VRL patient cohorts cumulatively totalling almost 200 individuals, including some patients treated with intravitreal rituximab and/or methotrexate therapy; while these studies indicate treatment remissions, the impact of the local therapy specifically is not readily dissected since multiple approaches to treatment are included.

In 2014, Larkin et al presented what is still the largest published experience with intraocular rituximab therapy to date, including 48 eyes of 34 patients, managed at clinics across 5 countries (ie. United States, Canada, Brazil, Germany and Australia).
The most common dosing interval in these eyes was monthly, and a median of 4 injections were administered per eye. Approximately two-thirds of eyes were also injected intraocularly with methotrexate, usually on the same day as the rituximab, and approximately two-thirds of patients were treated with more extensive cytotoxic therapies. Overall, complete and partial remissions were observed in 65% and 23% of treated eyes, respectively. For those eyes treated with intraocular chemotherapy alone, 53% of eyes experienced complete remission and 11% experienced partial remission. After a median follow-up of 18 months, VRL in 23% of eyes with initial complete remission had recurred.

The multi-national study reported by Larkin et al also detailed ocular adverse events experienced during the period of intraocular chemotherapy with rituximab. Complications were reported as (1) related to intraocular rituximab therapy (or unable to exclude the treatment as a cause), and (2) not related to intraocular rituximab therapy. Amongst the 48 treated eyes, complications included: cataract (19%), elevated intraocular pressure (4%), granulomatous anterior uveitis (2%), vitreous haemorrhage (2%) and rhegmatogenous retinal detachment (2%). A two-or-greater line loss in Snellen visual acuity was associated with the treatment in 4% of eyes. Granulomatous anterior uveitis with raised intraocular pressure also was reported by Hashida et al, but was considerably more common, affecting 35% of the 20 treated eyes. Retinal occlusive vasculopathy is a newly identified potential complication, reported in a 2019 case report of an 89-year-old man whose VRL was treated with ocular chemotherapy.

The intravitreally injected dose of rituximab used by the multiple clinicians who have reported on this treatment of VRL to date is consistently 1 mg (in 0.1 mL). However, there are marked differences in the frequency of the injections. In the study reported by
Larkin et al,20 ophthalmologists administered at a frequency that varied from single or “as indicated” injections to 2-monthly injections. While rituximab is administered intravitreally in the vast majority studies, one report from the Massachusetts Eye Research and Surgery Institution described intracameral injection of the drug.47 Hashida et al56 have reported on a waning in effectiveness of intravitreal rituximab injections: resistance is well described in the field of systemic lymphoma treatment, with various mechanisms proposed, including altered CD20 expression or signalling, increase in the apoptotic threshold of the lymphomatous cells, modulation of complement activity and/or reduced cellular cytotoxicity.61

Other intraocular chemotherapy

Thiotepa

As reported by De Smet et al,13,15 the first patient with VRL treated with intraocular chemotherapy had intravitreal injections of thiotepa (2 mg in 0.1 mL), in addition to methotrexate. Thiotepa is an organophosphorus alkylating agent, which results in crosslinking of the double-stranded DNA helix and interferes with DNA replication.62 This drug was added because, at that time, thiotepa was the only drug that had been used intravitreally – for treatment of retinoblastoma63 – and De Smet et al could not be certain methotrexate alone would be sufficiently cytotoxic for VRL. However, the injections of thiotepa were associated with acute, high rises in intraocular pressure resulting in loss of visual acuity, despite aspiration of vitreous fluid prior to the injection procedure. Given this complication, and the concurrent work from Fishburne et al29 showing methotrexate alone was sufficient to induce VRL remission, intraocular thiotepa therapy did not become part of standard practice.
Melphalan

In 2017, Shields et al\textsuperscript{21} published a brief report of intraocular melphalan therapy for VRL, following their treatment of three eyes of two patients with intravitreal injections (10 μg in 0.1 mL). Melphalan is a phenylalanine derivative of nitrogen mustard and an alkylating agent.\textsuperscript{64} One patient – a 92-year-old woman with bilateral primary VRL – experienced clinical remission of the tumour within 3 weeks of single intravitreal injections. Subsequent tumour recurrences in one eye were controlled with 6 bimonthly injections, and there were no recurrences in the other eye during 19-month follow-up. The second patient – a 65-year-old male with bilateral VRL – was treated with intravitreal melphalan in one eye and intravitreal methotrexate in the other eye. One injection of melphalan was sufficient, while 19 injections of methotrexate were required, for control of the tumour. The group observed no retinal toxicity in these patients, and have continued to develop this form of ocular chemotherapy, with a total of 12 patients reported in their recent description of all patients with VRL treated at the Wills Eye Hospital Ocular Oncology Service over a period of 35 years.\textsuperscript{48} The therapy has been adopted by at least one other centre: in 2019, Damato et al\textsuperscript{65} presented an audit of 10 patients with VRL treated at University of California, San Francisco, one of whom was successfully treated with intravitreal melphalan injections.

Corticosteroids

In discussing their use of combination methotrexate and thiotepa intraocular chemotherapy for VRL, De Smet et al\textsuperscript{15} suggested the use of corticosteroid as an alternate second agent for the treatment of VRL: “(S)ingle agent treatment in the setting of recurrent tumour is not usually recommended. Another potential choice is direct intraocular treatment with dexamethasone or a long acting steroid preparation”. Corticosteroids have lymphocytotoxic effects, which is why VRL masquerading as uveitis may show partial response to treatment with different corticosteroid preparations.
that are prescribed before the diagnosis of lymphoma is recognised.\textsuperscript{1} While most ophthalmologists combine methotrexate and rituximab as multi-agent chemotherapy for VRL, some groups include intravitreal corticosteroid in their management of VRL.\textsuperscript{22}

**Role of intraocular chemotherapy for vitreoretinal lymphoma**

The place of intraocular chemotherapy, and eye-directed therapies in general, in the management of VRL continues to be intensely debated, particularly in the setting of a primary tumour without other CNS involvement. The International PCNSL Collaborative Group used retrospectively collected data in two studies, published in 2007 and 2008, to address the role of ocular or local therapy – including intraocular chemotherapy with methotrexate or ocular irradiation – in VRL.\textsuperscript{66,67} In their study of 83 HIV-negative patients with primary VRL, progression-free and overall survival were comparable for patients treated with local therapy alone versus patients treated with more extensive therapy (with or without local therapy).\textsuperscript{64} The investigators concluded that local therapy alone might be used in this setting, for reduced treatment toxicity without negative impact on prognosis. In their study of 221 HIV-negative patients with PCNSL and VRL, the risk of relapse in the eye was not reduced by adding local therapy to the treatment schedule: progression-free survival was significantly extended, but overall survival was similar for patients treated with or without local therapy, in addition to more extensive treatments.\textsuperscript{67} The investigators surmised that local treatment was appropriate for patients with PCNSL and VRL, to give prolonged remission of the ocular disease. On the basis of these studies primarily, 2015 European Association for Neuro-Oncology Guidelines state that VRL in PCNSL should be treated as PNCSL, and that primary VRL may be managed with systemic therapy or local treatment, including intraocular chemotherapy.
Studies conducted since the 2015 European Association for Neuro-Oncology Guidelines were written have provided different perspectives on the effectiveness of eye-directed therapies – most often intraocular methotrexate therapy – in prolonging the onset or progression of CNS disease in patients with VRL. In 2015, Riemens et al reported data that were collected across 17 European centres, comparing 75 patients who were treated with local, extensive and combined local and extensive therapies for primary VRL: rates for development of CNS involvement and death were the same across treatment groups. In contrast, as reported in 2019, for 66 patients with VRL treated at Mayo Clinic with systemic and ocular therapy (primarily intravitreal methotrexate, rituximab and/or corticosteroid therapy) had significantly longer failure-free and CNS relapse-free survival, but no increase in overall survival than patients treated with local or systemic treatment alone. A smaller 2018 report from Charles University and General Hospital University (Prague, Czech Republic) provided additional data in support of a combined extensive and local treatment approach to VRL: in 10 patients with primary VRL, combined therapy with intravitreal methotrexate extended progression-free survival, but not overall survival. Two non-comparative studies from Japan involving 27 patients with VRL provide further support for combination treatment, including intravitreal methotrexate as ocular therapy, for primary VRL. While the best approach to managing VRL continues to be discussed, choice of treatment also will depend on general physical health and medical history, as noted in the 2015 European Association for Neuro-Oncology Guidelines.

Conclusion

Intraocular chemotherapy was originally described as a treatment option for VRL over 20 years ago. Clearly the treatment – presently in the form of methotrexate, rituximab and melphalan – is effective in inducing intraocular tumour remissions, with an
acceptable side effect profile. Patients benefit symptomatically from the resolution of vitreous and/or retinal infiltration. Additionally, locally delivered therapy spares the patient potentially serious complications of more extensive anti-lymphoma therapies. This is a particularly important consideration since the majority of patients with VRL are older adults. Over the coming 5 to 10 years, therapeutic advances may be expected in two main areas: drugs and modes of delivery. As reviewed recently by Touhami et al., a number of new biologic agents – such as the programmed cell death protein-1 blocker, nivolumab, and bruton tyrosine kinase inhibitor, ibrutinib – show promise for management of PCNSL, and might become candidates for intraocular injection. In parallel, experimental studies in the rabbit seek to reduce the number of injections with a biodegradable intraocular drug delivery device, or to avoid intraocular injections entirely by iontophoresis. Ultimately, the goal in treating VRL and PCNSL is cure, and ongoing clinical research and international collaborative effort will be important for defining the role of – including specific protocols for – intraocular chemotherapy in achieving this aim. An internationally-based VRL registry that tracks results of diagnostic testing, plus the range of treatments and their outcomes, is presently under development, and should provide valuable real-world data that inform the use of intraocular chemotherapy for this rare cancer.
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References


47. Abu Samra K, Oray M, Ebrahimiadib N, Lee S, Anesi S, Foster CS. Intraocular lymphoma: descriptive data of 26 patients including clinico-pathologic features,


64. National Center for Biotechnology Information. *Melphalan.*


