



The evaluation and treatment of primary intraocular lymphoma

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Abstract

Primary intraocular lymphoma (PIOL) is a relatively rare form of Non-Hodgkin's Lymphoma arising in the lymphoid tissues of the eye. It is highly correlated with primary CNS lymphoma (PCNSL) and it is estimated that up to 80% of patients presenting with PIOL will eventually manifest intracranial malignancy, which is the largest contributor to mortality. Most patients present with nonspecific visual symptoms, including floaters and blurry vision, and are often initially diagnosed with uveitis or retinitis. Definitive diagnosis requires biopsy of malignant tissues with demonstration of malignant lymphoid cells. Optimal therapy is to this point undefined, and the available literature is limited to case reports and retrospective series. Currently employed therapies include the use of localized external beam radiation therapy (EBRT), whole brain radiation therapy (WBRT), systemic chemotherapy, intrathecal chemotherapy, and, most recently, direct intravitreal (IVT) chemotherapy. While radiation therapy and chemotherapy can produce a high response rate, they have not been shown to effectively prevent relapse or the incidence of CNS spread. Methotrexate has been the most popular therapy used for the treatment of intraocular lymphoma. It has been administered systemically, intrathecally or intravitreally. However due to multiple mechanisms of resistance developed by lymphoma cells against methotrexate, this drug has been unable to prevent disease recurrence. The newest, and perhaps most promising, reported therapy includes the use of rituximab anti-CD20 monoclonal antibody either alone or in combination chemotherapy via intrathecal or IVT administration. Most cases in the literature employ combinations of available therapies, and there are no comparative studies of significant power to date. Multicenter collaboration will be required to determine the true relative efficacy and adversity of the therapeutic options available.

keywords: Primary intraocular lymphoma, methotrexate, intravitreal rituximab

Introduction

Primary intraocular lymphoma (PIOL), also known as primary vitreoretinal lymphoma (PVRL), is a rare subset of primary central nervous system lymphoma (PCNSL) arising in the retina, vitreous, subretinal pigment epithelium, or optic nerve head [1]. Intraocular lymphoma can arise primarily within the lymphoid tissues of the eye or due to metastatic spread of hematopoietic malignancy from the CNS. The disease is classified as PIOL if, at the time of diagnosis, the disease is limited to the eye with no intracranial involvement [2]. Vitreoretinal lymphoma with concomitant CNS disease is classified as PCNSL with ocular involvement [2]. It has been shown that up to 80% of patients with PIOL will be subsequently diagnosed brain lymphoma, and among those presenting with PCNSL up to 25% have concomitant ocular involvement [3]. For this reason it is thought that definitive management of PIOL may improve morbidity and mortality by preventing spread to the brain and leptomeninges [4].

Given its rarity, PIOL has been difficult to study. To date, no formal standards exist for the treatment of this condition, but many therapies have been experimentally employed. For those with no concomitant CNS disease, high dose intravenous (IV) methotrexate with adjuvant local radiation [5,6] and intraocular methotrexate injections [7-9] have been popular in the literature.

For those with comorbid CNS malignancy, whole brain radiation therapy (WBRT) and IV or intrathecal (IT) chemotherapy in conjunction with intravitreal chemotherapy have been used [10-12]. The most novel therapy for the treatment of PIOL involves the use of rituximab, a humanized antibody targeting CD20+ B cells, in either IV or intravitreal administration [13,14]. Because several treatment modalities have been reported in the literature, many authors have called for further research into the comparative effectiveness of the available treatments and the establishment of treatment guidelines thereof [1,15,16]. This paper provides an up-to-date review of the multiple interventions currently employed in PIOL management, and to our knowledge contains the most comprehensive meta-analysis of case reports and retrospective series of novel therapies to date. With this we hope to better guide further investigation into the comparative effectiveness of novel methods for treating PIOL.

Incidence and Distribution

PIOL is the most common lymphoma of the eye [17]. A 20-year retrospective study at a large Canadian hospital estimated the incidence of PIOL in British Columbia to be between 0.017-0.048 per 100,000 people between 1990 and 2010 [18]. Still, since no national registry or central database for intraocular lymphoma exists, the true incidence of PIOL is unknown. PCNSL is both

more common and more closely monitored, and thus easier to quantify [19]. The Central Brain Tumor Registry of the United States (CBTRUS) published the incidence PCNSL in the U.S. as 0.46 per 100,000 person-years between 2004-2007 and 0.45 per 100,000 person-years between 2005-2009 [19,20]. Multiple case series have published a rate of 15-25% for PIOL in patients with PCNSL [17,21-23]. Chan *et al.*, combined the case reports and the CBTRUS data and estimated that, between 2005 and 2009, 20% of the 1,355 annual cases of CNS lymphoma included intraocular involvement [17]. Therefore, approximately 271 new cases of PIOL occur in conjunction with PCNSL each year in the United States [17]. It is proposed that the number of individuals diagnosed with PIOL without other CNS involvement on presentation ranges from 33 to 50 annually [2,17]. Based on these data, it is reasonable to conclude that the number of total new cases of PIOL in the United States approaches 300 cases per year.

The reported incidence of PCNSL, and consequently the incidence of PIOL, in the literature increased between the 1970s to the 1990s [24]. Recent evidence, however, suggests that the rate of PCNSL diagnosis has flattened, or even begun to decrease [25]. As noted above, the incidence of PCNSL per the CBTRUS has remained stable at 0.45-.046 per 100,000 person-years [19]. As noted by Chan *et al.*, data from 1990-1994 showed an incidence of 0.43+/- 0.02 per 100,000 person-years, suggesting no change over the most recent two decades [17,26]. Other sources indicate that incidence has decreased since the 1990's, and is attributable to the decreased of HIV-related immune deficiency in the advent of effective antiretroviral therapy [27]. We conclude from these data that there is currently insufficient evidence to demonstrate that the incidence of PIOL has significantly changed in recent decades.

The most important risk factors for PCNSL are HIV status and Epstein-Barr virus infection status [28,29]. There are no other known risk-factors for PCNSL or PIOL, though there have been reported cases of PIOL secondary to ocular toxoplasmosis [30].

Diagnosis and Differential Diagnosis

Diffuse Large B-Cell Lymphoma (DLBCL) is the most common systemic lymphoma, and makes up 31% of all Non-Hodgkin's Lymphoma (NHL) [25]. Among PCNSL, upward of 90% are comprised of DLBCL, with the remainder comprised of undifferentiated lymphoma, T-cell lymphoma, and Burkitt lymphoma such that up to 98% are classified as some form of NHL [31,32].

The literature reports anywhere between 60-90% of patients present with bilateral PIOL [2,21]. The majority of patients that present with ocular involvement will later develop CNS involvement as well [11]. Chan *et al.*, reported that 54% of the patients in their case series had PCNSL [17]. Cassoux *et al.*, found that 66% of their PIOL patients developed PCNSL over time [33]. The average reported rate for PCNSL development in PIOL patients ranges from 50-80% [11,17,33].

The presenting symptoms of patients with PIOL are nonspecific and benign. Patients often complain of seeing floaters or blurred vision 1-2 years prior to diagnosis [4,17]. As the disease progresses, it can mimic the inflammation of uveitis and is often inappropriately treated with corticosteroids [4,34,35]. Although there is evidence that measurable differences in the ratios of interleukin-6, interleukin-10, and interferon- γ may allow for the differentiation between inflammatory uveitis and lymphomatous uveitis, only elevations in IL-10 are typically measured in clinical practice and these have not proven sensitive or specific [36]. Occasionally, PIOL has been reported to mimic viral retinitis, and has been treated with antiviral medication [37].

Ophthalmoscopic examination may reveal perivascular sheathing similar in appearance to vasculitis [21]. Patients can also have salmon-colored deposition resembling peripheral drusen or fundus flavimaculatus [21].

Definitive diagnosis of PIOL requires identification of malignant lymphoid cells from ocular tissue or CSF [38]. Several techniques exist to obtain the required tissue, including: aqueous aspiration of the vitreous fluid, diagnostic vitrectomy, diagnostic retinal biopsy, diagnostic choroidal biopsy, or diagnostic enucleation as the case requires [12,17,34,38,39]. The workup should include chest radiography, complete blood count, erythrocyte sedimentation rate, and routine blood chemistries to rule out other sources of inflammatory uveitis, as well as complete neurologic examination, brain CT and MRI [39]. Lumbar puncture to evaluate CSF for atypical lymphoid cells in order to rule out concomitant CNS malignancy is important [39]. Positive cells in the CSF will indicate leptomeningeal disease, which is present in up to 42% of patients with PCNSL and indicates the use of a therapeutic regimen with high CNS penetration [40,41].

Treatment

Treatment regimens for PCNSL can be broadly grouped into two categories: systemic and local. Generally, the prevailing consensus is to employ local therapies for restricted ocular disease (PIOL) and to reserve systemic therapy for those with CNS disease [1,15,17]. Local therapy is typically considered the intervention of choice when thorough neurologic work-up is non-revealing in light of a histological diagnosis of intraocular lymphoma [17]. The goal of local therapy is to both eradicate intraocular disease and prevent subsequent spread to the CNS [11]. Most authors, including Chan *et al.*, recommend a multidisciplinary approach in treating PIOL with input from a collaborative team of neuro-oncologists and ophthalmologists [42].

While some large case series have reported no difference in disease progression when comparing systemic versus local therapy, there have been no conclusive results to this effect [1,17]. Local therapy typically involves either local radiation therapy or IVT methotrexate, whereas systemic therapies include WBRT, systemic chemotherapy, or intrathecal

Table 1. Radiotherapy and Chemotherapy for Primary Intraocular Lymphoma.

Author	Therapy	Eyes Treated	Primary Endpoint	Median Overall Survival	Response Rate	Relapse Rate	Median Follow-up
Margolis <i>et al.</i> , [44]	WBRT	13	Remission Duration	12 months	69%	22%	7.5 months 24 months
Hoffman <i>et al.</i> , [46]	WBRT; IV/IT CHOP, EPOCH and/ or MTX	18	Survival	16 months	-	79%	14.5 months -
Mikami <i>et al.</i> , [47]	EBRT	22	3-Year Survival	89% at 36 months	95%	55%	28 months 36 months
Hormigo <i>et al.</i> , [4]	EBRT; WBRT; IV MTX, VCR, PCB, CHOP and/or Ara-C	17	Survival	39 months	82%	79%	16.5 months -
Isobe <i>et al.</i> , [45]	EBRT; PCI; IV HD-MTX, MTX or CHOP	15	Survival	41 months	87%	-	-
Sandor <i>et al.</i> , [50]	IV HD-MTX, TTP, VCR, DXS; IT Ara-C, MTX	14	Survival	68.8% at 54 months	79%	36%	-
Batchelor <i>et al.</i> , [52]	HD-MTX	9	Remission Duration	-	44%	43%	17 months
Smith <i>et al.</i> , [56]	IVT MTX; IV cyclophosphamide, procarbazine, MTX, VP-16 or Ara-C	26	Safety, Response Rate	62.5% at 18.5 months	100%	-	18.5 months
Frenkel <i>et al.</i> , [8]	IVT MTX	44	Safety, Response Rate	-	100%	48%	17 months 16.2 months

WBRT, whole brain radiation therapy; IV, intravenous; IT, intrathecal; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; EPOCH, etoposide, doxorubicin, vincristine, cyclophosphamide, and prednisone; MTX, methotrexate; VCR, vincristine; PCB, procarbazine; Ara-C, cytarabine; EBRT, external beam radiation therapy; PCI, prophylactic cranial irradiation; HD-MTX, high dose methotrexate; TTP, thiopeta; DXS, dexamethasone; IVT, intravitreal; VP-16, etoposide.

chemotherapy. Here we will compile the available literature in order to review the progress made thus far towards defining optimal therapy in PIOL and PCNSL with ocular involvement, detailing advances in radiation therapy, chemotherapy, and biological therapy.

Radiation Therapy

Early local interventions for PIOL primarily involved radiation monotherapy [43] Margolis *et al.*, originally advocated WBRT as the primary intervention due to potentially beneficial effects on the high co-incidence of CNS malignancy [44]. Since that time, there has been broader acceptance of local therapy, which seeks to avoid the high rate of relapse observed in systemic chemotherapies and the high morbidity associated with WBRT and its well-known association with radiation leukoencephalopathy [11].

Localized external beam radiation therapy (EBRT) involves exposure to the entirety of both eyes without brain exposure and has become the radiation modality of choice in the absence of CNS malignancy [17]. Dosing typically entails a total of 35-50 Gy delivered in 1.5-2.0 Gy fractions using a pair of lateral opposed fields of photon beams [11,17,45]. Reports indicate that rates of visually significant radiation-induced retinopathy are low in patients undergoing EBRT, and that

typically no attempt is made to spare the lens given the risk of missing malignancy in the anterior vitreous and the ease of surgical cataract repair [4,5,45]. However, Pe'er *et al.*, postulate that the true incidence of radiation retinopathy is likely masked by patient mortality and the resulting short follow-up period status-post treatment [11]. Other adverse events noted in the literature include: conjunctivitis, dry eyes, punctate keratopathy, vitreous hemorrhage, optic atrophy, and neovascular glaucoma [4,11,45,46]. These effects are reportedly rare, however, as Mikami *et al.*, utilized radiation monotherapy in 22 immunocompetent patients over a 12-year time period and described cataract formation as the only major adverse development [47]. Although they achieved 95% local control at 3 years of follow-up, 55% of patients experience intracranial relapse of disease at a median of 28 months after treatment [47].

Most groups now advocate combination therapy, employing both EBRT and systemic or intrathecal chemotherapy, primarily methotrexate based, to enhance the response to irradiation [11,48]. With this method the results have been modest, with none of the reviewed literature showing complete response in all treated eyes (Table 1). Margolis *et al.*, reported complete remission in 9/13 eyes with recurrence in 2/9 eyes using WBRT [44]. Hoffman *et al.*, reported 21% survival of the 14 patients

in series with all but 1 of the surviving suffering relapse [46]. Hormigo *et al.*, used EBRT/WBRT or combination radiotherapy and systemic methotrexate based chemotherapy in 13 eyes, reporting complete remission in 10/13 eyes with partial response in 1/13 and CNS relapses in 2 patients responding to therapy [4]. Isobe *et al.*, reported complete remission in 13/15 patients with using a combination of EBRT, systemic chemotherapy, and prophylactic cranial irradiation (PCI), but found that PCI did not affect intracranial recurrence [45]. However, when Berenbom *et al.*, performed a chart review of 12 patients and 21 eyes affected by PIOL, they noted that 7/7 patients receiving EBRT with or without chemo experienced no recurrence whereas 2/4 receiving chemo alone did suffer a recurrence [5]. Although this study was retrospective and non-controlled with a small sample size, it does suggest, as Berenbom and colleagues point out, that EBRT may yet be seen as a first-line therapy in PIOL [5].

Chemotherapy

Demonstrating an effective and appropriate chemotherapeutic regimen for PIOL has been made difficult by the rarity of the diagnosis and the multitude of the pharmacologic interventions available. One case series alone employed multiple combinations of 10 chemotherapies in 11 patients, demonstrating the haphazard approach utilized in the majority of the literature [49]. Of the available chemotherapeutic options, the most commonly reported for the treatment of PIOL included some combination of methotrexate, thiotepa, vincristine, dexamethasone, cytarabine, CHOP (cyclophosphamide, doxorubicin/Adriamycin, vincristine, and prednisolone), cisplatin, temozolomide, and EPOCH (etoposide, prednisolone, vincristine, cyclophosphamide, and doxorubicin). As mentioned above, in a retrospective chart review, Hoffman *et al.*, demonstrated that 21% of patients treated with a combination of radiotherapy and a complex chemotherapy regimen (involving combinations of CHOP, methotrexate, dexamethasone, cytarabine, cisplatin, and EPOCH) achieved 5-year survival [46].

High dose methotrexate (HD-MTX) in IV or intrathecal administration is currently the most commonly utilized therapy for PIOL and PCNSL with ocular involvement in the US [11]. Methotrexate-based chemotherapy is now generally considered to be the best first line therapy for chemotherapy-naïve PIOL patients, and is the recommended treatment by prominent authors [42]. Sandor *et al.*, demonstrated the efficacy of systemic chemotherapy alone with a combination of high dose (8.4 g/m²) IV methotrexate with leucovorin rescue, thiotepa, vincristine, dexamethasone, and intrathecal cytarabine and methotrexate in 14 nonimmunocompromised patients. They reported 100% response rate but with high relapse rate, with 5/14 patients relapsing within 4.5 years of follow-up [50]. Given these findings, most authors recommend against systemic chemotherapy alone in the management of PIOL, instead suggesting a combination radiotherapy

and chemotherapy approach due to the high relapse rate of chemotherapy alone [51].

Batchelor *et al.*, employed high dose (8 g/m²) IV methotrexate monotherapy in 9 patients and demonstrated the presence of micromolar concentrations in both the vitreous and the aqueous fluid, with lower levels present in the vitreous in 5/6 patients in whom both chambers were assayed. 4/9 patients experienced sustained remission, and of those that relapsed, two demonstrated micromolar concentrations of methotrexate in the vitreous fluid. The authors hypothesized that the low penetration into the vitreous may be responsible for the high relapse rate of PIOL in treated patients [52]. To this end, Henson *et al.*, demonstrated the vitreous humor levels of methotrexate to be 100x lower than the serum concentration and 10x lower than the aqueous humor concentration 4 hours after HD-MTX infusion, the timing of peak concentration in the vitreous fluid in animal models [53,54].

Following these findings, the application of intravitreal (IVT) injections of methotrexate to obtain high target-tissue concentrations became more popular. Fishburne *et al.*, were the first to trial this therapy in 1997, reporting that after over a year of weekly 400 pg injections only 1/7 eyes treated suffered from significant loss of vision and none experienced any ocular toxic reaction [55]. De Smet and colleagues performed vitreous samplings after IVT injections of methotrexate, finding that the vitreous eliminates methotrexate by first-order kinetics, and that IVT injections allowed for prolonged tumoricidal concentrations in the target tissue [7]. Smith *et al.*, put these findings to the test, employing IVT injections of 400 µg in 26 eyes [56]. They found clearance of malignant cells in 26/26 eyes after a maximum of 12 injections but did not make comment on relapse rate or changes in life expectancy. Common complications included cataracts, corneal epitheliopathy, vitreous hemorrhage, optic atrophy, and sterile endophthalmitis [56]. The largest study to date of the efficacy and safety of IVT methotrexate for PIOL was performed by Frenkel *et al.*, In a 10-year retrospective study, Frenkel and colleagues treated 44 eyes with IVT therapy and found that 95% were cleared of malignant cells with 13 or less injections, and 100% were cleared of malignant cells after 25 injections [8]. While 14/29 patients succumbed to systemic or CNS lymphoma with a median of 17 months status-post trial, the authors report zero ocular recurrence in a follow-up time of 3 years [8].

However, as IVT methotrexate has become more popular, reports of resistance to IVT methotrexate have begun to surface. In a case report of a patient with recurrent PIOL, Sen *et al.*, employed immunocytochemistry to demonstrate aberrations in multi-drug resistance protein intraocular lymphoma cells [57]. The researchers also found that decreased reduced folate carrier proteins and reduced levels of folate binding protein (FBP) among intraocular lymphoma cells [57]. The mechanisms employed by lymphoma cells to resist methotrexate therapy are quite varied. Once methotrexate

enters the cell it becomes polyglutamated, a form which is a potent inhibitor of dihydrofolate reductase (DHFR) [58]. These polyglutamated forms of methotrexate are broken down to the monoglutamated form in the lysosomes by the enzyme γ -glutamyl hydrolase and thus effused from the cell [58]. Bertino *et al.*, described that alterations in each step of this process can lead to resistance to methotrexate therapy [58]. Five general mechanisms of resistance have been described in the literature [58-61]. The first mechanism is impaired transport of methotrexate across the cellular membrane. The second mechanism is decrease or lack of polyglutamation [58]. The third mechanism is increase in DHFR [58]. The fourth mechanism is consistent with mutated DHFR which leads less binding of methotrexate [58]. The fifth mechanism described in the literature is the increased level of lysosomal enzyme γ -glutamyl hydrolase, which hydrolyses the glutamated methotrexate quicker and leads to faster excretion from the cell [58]. Drug resistance is also mediated by tumor suppressor genes. Research has showed that acute lymphocytic leukemia cells with mutated p53 gene can undergo gene amplification after exposure to methotrexate [58,60]. All these mechanisms of resistance lead to a high failure rate of the IV methotrexate therapy. Therefore, in conjunction with the large majority of patients that also suffer from CNS or systemic lymphoma, the salience of IV methotrexate for PIOL treatment, in isolation, towards extending life expectancy is questionable.

Rituximab

Rituximab is a monoclonal mouse-human chimaeric IgG1- κ antibody that binds to the CD20 antigen, which is found on mature B lymphocytes [62]. Studies investigating Rituximab in combination therapy for systemic aggressive NHL were promising, leading to the investigation of rituximab as a potential tool in the treatment of PIOL and PCNSL [62,63]. Batchelor and colleagues led the largest study to date employing IV rituximab (375mg/m²) in 12 patients that had failed methotrexate therapy, demonstrating response in 5/12 patients in this difficult patient population [64].

Rituximab cannot easily cross the blood-brain barrier (BBB), however, and recent pharmacological studies have demonstrated that CNS levels of rituximab are approximately 0.1% of serum levels after IV administration of the drug [64,65]. While there are some reports of demonstrable effects of IV rituximab therapy likely secondary to localized disruption of the BBB at the tumor site, other authors have demonstrated that IV administration does not impact the rate of CNS relapse [64,66]. Phase I trials have demonstrated the tolerable administration of rituximab via the intrathecal route employing an Ommaya reservoir at 10mg and 25mg dose levels, leading to the broader study of rituximab as mono- and combination therapy for PCNSL [65]. More recent investigation has demonstrated the safety of intraocular injections of rituximab at 1mg dosage in animal models and humans [67,68]. Furthermore, animal models have demonstrated that

IVT rituximab injections fully penetrate the retina with a half-life of 4.7 days in both the vitreous and aqueous fluid, and are thus effective at reaching target tissues in PIOL [69,70]. Mineo *et al.*, demonstrated the efficacy of intravitreal and intracerebral rituximab injections in mice transfected with lymphomatous CD20 positive B cells, reporting that over half the mice injected with rituximab demonstrated total eradication of graft cells and the remaining half all demonstrated inhibition of tumor progression [71]. This has led to a significant speculation regarding the potential future role of rituximab in treating PIOL and ocular recurrence in PCNSL, though the data of such efficacy is limited thus far.

Most data regarding the efficacy of rituximab in treating PIOL currently comes from case reports and a few retrospective case series. Vosganian *et al.*, report treating a 65 year old woman with IV methotrexate (4g/m²) and IV rituximab (500mg/m²) followed by a total of 36 Gy EBRT with complete remission for 16 months, at which point she progressed to PCNSL [72]. Turaka *et al.*, report treating one patient with bilateral PIOL with IVT methotrexate (500 μ g dose) and IVT rituximab (1 mg dose) who experienced complete remission [73]. Yeh *et al.*, report a case of an 83 year old woman with PIOL treated with combination IVT rituximab (1 mg dose) and methotrexate (400 μ g dose); the patient was reported to be in complete remission with no progression to CNS involvement or relapse at 18 months follow-up [14]. Although these authors express optimism for the use of rituximab in PIOL, little can be made from these case reports alone. These results do, however, further emphasize the need for prospective investigation into the competing treatments for PIOL.

Hashida *et al.*, reported the largest series to date featuring IVT rituximab. They describe treating 20 eyes of 13 patients who had already demonstrated adverse effects from IVT methotrexate with 1 mg IVT injections of rituximab monotherapy. They reported ocular recurrence in 11/20 eyes after a follow-up interval of three months, but describe that ocular lesions "improved" in 13/13 patients but that CNS progression occurred in 9/13 patients over the full follow-up period of 31 months [74]. As many of the featured authors have stated, the appropriate dosage and treatment regimen for rituximab in PIOL and PCNSL is still unknown and should be considered an experimental, if promising, therapeutic option for the rare patients that present for clinical trials for this rarer still disease (Table 2).

Conclusion

Though no standardized recommendation exists for the treatment of PIOL or PCNSL with ocular involvement, huge advances have been made in the past three decades. The efficacy of combined radiotherapy and chemotherapy has been put to the test in the most feasible method possible for such a rare condition, and numerous scientific advances have allowed for the detection and injection of chemotherapeutic agents directly within the vitreous fluid. The advent of biologics

Table 2. Rituximab in the Treatment of Primary Intraocular Lymphoma.

Author	Route	Dose	Combination	Eyes Treated	Response Rate	Relapse Rate	Median Relapse	Median Follow-up
Batchelor et al., [60]	IV	375 mg/m ²	-	PCNSL	5/12	4/5	19 months	64.3 months
Vosgianian et al., [68]	IV	500 mg/m ²	HD-MTX, EBRT	1	1/1	1/1	16 months	19 months
Turaka et al., [69]	IVT	1 mg	IVT MTX	2	2/2	0/2	-	33.5 months
Yeh et al., [14]	IVT	1 mg	IVT MTX	1	1/1	0/1	-	18 months
Hashida et al., [70]	IVT	1 mg	-	20	20/20	11/20	3 months	31 months

IV, intravenous; IVT, intravitreal; HD-MTX, high dose methotrexate; EBRT, external beam radiation therapy; MTX, methotrexate; PCNSL, primary central nervous system lymphoma.

like rituximab sparks a great hope in the community for a targeted and efficacious therapy. Some experts theorize that individually-tailored medicine is the future of the treatment for PIOL, and that genomics will play a role in treatment choice as time progresses [75]. For now, we report the facts as they are regarding the previous standards of PIOL care and express our own optimism regarding the efficacy of intravitreal therapy, specifically with rituximab. We join with expert opinion in calling for multicenter collaboration in the development of comparative studies to determine the true relative efficacy and adversity of the therapeutic options available.

Competing interests

The authors declare that they have no competing interests.

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