

Use of intravitreal rituximab for treatment of vitreoretinal lymphoma

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ABSTRACT

Aim Vitreoretinal lymphoma is a diffuse large B cell non-Hodgkin lymphoma. Targeting malignant cells with rituximab is being used increasingly as local chemotherapy, but information on this treatment is scant. We aimed to describe current therapeutic approaches, as well as responses to and complications of, intravitreal rituximab in patients with vitreoretinal lymphoma.

Methods Clinical data were collected in a standardised manner retrospectively on patients with vitreoretinal lymphoma treated with intravitreal rituximab.

Results 48 eyes (34 patients) with vitreoretinal lymphoma were treated with a median of 3.5 intravitreal injections of rituximab (1 mg/0.1 mL) for new diagnosis (68.8%), progressive disease (29.9%) and maintenance therapy (2.1%). Intravitreal rituximab±methotrexate was the sole treatment in 19 eyes (39.6%). 31 eyes (64.6%) eyes achieved complete remission, after a median of 3 injections; 7 of these eyes developed recurrent disease. 11 eyes (22.9%) achieved partial remission. Although rituximab may have contributed to complications reported in 12 eyes (25.0%), a 2-line loss of Snellen visual acuity occurred in only 2 of those eyes (4.2%).

Conclusions Approaches in rituximab-based intravitreal chemotherapy vary widely, but our findings suggest that this treatment may be safe and effective in inducing remission in a majority of eyes with vitreoretinal lymphoma.

INTRODUCTION

Vitreoretinal lymphoma, which represents a subset of the intraocular lymphomas, is a posterior segment tumour that typically occurs in persons aged over 60 years.^{1 2} In the majority of cases, vitreoretinal lymphoma is classified as a diffuse large B cell non-Hodgkin lymphoma.³ While the majority of patients present with visual disturbances, including reduced vision and floaters, most succumb to the malignancy due to extraocular central nervous system (CNS) involvement.^{4 5} A definitive treatment to cure vitreoretinal lymphoma remains elusive. External-beam ocular radiotherapy⁶ and/or intraocular chemotherapy⁷⁻⁹ have been employed by the vitreoretinal surgeons or uveitis subspecialists who frequently manage this disease, in order to achieve control locally while avoiding systemic toxicity. Intravitreally injected methotrexate alone is the most widely used form of intraocular chemotherapy, and although this approach is highly effective in inducing remission, several

limitations remain with its use in vitreoretinal lymphoma. As originally described,¹⁰ the treatment schedule is intensive, involving injections biweekly during the 1st month and weekly during the 2nd month. The therapy may be complicated by toxic keratopathy.^{7 8} Finally, recurrence remains a problem for individuals who enjoy relatively prolonged survival.⁸ These issues have motivated a search for alternative local chemotherapeutic options for patients with vitreoretinal lymphoma.

Rituximab is a mouse-human chimeric monoclonal antibody that targets the CD20 protein on the surface of benign and malignant B cells; multiple cellular effects of rituximab result ultimately in the depletion of B cell populations.¹¹ Combining rituximab with standard chemotherapy for systemic diffuse large B cell lymphoma has resulted in a substantial decrease in the mortality of this tumour.¹² With rare exception, vitreoretinal malignant B cells express CD20.³ The first evidence that rituximab might have therapeutic benefit in vitreoretinal lymphoma came from the phase I trial of intravitreal rituximab for CNS lymphoma reported by Rubenstein *et al.*¹³ In this study, each of two patients with associated eye involvement experienced reduction in the intraocular tumour. Subsequently, case reports and single centre case series have described the use of intravitreal rituximab to treat up to 30 patients with vitreoretinal lymphoma.¹⁴⁻²¹

Although there is limited published experience on the use of intravitreal rituximab injections for vitreoretinal lymphoma, informal discussion with vitreoretinal surgeons and uveitis specialists indicates that this form of treatment is being employed increasingly. We compiled clinical information retrospectively and in a standardised manner for 48 eyes of 34 patients with vitreoretinal lymphoma who had been treated with intravitreal rituximab injections at 1 of 12 subspecialty ophthalmic clinics internationally. These data provide a description of the therapeutic approaches being used, as well as responses and complications for this form of treatment.

METHODS

Ophthalmologists who had treated patients with vitreoretinal lymphoma with rituximab were identified through an electronically communicated survey of the American Uveitis Society. Additional clinicians were recruited at the Association for Research in Vision and Ophthalmology 2011 Annual Meeting, after initial results of the project were presented at that meeting. For each case treated, ophthalmologists collected

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clinical data in a standardised manner retrospectively, using a data collection sheet that was approved by the Oregon Health & Science University Institutional Review Board. One case was previously published as a case report.¹⁷

On the data collection sheet, background clinical information included: gender; race; age at presentation with lymphoma; and results of HIV testing. Description of the vitreoretinal lymphoma included: initial site of lymphoma; laterality of ocular involvement; extraocular involvement(s); method(s) of diagnosis; and previous treatment(s) of lymphoma, including focal ocular treatment (ie, ocular chemotherapy and radiotherapy) and/or extensive treatment (ie, systemic and intrathecal chemotherapy, whole brain irradiation and stem cell transplantation). Treatment with intravitreally injected rituximab was described by: dose; dosing frequency; total number of injections; duration of treatment course; other intravitreal chemotherapy and timing in relation to intravitreal rituximab injections; and other focal ocular treatment and/or extensive treatment. Measures of treatment effectiveness and safety included: induction of remission and, if applicable, number of injections to remission; and occurrence and timing of relapse; Snellen visual acuities at start and finish of treatment course; and ocular complications during or after treatment course. Duration of follow-up from 1st day of treatment was also recorded. Complete remission was defined according to criteria published by the International Primary CNS Lymphoma Collaborative Group,²² as the absence of cells in vitreous and resolution of any previously documented retinal or optic nerve infiltrates. If treatment was followed by reduction, but not disappearance, of vitreal cells and/or partial resolution of infiltrates, remission was described as partial.

RESULTS

Clinical data were collected for 34 patients who suffered from vitreoretinal lymphoma and were treated with intravitreal injection of rituximab. Of the 34 patients, 19 (55.9%) were female and 15 (44.1%) were male; and there were 30 (91.2%) Caucasians, 2 (5.9%) Asians and 1 (2.9%) Hispanic. Patient age at presentation with vitreoretinal lymphoma ranged between 39 years and 86 years (median=63 years). None of the 19 persons (55.9%), for whom relevant information was available, were infected with HIV. In 25 patients (73.5%), the extraocular CNS was involved with lymphoma, and 3 of these patients had systemic involvement. Eye was the initial site of involvement in 21 patients (61.8%). Vitreoretinal lymphoma was bilateral in 26 cases (76.5%). Follow-up period was up to 54 months (median=11 months); at the end of the study, of the 34 subjects, 26 (76.5%) were alive, 7 (20.6%) were deceased and 1 (2.9%) was lost to follow-up.

Diagnosis of vitreoretinal lymphoma was made by evaluation of the vitreous in 26 of 33 patients (76.5%). Testing took the form of: cytology (n=25, 73.5%); immunophenotyping (n=14, 41.2%); PCR for immunoglobulin H rearrangements (n=10, 29.4%); and/or cytokine analysis, involving measurement of interleukin (IL)-10 and/or IL-6 levels (n=9, 26.5%). One patient (2.9%) was diagnosed with vitreoretinal lymphoma from a chorioretinal biopsy. In seven patients (20.6%), diagnosis rested on examination of extraocular tissue, including brain in six patients and spleen in one patient. Prior to initiation of treatment with intravitreal rituximab, 23 patients (67.6%) were treated with focal ocular treatment or extensive treatment for intraocular and/or extraocular lymphoma. Characteristics of the study cohort are presented in table 1.

A total of 48 eyes of the 34 patients were treated with intravitreal injection(s) of rituximab for three indications: (1) new diagnosis (n=33, 68.8%); (2) progressive disease (n=14,

Table 1 Characteristics of the study cohort (n=34 persons)

Variable	Number of patients (%) or range (median)
Female gender	19 (55.9)
Age (years)	39–86 (63)
Race or ethnicity	
Caucasian	31 (91.2)
Asian	2 (5.9)
Hispanic	1 (2.9)
HIV status	
Negative	19 (55.9)
Positive	0 (0)
Unknown	15 (44.1)
Extraocular CNS lymphoma	25 (73.5)
Bilateral ocular involvement	26 (76.5)
Method(s) of diagnosis	
Vitreous analysis	26 (76.5)
Cytology	25 (73.5)
Immunophenotyping	14 (41.2)
PCR (IgH rearrangement)	10 (29.4)
Cytokine analysis (IL-10 or IL-10:IL-6)	9 (26.5)
Chorioretinal biopsy	1 (2.9)
Extraocular tissue biopsy	7 (20.6)
Brain	6 (17.6)
Spleen	1 (2.9)
Previous treatment	
None	11 (32.4)
Focal ocular treatment	11 (32.4)
Other intravitreal chemotherapy*	9 (26.5)
Ocular irradiation	4 (11.8)
Extensive treatment	20 (58.8)
Systemic chemotherapy	19 (55.9)
Intrathecal chemotherapy	1 (2.9)
Whole brain irradiation	7 (20.6)
Stem cell transplantation	1 (2.9)
Follow-up interval (months)	<1–54 (11)
Status at end of study	
Alive	26 (76.5)
Dead	7 (20.6)
Unknown	1 (2.9)

CNS, central nervous system; IgH, immunoglobulin H; IL, interleukin.

*In all cases, other intravitreal chemotherapy was with methotrexate (0.4 mg/0.1 mL).

29.9%); and (3) maintenance therapy (n=1, 2.1%). The dose used for all treatments was 1 mg/0.1 mL. Number of injections ranged between 1 and 17 (median=4 injections). Dosing intervals ranged widely; the most common dosing frequency was monthly in 19 eyes (39.6%). Thus, the course of treatment with intravitreally injected rituximab extended up to 15 months (median=2 months). Of the 48 eyes, 18 (37.5%) were injected intravitreally with rituximab only; 30 eyes were injected with methotrexate (0.4 mg/0.1 mL). Intravitreal injections of additional medications were given on the same day in the majority of cases (n=26 of 30 eyes, 86.7%). Nineteen eyes (39.6%) received no treatment other than intravitreally injected chemotherapy; for 29 eyes (60.4%), patients were also treated with extensive chemotherapy (as defined above). Intravitreal rituximab treatment is described in table 2.

Of the 48 treated eyes, 31 (64.6%) demonstrated complete remission, 11 (22.9%) demonstrated partial remission; and 4 (8.3%) had no response. For two eyes (4.2%), remission could

not be judged because they were clinically free of lymphoma when treatment was initiated; for one eye, lymphoma was in remission and treatment was given to maintain remission, and for one eye, the diagnostic vitrectomy resulted in clinical clearing of vitreous cells. For the 31 eyes that demonstrated complete remission, clearing of vitreous cells or retinal or optic nerve infiltrates occurred following a median of three injections (range=1–10 injections). Of these 31 eyes, 10 (32.3%) were treated with only intravitreal rituximab±methotrexate. Of the 11 eyes in partial remission, 2 (18.1%) were treated with only intravitreal rituximab±methotrexate. Seven of the 31 eyes that achieved complete remission developed recurrent disease between 5 months and 26 months (median=17.5 months) from the date of first injection.

Complications were reported for 15 (31.3%) of the 48 treated eyes. These complications were classified as either potentially related to the intravitreal rituximab injection, or clearly unrelated to the therapy. The former group included: cataract in nine eyes (18.8%); elevated intraocular pressure in two eyes (4.2%); granulomatous anterior uveitis in one eye (2.1%); vitreous haemorrhage in one eye (2.1%); and rhegmatogenous retinal detachment in one eye (2.1%). Eight of the nine eyes with cataract and the eye with retinal detachment had undergone vitrectomy. Complications that were observed, but had causes other than intravitreal rituximab injection, included:

methotrexate-related keratopathy⁸ in two eyes (4.2%); blood-brain barrier disruption-associated maculopathy²³ in two eyes (4.2%); secondary lymphomatous glaucoma in one eye (2.1%); choroidal neovascular membrane at the site of an old chorioretinal scar in one eye (2.1%); and lymphomatous exudative retinal detachment in one eye (2.1%). Outcomes of intravitreal rituximab treatment, including complications, are summarised in table 3.

Five of the injected 48 eyes experienced significant loss of vision, defined as loss of two or more lines of Snellen visual acuity. In three cases, loss of vision was clearly caused by pathologies that were unrelated to intravitreal injection of rituximab: (1) blood-brain barrier disruption-associated maculopathy; (2) lymphomatous exudative retinal detachment; and (3) choroidal neovascular membrane at the site of an old chorioretinal scar. In the other two cases, intravitreal injection of rituximab may have been responsible for vision loss, although both eyes had also undergone vitrectomy, which may also have been causative: (4) cataract; and (5) rhegmatogenous retinal detachment. Snellen fraction visual acuities pre-intravitreal and post-intravitreal rituximab treatment are shown graphically in figure 1.

DISCUSSION

Intravitreally delivered rituximab is being employed increasingly as a form of local chemotherapy for vitreoretinal lymphoma. On the other hand, there is a paucity of literature relating to effectiveness and safety of this approach, as well as the optimal treatment regimen. By drawing on experience of 12 subspecialty clinics internationally, and collecting information relating to 34 patients (and 48 eyes) with vitreoretinal lymphoma in standardised format, we are able to present a unique overview of this treatment modality. In our study, the most common indication

Table 2 Description of intravitreal rituximab treatment (n=48 eyes)

Variable	Number of eyes (%) or range (median)
Indication for treatment	
New diagnosis	33 (68.8)
Progressive disease	14 (29.2)
Maintenance therapy	1 (2.1)
Dose	
1 mg/0.1 mL	48 (100)
Dosing frequency	
Single treatment	4 (8.3)
Weekly	2 (4.2)
2-Weekly	10 (20.8)
Monthly	19 (39.6)
6-Weekly	1 (2.1)
2-Monthly	1 (2.1)
Variable	11 (22.9)
Total number of injections	1–17 (3.5)
Duration of treatment (months)	<1–15 (2)
Other treatment	
None	8 (16.7)
Focal ocular alone	11 (22.9)
Other intravitreal chemotherapy*	11 (22.9)
Extensive treatment alone	9 (18.8)
Systemic chemotherapy	8 (16.7)
Stem cell transplantation	1 (2.1)
Focal ocular and extensive treatment	20 (41.7)
Other intravitreal+systemic chemotherapy	15 (31.2)
Other intravitreal+intrathecal chemotherapy	2 (4.2)
Other treatment combination†	3 (6.3)

*In all cases, intravitreal chemotherapy was with methotrexate (0.4 mg/0.1 mL).

†Other combinations of focal ocular and extensive treatment included: other intravitreal+systemic chemotherapy+whole brain irradiation (n=1); ocular irradiation+intrathecal chemotherapy (n=1); other intravitreal+intrathecal+systemic chemotherapy+whole brain irradiation (n=1).

Table 3 Outcomes of intravitreal rituximab treatment

Variable	Number of eyes (%) or range (median)
<i>Treated eyes (n=48)</i>	
Remission	
Complete	31 (64.6)
Partial	11 (22.9)
None	4 (8.3)
Not applicable	2 (4.2)
Complications	
Related to treatment (or unable to exclude treatment as a cause)	12 (25.0)
Cataract	9 (18.8)
Elevated intraocular pressure	2 (4.2)
Anterior uveitis	1 (2.1)
Vitreous haemorrhage	1 (2.1)
Retinal detachment	1 (2.1)
None	36 (75.0)
Not related to treatment	6 (12.5)
Keratopathy	2 (4.2)
Maculopathy	2 (4.2)
Glaucoma	1 (2.1)
Choroidal neovascularisation	1 (2.1)
Retinal detachment	1 (2.1)
<i>Eyes with complete remission (n=31)</i>	
Number of injections to remission	1–10 (3)
Relapse	6 (19.4)
Time to relapse (months from day of first treatment)	5–26 (17.5)

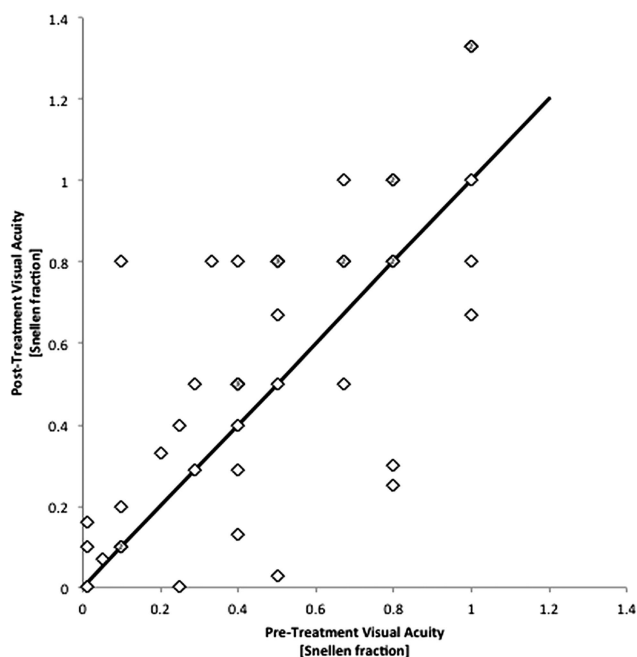


Figure 1 Graph showing Snellen visual acuity fraction for 42 eyes with vitreoretinal lymphoma, pre-treatment and post-treatment with intravitreal rituximab. For six eyes, pre-treatment and/or post-treatment visual acuities could not be quantified or were not recorded; one of these eyes had loss of visual acuity exceeding two Snellen lines.

for intravitreal rituximab injection was newly diagnosed tumour, but the treatment was also employed in cases of progressive disease and to maintain remission. Courses of intravitreal rituximab (median of 3.5 injections of 1 mg/0.1 mL rituximab per eye) were administered alone, or in combination with other local and/or systemic chemotherapeutic and radiotherapeutic approaches. Approximately two-thirds of eyes were treated concurrently with intravitreal methotrexate. Remission was observed in over 90% of the 46 treated eyes in which response could be judged, and was complete in the two-thirds of these. Complications were observed in approximately a third of treated eyes, and two eyes suffered significant visual acuity loss that may have been related to treatment.

In our study, 31 (64.6%) of 48 lymphomatous eyes treated with intravitreal rituximab demonstrated a complete remission. The use of extraocular treatments often complicates interpretation of the effectiveness of local therapies for vitreoretinal lymphoma. Our series included 15 patients who received no treatment other than intravitreal rituximab±methotrexate; 9 (60%) of these patients had complete remission, representing a similar percentage to that recorded for the entire group. The literature contains reports of up to 30 patients with vitreoretinal lymphoma receiving intravitreal rituximab injections.^{14–21} Effectiveness of the treatment is not documented for all 30 cases, but cases of non-responsiveness are not described. In the largest case series to date, Hashida *et al*,¹⁹ described the treatment of 20 eyes of 13 patients with isolated vitreoretinal lymphoma by four weekly injections of intravitreal rituximab; all patients experienced clinical benefit. Importantly, in presenting results for a relatively large group of patients, our study identified cases that did not respond (8.3%) or responded partially (22.9%) to the treatment. Seven (22.6%) of the 31 eyes that were judged to respond completely to intravitreal rituximab treatment developed recurrent disease an average of 17.5 months from the date of first injection. Thus, the intravitreal rituximab-based protocols

were not superior to intravitreal methotrexate alone in terms of preventing relapse.

Habot-Wilner *et al*,²⁴ observed no clinical, histological or functional ill-effects up to 4 weeks after the intravitreal injection of rituximab (0.1 mg/1 mL) in the rabbit, but expression of glial fibrillary acidic protein by Müller cells suggested retinal stress. To be as conservative as possible in evaluating the safety of the new therapy, we recorded any complications observed during the course of intravitreal rituximab. Twenty-five per cent of 48 eyes suffered complications that may have been related to this treatment. Significant vision loss was recorded for two of these eyes. Cataract was by far the most common complication, affecting 18.8% of eyes. It is uncertain if intravitreal rituximab injections contributed to the development or progression of cataract, since most patients with vitreoretinal lymphoma were of a consistent age for the condition. In addition, eight of the nine eyes with cataract had been treated with vitrectomy, which is well known to cause this complication.²⁵ One patient suffered a retinal detachment secondary to a retinal tear that might have been caused by intravitreal injection of rituximab, but was likely caused by vitrectomy, being the more invasive procedure. Two cases of raised intraocular pressure and a case of granulomatous anterior uveitis were more clearly related to the intravitreal rituximab treatments. In the series reported by Hashida *et al*,¹⁹ both these complications were described, albeit at higher frequency. One vitreous haemorrhage was observed and is a recognised complication of intravitreal injection.²⁶ In addition, 12.5% of 48 eyes suffered complications that were clearly related to the disease or other aspects of therapy, including methotrexate-related keratopathy. Notably, keratopathy was relatively uncommon among our patients, when compared with patients treated with standard methotrexate protocols (ie, 4.2% vs 58–100%^{7–9}).

Rituximab was delivered intravitreally in a dose of 1 mg/0.1 mL for all our cases. Selection of this dose related in part to convenience, since the medication was commercially available for systemic administration at a concentration of 10 mg/mL. However, the dose was also consistent with results of preclinical evaluations. Based on their studies conducted in the New Zealand white rabbit, Kim *et al*²⁷ estimated that the intravitreal concentration of rituximab would remain over 10 ng/mL for 72 days after intravitreal injection of 1 mg/0.1 mL; unrelated work in Dutch-belted rabbits showed that the same treatment resulted in deposition of drug through the entire thickness of retina.²⁸ Mice transplanted intraocularly with human CD20-transfected mouse lymphoma cells, to simulate human vitreoretinal lymphoma, experienced significantly delayed progression or cure of tumour following intravitreal injection of 5 µg/0.5 µL rituximab.²⁹

While the dose of rituximab was uniform, there was considerable variation in the frequency at which the drug was administered to our patients, as well as the total number of treatments that were given. This wide variation is also found in previous reports that provide a dosing schedule.^{14–17 19 20} Reported dosing intervals include single injections, multiple injections given at variable intervals, and multiple injections given at fixed intervals ranging from weekly to monthly. The number of treatments varies between 1 and 18 injections per eye. While lack of standardisation to a treatment schedule is not unexpected at the introduction of new therapy, it complicates interpretation of the clinical experience and therefore is an important area for future study. A majority of eyes (62.5%) in our series were treated with the combination of rituximab and methotrexate. In treatment of other forms of diffuse large B cell lymphoma, rituximab is combined with non-biological chemotherapeutic agents as

standard.¹² Extrapolating the principle to intraocular chemotherapy supports using a combination of the two drugs.

In summary, our study describes clinical outcomes of intravitreal rituximab chemotherapy in patients with vitreoretinal lymphoma. Common to other studies on this rare condition, our conclusions are limited by the small number of subjects and the retrospective nature of the data collection. However, our patient cohort is the largest reported to date in any study of local chemotherapy for vitreoretinal lymphoma. Additionally, data collection was standardised across all cases. Our data suggest that intravitreal rituximab is a safe therapeutic approach for vitreoretinal lymphoma. They also support the effectiveness of this therapy, but not in all cases as has been suggested by previous reports with smaller numbers of subjects. Although not superior to single-agent intraocular chemotherapy with methotrexate in terms of preventing tumour recurrences, the number of injections and the occurrence of keratopathy were reduced in our rituximab-based treatment protocols, in comparison with those reported for protocols using methotrexate alone.^{7 8}

A major strength of our work is its multicentre nature, which has provided an overview of therapeutic approaches across multiple clinical practices. An important message is that there is considerable variation in intravitreal rituximab protocols between centres. This factor makes it impossible to recommend an optimal treatment schedule. The rare occurrence of the tumour and ongoing medical advances for treatment of systemic B cell lymphoma, which are likely to be considered for vitreoretinal lymphoma, create difficulties for evaluating any treatment, even by multicentre randomised controlled trial. Thus, while uncertainty remains regarding an optimal rituximab-based approach, a new antihuman CD20 antibody with enhanced affinity for CD16—and superior tumoricidal activity in the mouse model of vitreoretinal lymphoma—is under consideration for Phase I/II clinical trials.³⁰ Since results of any multicentre clinical trial may be outdated before coming to press, a more successful approach to evaluating new and established treatments of vitreoretinal lymphoma may be an international registry.

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