Diagnosis and management of primary intraocular lymphoma: an update

Kristoph Jahnke[1]
Eckhard Thiel[1]
Lauren E Abrey[2]
Edward A Neuwelt[3]
Agnieszka Korfel[1]

[1]Department of Hematology, Oncology and Transfusion Medicine, Charité-Universitätsmedizin Berlin, Campus Benjamin Franklin, Berlin, Germany; [2]Department of Neurology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA; [3]Departments of Neurology and Neurosurgery, Oregon Health and Science University, Portland, OR, USA

Abstract: Despite recent advances in diagnosis and treatment, the prognosis of primary intraocular lymphoma (PIOL) remains poor, and the optimal treatment has yet to be defined. This review presents an overview of the current status of PIOL with a focus on recent advances in diagnosis and treatment. Recent studies show a decreasing time interval from symptom presentation to diagnosis, likely due to increased awareness of the disease and improved diagnostic tools. Advances in the pathologic characterization of PIOL have been made over the past years, and the development of PIOL animal models can offer the opportunity to study aspects of PIOL pathology, pathogenesis and treatment. Regarding treatment of PIOL, recent larger case series favor the use of systemic chemotherapy plus local ocular treatment as first-line management for patients with concomitant PIOL and PCNSL. For patients with isolated PIOL, the current trend focuses on local first-line treatment and early diagnosis of PIOL. Future studies are needed to confirm these trends. Future directions in the management of PIOL should include studies about pathogenesis, prognostic factors, and treatment optimization. In the future, monoclonal antibodies and radioimmunotherapy could prove useful for PIOL treatment.

Keywords: chemotherapy, diffuse large B-cell lymphoma, non-Hodgkin's lymphoma, primary central nervous system lymphoma, primary intraocular lymphoma, radiotherapy

Introduction

Primary intraocular lymphoma (PIOL) is a malignant non-Hodgkin's lymphoma (NHL) which either occurs independently to, or in association with primary central nervous system lymphoma (PCNSL). It involves the retina, the vitreous chamber and/or the optic nerve and has to be distinguished from secondary intraocular lymphoma (IOL), an ocular manifestation of systemic NHL, which predominantly infiltrates the uveal tract, particularly the choroid (Whitcup et al 1993; Coupland et al 2004). The incidence of PCNSL is 0.3% per 100,000 person years in immunocompetent individuals and 4 to 5 per 1000 person years in patients with AIDS (Cote et al 1996; Behin et al 2003). PIOL has become more frequent due to a threefold increase in the incidence of PCNSL from 1973 to 1984 (Eby et al 1988), but the incidence of PCNSL has stabilized recently (Kadan-Lottick et al 2002). Ocular involvement develops in about 15 to 25% of patients with PCNSL (Hochberg and Miller 1988; Levy-Clarke et al 2005) and is bilateral in 80% of cases (Freeman et al 1987). Sixty to 80% of patients with initial PIOL eventually develop central nervous system (CNS) disease with a mean of 29 months (Freeman et al 1987; Whitcup et al 1993; Akpek, Ahmed et al 1999). Most PIOL are diffuse large B-cell lymphomas (DLBCL), according to the updated World Health Organization (WHO) lymphoma classification (Jaffe et al 2001); secondary IOL usually corresponds to the subtype of systemic lymphoma (Coupland et al 2004). Intraocular T-cell lymphomas are rare, and most cases occur secondary to primary cutaneous or other systemic T-cell lymphomas, whereas only few T-IOL cases without systemic involvement have been described (Char, Ljung, Deschenes et al 1988; Coupland et al 1999; Coupland, Anastassiou et al 2005).

Correspondence: Kristoph Jahnke
Department of Hematology, Oncology and Transfusion Medicine, Charité-Universitätsmedizin Berlin, Campus Benjamin Franklin, Hindenburgdamm 30, D-12200 Berlin, Germany
Tel +49 30 8445 2337
Fax +49 30 8445 4468
Email kristoph.jahnke@charite.de

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The prognosis of PIOL, particularly when concomitant cerebral involvement is present, is poor with a two-year overall survival (OS) of 39% (Ferreri et al 2002) and a median OS of 33 months (with brain involvement) and 57 months (isolated PIOL), respectively (Grimm, Pulido, Jahnke et al 2006; Grimm, Pulido, Omuro et al 2006). The optimal treatment of PIOL is controversial and has yet to be defined, mainly due to treatment data being limited to small studies and case reports. The aim of this review is to present an overview of current diagnosis and management of PIOL, focusing on recent advances in diagnosis and treatment.

Pathogenesis

The pathogenesis of PIOL/PCNSL remains unknown. In immunosuppressed patients, PCNSL is almost invariably associated with a latent infection of the B-cells by the Epstein-Barr virus (Chan et al 1999, 2002; Tuaillon and Chan 2001). Furthermore, PCNSL occurs much more frequently among AIDS patients than in immunocompetent individuals (Cote et al 1996). In immunocompetent persons, human herpesvirus-8 and Toxoplasma gondii have been implicated in the pathogenesis of PCNSL (Chan et al 1999, 2002; Tuaillon and Chan 2001). Chemokines, substances involved in the chemotaxis of leukocytes during inflammatory processes, could play a role in PIOL pathogenesis. The chemokine receptors CXCR4 and CXCR5 are expressed on B-cells, whereas their chemokine ligands, CXCL12 (SDF-1) and CXCL13 (BLC), were detected in the retinal pigment epithelium, suggesting a role of receptor-ligand interactions in the homing of PIOL cells to the retinal pigment epithelium (Chan et al 2003). There also is evidence that chemokines and their receptors may be involved in PCNSL pathogenesis (Smith et al 2003; Jahnke, Coupland et al 2005).

Clinical presentation and diagnosis

General considerations

PIOL usually presents in the fifth and sixth decade as a nonspecific, chronic and relapsing uveitis and vitritis resistant to corticosteroids. There appears to be a slight male predominance for this disease (Schabet 1999). Because of its gradual onset and ability to imitate other ocular syndromes, delays are common before the diagnosis of PIOL is established (Barr et al 1975; Char, Ljung, Miller et al 1988; Whitcup et al 1993; Cassoux et al 2000; Rothova et al 2001; Coupland et al 2003; Davis et al 2004; Zaldivar et al 2004). A median interval of 21–24 months from the onset of ocular symptoms to definitive diagnosis has been reported in the older literature (Barr et al 1975; Char, Ljung, Miller et al 1988; Peterson et al 1993; Whitcup et al 1993). More recent data, however, suggest that the diagnosis can be achieved within 12 months in 80% of patients (Akpek, Ahmed et al 1999) or within a median of 6 months (Jahnke, Korfel et al 2006). The delays in diagnosis establishment have become shorter due to a number of reasons. These include: (1) an increased awareness by clinicians and pathologists of the disease; and (2) the increased use of improved diagnostic tools, such as chorioretinal biopsy, immunocytology/-histology, biochemical analysis and polymerase chain reaction (PCR). The cytolytic effect of corticosteroids on lymphoma cells can negatively impact the diagnostic yield; thus, the administration of corticosteroids should be avoided before specimen sampling (Whitcup et al 1993).

History and ophthalmic examination

PIOL most commonly presents as a chronic uveitis and vitritis, initially responsive but later refractory to corticosteroids. Because of its insidious onset, relapsing-remitting nature and ability to mimic several other conditions resulting in uveitis syndromes (eg, tuberculosis, sarcoidosis, toxoplasmosis, acute retinal necrosis, multifocal choroiditis) (Chan and Wallace 2004), the clinical presentation of PIOL is commonly referred to as masquerade syndrome (Char, Ljung, Miller et al 1988; Whitcup et al 1993; Cassoux et al 2000; Rothova et al 2001; Coupland et al 2003, 2004; Davis 2004; Zaldivar et al 2004). Patients mainly complain of blurred vision, floaters and painless vision loss. Less frequent symptoms consist of red eye, ocular pain and photophobia (Freeman et al 1987; Char, Ljung, Miller et al 1988; Peterson et al 1993; Whitcup et al 1993; Akpek, Ahmed et al 1999; Cassoux et al 2000; Buggage et al 2001; Chan et al 2002; Chan and Wallace 2004; Coupland et al 2004; Davis 2004; Zaldivar et al 2004; Levy-Clarke et al 2005; Jahnke, Korfel et al 2006).

Vitritis is the most common finding upon ocular examination. Fundus examination typically reveals characteristic retinal or subretinal yellow infiltrates (Chan and Wallace 2004; Levy-Clarke et al 2005). Subretinal fibrosis and atrophy of the retinal pigment epithelium may be evident if these lesions resolve (Dean et al 1996).

Fluorescein angiography and ultrasound can be helpful adjuncts in the diagnosis of PIOL. Fluorescein angiography frequently reveals window defects (indicating tumor infiltrates), hypofluorescent lesions, vasculitis, granulations, late staining and blockage at the level of the retinal pigment epithelium, whereas signs of inflammation like perivascular leakage and macular edema are typically lacking (Cassoux et al 2000; Velez et al 2002). Ultrasound may reveal debris

in the vitreous, choroidal and scleral thickening, widening of the optic nerve, elevated lesions in the choroid and retinal detachment (Ursea et al 1997).

Pathologic diagnosis

Vitreous sampling and cytologic diagnosis

Cytologic examinations of vitreous samples are generally the first step in the pathologic diagnosis of PIOL. Vitreous specimens can be obtained by pars plana (three-port) vitrectomy or vitreal or fine needle aspiration (Davis et al 1992; Whitcup et al 1993; Lobo and Lightman 2003; Coupland et al 2004). Anterior chamber aspiration cytology enhanced by the cytospin technique may provide a less invasive alternative to vitrectomy (Finger et al 2006). The vitreous frequently contains neoplastic cells which form sheets, and cells in the anterior chamber are present in 50%–75% of patients (Peterson et al 1993; Whitcup et al 1993; Bardenstein 1998; Velez et al 2000; Hoffman et al 2003; Coupland et al 2004; Chan and Wallace 2004; Jahnke, Korfel et al 2006). Rapid processing is crucial due to the usually small number of neoplastic cells in the specimen that may be undergoing necrosis.

Chorioretinal biopsy, fine-needle aspiration biopsy and enucleation

If vitrectomy specimens have been insufficient to establish a final diagnosis, a chorioretinal biopsy or fine-needle aspiration biopsy should be considered. These techniques are more likely to yield a sufficient concentration of neoplastic cells (Kirmani et al 1987; Levy-Clarke et al 2001; Tuaillon and Chan 2001; Bechrakis et al 2002; Coupland et al 2003). If all the above-mentioned diagnostic procedures have failed, enucleation of a blind eye may be considered, especially if the eye is painful due to secondary glaucoma.

Immunophenotyping

Flow cytometry and immunohistochemistry are able to identify lymphoma cells and demonstrate their monoclonality by B-cell and plasma cell markers (CD19/20/22, BCL-6, MUM1) and kappa or lambda light chain restriction. However, the accuracy of flow cytometry is variable among different centers. Some studies found flow cytometry more accurate than conventional cytology in the diagnosis of PIOL, whereas other studies reported the opposite finding (Char, Ljung, Deschenes et al 1988; Davis et al 1997; Rothova et al 2001).

A study comparing 50 cases of PIOL/PCNSL with 50 systemic DLBCL specimens regarding the expression of a variety of B-cell associated immunoglobulin transcription factors using immunohistochemistry found notable differences between both groups. For example, immunoglobulin expression could be demonstrated in 92% of PIOL/PCNSL but in only 54% of systemic DLBCL, thus providing evidence that PIOL/PCNSL and systemic DLBCL represent distinct entities with PIOL/PCNSL derived from mature B-cells that have undergone the germinal center reaction (Coupland, Loddenkemper et al 2005).

Interleukins

The cytokines interleukin (IL)-6 and IL-10 have been implicated in the discrimination of PIOL and ocular inflammatory processes. Neoplastic B-lymphocytes preferentially secrete IL-10, whereas IL-6 is associated with inflammation (Chan et al 1995; Choi et al 2006). Vitreal levels of these cytokines can be detected by enzyme-linked immunosorbent assay. An association of PIOL with an increased (>1) IL-10 to IL-6 ratio has been reported (Chan et al 1995; Whitcup et al 1997; Cassoux et al 2001; Wolf et al 2003). However, another report found an elevated ratio in only 8/14 patients and a ratio of <1 in one patient with PIOL (Akpek, Maca et al 1999).

Molecular studies

Over the recent years, PCR has emerged as a useful adjunct in the diagnosis of PIOL, and can increase diagnostic sensitivity and specificity compared to other diagnostic tools. PCR and microdissection for gene rearrangements of the immunoglobulin heavy (IgH) chain gene has proven useful for demonstrating monoclonality of a B-cell population in PIOL and PCNSL (Shen et al 1998; Coupland et al 2003; Jahnke, Hummel et al 2006). In a recent study, the sensitivity value of immunoglobulin IgH rearrangement analysis (0.64) was superior to that of vitreous fluid cytopathology (0.24) and flow cytometry (0.36), whereas the specificity value was 1.0 with all three methods (Baehring et al 2005). PCR of the third hypervariable or complementary determining region (CDR3) of the IgH variable region is frequently used (Chan 2003; Gorochov et al 2003). New primers have recently been developed by a European concerted action to increase the chances of detecting monoclonality in lymphoproliferations (van Dongen et al 2003). PCR and microdissection have also been used for the detection of the t(14; 18) translocation (ie, translocation between the genes for BCL-2 and IgH) (Shen et al 1998; Wallace at al 2006). There is evidence that PIOL has unique patterns of BCL-2, BCL-6 and BCL-10 expression as compared to systemic DLBCL and PCNSL, with PIOL resembling germinal center B-cell DLBCL (Wallace et al 2006). The notion that PIOL is derived from mature B-cells

that have undergone the germinal center reaction could be further underscored in a recent study with 16 PIOL cases analyzing somatic hypermutations in clonally rearranged IgH chain variable regions (Coupland, Hummel, Muller et al 2005). It has been widely hypothesized that cerebral and ocular lymphoma manifestations in PCNSL patients with ocular involvement are derived from the same neoplastic clone, and this could recently be shown by IgH PCR analysis in one patient (Coupland, Hummel, Stein et al 2005). The close relationship between PIOL and PCNSL could be substantiated in a recent study, demonstrating the presence of the same variable region of the clonally rearranged IgH chain gene in three out of six cases of oculocerebral lymphoma (Coupland, Hummel, Muller et al 2005).

Diagnosis and response evaluation in PIOL and PCNSL: International workshop recommendations

Baseline evaluation

Since PIOL is closely related to PCNSL and vice versa, every PIOL and PCNSL patient must be thoroughly evaluated for both the presence of cerebral and ocular disease. In an effort to standardize baseline evaluation, response criteria and management of PIOL and PCNSL, the International PCNSL Collaborative Group (IPCG) has recently published guidelines and recommendations for the diagnosis and management of PIOL and PCNSL (Abrey et al 2005).

Baseline clinical and laboratory evaluation should include a comprehensive physical and neurological examination and the recording of parameters that have been implicated as prognostic factors in PCNSL, eg, age, performance status, and serum lactate dehydrogenase (Ferreri, Blay et al 2003). Peripheral lymph nodes should be examined in all patients and the testes in elderly men to search for systemic disease. All patients should be tested for HIV infection. Evaluation of neurocognitive function is important to monitor treatment success and possible treatment-related neurocognitive decline.

A gadolinium-enhanced magnetic resonance imaging (MRI) scan is the imaging method of choice for PCNSL. Computed tomography (CT) should be used only if MRI is contraindicated or unavailable. The role of MRI and CT for visualizing ocular involvement is limited since they lack sensitivity and specificity. In seven patients with biopsy-proven PIOL, only four had ocular findings on imaging, and these were not specific for PIOL (Kuker et al 2002). For the exclusion or confirmation of ocular disease, a slit-lamp examination should be performed.

Patients should undergo cytologic cerebrospinal fluid (CSF) evaluation for the presence of leptomeningeal involvement, and total protein should be recorded in all patients since it has been reported as a prognostic factor in PCNSL (Ferreri, Blay et al 2003).

Occult systemic disease has been reported in up to 17% of patients initially thought to have isolated CNS involvement (Nelson et al 1992; O'Neill et al 1995; Ferreri et al 1996; Jahnke, Hummel et al 2006). Thus, a complete systemic staging is warranted in every patient, including CT scans of the chest, abdomen and pelvis and bone marrow aspirate and biopsy.

All PIOL and PCNSL patients should have histopathologic or cytologic confirmation of the diagnosis. The preferred diagnostic procedures are stereotactic biopsy for parenchymal mass lesions, CSF analysis in patients with leptomeningeal involvement and vitrectomy in cases suspected of PIOL. Since histologic diagnosis and response assessment can be affected by the administration of glucocorticosteroids, their administration should be avoided whenever possible.

Response assessment and criteria

Gadolinium-enhanced MRI is the gold standard for the response assessment of parenchymal lesions. Detailed ophthalmologic examinations and CSF analysis are recommended only if these studies were positive at baseline or if clinically indicated by new signs and symptoms.The response criteria for parenchymal and CSF disease have been reported in detail in the manuscript summarizing the aforementioned IPCG Workshop (Abrey et al 2005). The response criteria for PIOL are summarized in Table 1.

Treatment and prognosis

An overview of clinical studies on the treatment of PIOL is provided in Tables 2 and 3.

General considerations about the treatment of PCNSL and PIOL

The treatment of PCNSL is significantly different from that of systemic NHL. Therapies effective for extra-CNS NHL have not been successful in PCNSL due to the inability of most chemotherapeutic agents to sufficiently cross the blood-brain barrier (Schultz et al 1996; O'Neill et al 1999; Mead et al 2000). As opposed to other brain tumors, there is no role for resection in the treatment of PCNSL; its use is limited to diagnostic purposes (Hunt et al 2006). Until the early 1990s, WBRT was considered the standard treatment

Table 1 Response criteria for PIOL as published by the IPCG (adapted from Abrey et al 2005)

Response	Corticosteroid dose	Ocular examination
Complete remission	None	Normal
Unconfirmed complete remission	Any	Minor retinal pigment epithelium abnormality
Partial remission	Irrelevant	Decrease in retinal infiltrate or vitreous cells
Progressive disease	Irrelevant	Recurrent or new ocular disease

of PCNSL. However, disease relapse almost invariably occurs, resulting in a median OS of only 12 months (Nelson et al 1992). Today, it is generally believed that high-dose methotrexate-based chemotherapy should be part of the first-line treatment for the vast majority of patients. With high-dose methotrexate alone, a response rate of 38 to 74% and a median OS of 22.8+ to 25 months have been reported (Herrlinger et al 2002; Batchelor T et al 2003; Herrlinger et al 2005). Methotrexate-based intensive multi-agent chemotherapy has led to a response rate of 71%, a median OS of 50 months, and a five-year OS of 43% (Pels et al 2003). Combined modality therapy with high-dose methotrexate-based chemotherapy followed by WBRT yields five-year OS rates up to 32% (DeAngelis et al 2002), but is associated with rates of neurotoxicity as high as 100% in patients over 60 years (Abrey et al 1998). Thus, postponing WBRT until progression or relapse has been suggested. Compared to combined modality therapy, intraarterial chemotherapy in conjunction with blood-brain barrier disruption seems able to yield equal response and survival rates while preserving neurocognitive function in PCNSL (McAllister et al 2000). The role of intrathecal therapy and high-dose chemotherapy followed by autologous stem cell support in PCNSL remains to be defined (Soussain et al 2001; Khan et al 2002; Abrey et al 2003; Ferreri, Abrey et al 2003; Illerhaus et al 2006).

The efficacy of systemic chemotherapy in PIOL depends on intraocular pharmacokinetics which are not yet fully understood. The blood-retinal barrier and the blood-aqueous barrier represent hindrances for diffusion of drugs from the blood into ocular tissues. The retinal vessels and the retinal pigment epithelium are the two sites of the blood-retinal barrier which represents the counterpart of the BBB in the eye (Raviola 1977; Cunha-Vaz 1979). The blood-aqueous barrier is a barrier between the blood and ocular tissues and fluids posterior to the iris plane (Freddo 2001). Drug penetration through these barriers depends on several drug characteristics, with lipid solubility playing the major role. The major advantage of systemic chemotherapy in PIOL is the simultaneous treatment of cerebral involvement which should be suspected in all patients with PCNSL, at least at a microscopic level.

Ocular radiotherapy

Local radiotherapy had been widely used in PIOL, as lymphoma cells are highly sensitive to radiation (Margolis et al 1980). Almost all patients, however, die of cerebral relapse after a median survival of 12–20 months (Fine and Mayer 1993; Ferreri et al 2002). Additionally, severe side effects of radiotherapy, eg, optic neuropathy, retinopathy, glaucoma, dry eye syndrome, corneal defects, and cataracts, led to permanent visual loss in some long-term survivors (Char, Ljung, Miller et al 1988; Buggage et al 2001). Furthermore, ocular radiation has no effect on the prevention of PCNSL and can only be administered once.

Intravitreal chemotherapy

Intravitreal drug instillation bypasses the ocular barriers, which significantly improves the intraocular delivery of hydrophilic drugs like methotrexate. Moreover, the toxicity seen with systemic treatment can be avoided. Therapeutic methotrexate doses are maintained over five days after intravitreal administration (de Smet et al 1999). In a study of four PIOL patients treated with intravitreal methotrexate, complete remission was achieved in all patients, and no relapses were observed with follow-up ranging from 9 to 19 months (Fishburne et al 1997). Similar results could be obtained in a larger study with 16 patients (Smith et al 2002). Combination therapy with intravitreal methotrexate and thiotepa yielded a sustained remission in one patient with relapsed PIOL (de Smet et al 1999). However, intravitreal therapy does not prevent disease in the CNS or the contralateral eye. Furthermore, complications such as cataracts, corneal epitheliopathy, maculopathy, vitreous hemorrhage and optic nerve atrophy, are frequently observed with intravitreal methotrexate administration (Smith et al 2002).

Systemic chemotherapy

Methotrexate, cytarabine, ifosfamide and trofosfamide are able to penetrate the blood-ocular barriers in cytostatic concentrations and therefore have been successfully used for the treatment of PIOL in intravenous or oral formulations (Baumann et al 1986; Strauchen et al 1989; de Smet et al 1996; Henson et al 1999; Batchelor T et al 2003; Batchelor TT et al 2003; Jahnke et al 2004; Jahnke, Wagner et al 2005).

Table 2 Summary of clinical studies over the past 20 years (in chronological order) using chemotherapy or immunotherapy alone as treatment for PIOL

Author(s) and year of publication	Treatment modality[a]	Chemotherapeutic agents[a]	No. of PIOL patients	Ocular response	Ocular relapses	Survival
Strauchen 1989	High-dose IV chemo	Cytarabine	6	5/6 (1 CR, 4 PR)	1/5	Not reported on an individual basis
Soussain 1996	High-dose IV chemo + autologous bone marrow transplantation	Thiotepa, busulfan, cyclophosphamide	5	5/5 (5 CR)	2/5	3 alive in CR at 26+ months, 2 alive after ocular relapse at 27+, 16+ months
Fishburne 1997	High-dose IA chemo + BBBD, IO chemo	MTX (as IO treatment)	4	4/4 (4 CR)	0/4	Not reported on an individual basis
Sandor 1998	High-dose IV chemo, IT chemo	Thiotepa, vincristine, MTX, dexamethasone, cytarabine	5	5/5 (3 CR, 2 PR)	0/5	3 alive in CR, 2 died of cerebral or spinal disease
De Smet 1999	IO chemo	MTX, thiotepa	1	1/1 (1 CR)	0/1	1 alive in CR at 30+ months
Soussain 2001	High-dose IV chemo + hematopoietic stem cell rescue	Thiotepa, busulfan, cyclophosphamide	11	10/11 (9 CR, 1 PR)	2/10	7 alive in CR, 1 alive with ocular PD, 2 died due to tumor progression, 1 died due to unknown causes; median follow-up 41 months for all study patients
Smith 2002	High-dose IV/IA chemo ± BBBD, IT chemo, PO chemo, IO chemo	MTX (as IO treatment)	16	16/16 (16 CR)	3/16	6 deaths, all due to intracranial progression
Abrey 2003	High-dose IV chemo + hematopoietic stem cell rescue	MTX, cytarabine, carmustine, etoposide, melphalan	2	2/2	1/2	1 in CR at 36.8+ months, 1 alive with intracranial disease at 37.4+ months
Batchelor, Kolak 2003	High-dose IV chemo	MTX	9	7/9 (6 CR, 1 PR)	3/7	4 alive in CR at 8+, 15+, 20+, 36+ months; 2 died of intracranial disease
Batchelor, Carson 2003	High-dose IV chemo	MTX	5	4/5 (4 CR)	Not reported on an individual basis	Not reported on an individual basis
Mason 2003	IT chemo	MTX, cytarabine	2	2/2	0/2	2 alive in CR at 5+ years
Jahnke 2004	PO chemo	Trofosfamide	2	2/2 (2 CR)	1/2	1 alive in CR at 8+ months, 1 alive with ocular relapse at 18+ months
Rubenstein 2004	IT immunotherapy	Rituximab	1	1/1	Not reported on an individual basis	Not reported on an individual basis
Jahnke 2005	High-dose IV chemo, PO chemo	Ifosfamide, trofosfamide	8	8/8 (6 CR, 2 PR)	2/8	5 alive in CR, 2 alive in PR, 1 died due to suspected intracranial progression; overall survival 6+ to 35+ months

[a]Patients may or may not have received all listed modalities and agents; see referenced articles for details.

Abbreviations: PIOL, primary intraocular lymphoma; IV, intravenous; CR, complete remission; PR, partial remission; IA, intraarterial; BBBD, blood-brain barrier disruption; IO, intraocular; MTX, methotrexate; IT, intrathecal; PO, oral.

Table 3 Summary of clinical studies over the past 20 years (in chronological order) using chemotherapy/immunotherapy and radiotherapy as treatment for PIOL

Author(s) and year of publication	Treatment modality[a]	Chemotherapeutic agents[a]	No. of PIOL patients	Ocular response	Ocular relapses	Survival
Valluri 1995	High-dose IV chemo, IT chemo, WBRT, ORT	MTX, cytarabine	3	3/3 (3 CR)	0/3	3 alive in CR 31+, 30+, 30+ months after completion of therapy
Cassoux 2000	Retrospective series with various modalities	Retrospective series with various regimens	44	Not reported on an individual basis	Not reported on an individual basis	12 alive in CR and 14 have died after an average follow-up of 33.1 months
Ferreri 2001	High-dose IV chemo, PO chemo, WBRT	Vincristine, MTX, procarbazine	2	2/2 (2 CR)	1/2	1 alive in CR at 44+ months; 1 died due to neurotoxicity after 24 months
Ferreri 2002	High-dose IV chemo, IT chemo, WBRT, ORT	MTX, cytarabine, CHOP	22	15/22 (13 CR, 2 PR)	9/15	2-year failure-free survival 34%, 2-year overall survival 39%
Hoffman 2003	Retrospective series with various modalities	Retrospective series with various regimens	10	Not reported on an individual basis	2	1 alive in CR at 103+ months, 1 alive with disease at 24+ months, 8 have died; median overall survival 16 months[b]
Hormigo 2004	(High-dose) IV chemo, IT chemo, PO chemo, WBRT, ORT	MTX, cytarabine, vincristine, procarbazine, thiotepa, CHOP, rituximab	31	29/31 (24 CR, 5 PR)	8/29	Median survival 60 months for isolated PIOL vs 35 months for PIOL + intracranial disease ($p < 0.05$)
Berenbom 2006	(High-dose) IV chemo, PO chemo, WBRT, ORT	MTX, vincristine, rituximab, procarbazine, cytarabine, carboplatin, dexamethasone	12	Not reported on an individual basis	2/12	1 alive in CR, 4 alive with cerebral disease, 7 died of cerebral disease
Grimm, Pulido, Omuru 2006	Retrospective series with various modalities	Retrospective series with various regimens	225	Not reported on an individual basis	Not reported on an individual basis	Median progression-free survival 18.7 months, median overall survival 33.1 months
Grimm, Pulido, Janke 2006	Retrospective series with various modalities	Retrospective series with various regimens	81	Not reported on an individual basis	47 total relapses: 30% ocular, 15% ocular + cerebral	Median progression-free survival 29.6 months, median overall survival 57 months
Isobe 2006	Chemo, WBRT, ORT	Retrospective series with various regimens	15	13/15 CR or CRu	1/13	Median overall survival 41 months, 2-year overall survival 74%
Jahnke, Korfel 2006	Retrospective series with various modalities	Retrospective series with various regimens	19	17/19 (13 CR, 4 PR)	6/17	Median progression-free survival 10 months, median overall survival 22.5 months[b]

[a]Patients may or may not have received all listed modalities and agents; see referenced articles for details.
[b]Survival data also includes patients with secondary intraocular lymphoma.
Abbreviations: PIOL, primary intraocular lymphoma; IV, intravenous; IT, intrathecal; WBRT, whole-brain irradiation; ORT, ocular radiation therapy; MTX, methotrexate; CR, complete remission; PO, oral; PR, partial remission; CHOP, cyclophosphamide/doxorubicin/vincristine/prednisone; CRu, unconfirmed complete remission.

Systemic therapy has the potential benefit of being able to treat concurrent CNS disease in PIOL.

Most studies on systemic chemotherapy for PIOL are high-dose methotrexate-based. In one study, nine patients with concurrent PCNSL and PIOL or isolated IOL were treated with intravenous methotrexate at a dose of 8 g/m^2. Micromolar concentrations of methotrexate were present in the vitreous in eight of eight patients, and were lower in the

vitreous compared with the aqueous in five of six patients in whom both chambers were assayed. Six complete ocular responses and one partial response were observed, and two patients had persistent PIOL despite detection of micromolar methotrexate concentrations. In the seven patients with concurrent PCNSL and PIOL, all had complete responses in the brain (Batchelor TT et al 2003). In a study using a similar treatment schedule for 25 patients with PCNSL of whom five had ocular involvement, ocular responses were observed in four patients, whereas all five responded in the brain, thus underscoring the ability of controlling concurrent cerebral disease with systemic chemotherapy (Batchelor T et al 2003).

Cytarabine alone at a dose of 2–3 g/m^2 achieved an ocular response in five out of six treated patients; however, four responses were only partial (Strauchen et al 1989).

A recent study with 10 IOL patients, among them two with secondary IOL, prospectively evaluated the efficacy and aqueous penetration of intravenous ifosfamide, oral trofosfamide and their active metabolites. Four patients had newly diagnosed and six relapsed disease. Ifosfamide doses ranged from 1500 to 2000 mg/m^2/day (days 1–3), and trofosfamide was given at a dose from 150 to 400 mg/day (continuous or intermittent administration). All patients responded, and progression-free survival (PFS) from first treatment was 6+ to 18 months. Active drug metabolites were detected in the aqueous humor in six of six patients treated with ifosfamide, and in one out of three patients treated with trofosfamide (Jahnke, Wagner et al 2005).

Intrathecal chemotherapy

In two patients with recurrent PIOL, intrathecal administration of methotrexate and cytarabine resulted in a sustained complete remission (Mason et al 2003).

Marked improvement in ocular lymphoma has been reported in one patient treated with intrathecal rituximab in a phase I study (Rubenstein et al 2004).

High-dose chemotherapy and autologous stem cell transplantation

High-dose chemotherapy followed by autologous stem cell support has been used for relapsed or refractory PIOL or PCNSL. In a study with 22 relapsed or refractory PCNSL/PIOL patients, two of the three patients with isolated PIOL achieved a sustained complete response, whereas the third patient relapsed in the eye after three months and died secondary to tumor progression. Five of eight patients with concomitant CNS and ocular disease had a partial or complete response. Five patients died from treatment complications, including two deaths from neurotoxicity (Soussain et al 2001).

In a similar study on intense chemotherapy with stem cell rescue with 14 PCNSL patients, two had ocular disease. One responded completely, whereas the second patient achieved a transient complete response after chemotherapy, but relapsed before stem cell rescue (Abrey et al 2003).

Treatment recommendations

Due to the rarity of this condition, literature on the treatment of PIOL mainly consists of an abundance of small case series which are difficult to compare (see above and Tables 2 and 3), and the treatment of choice for PIOL therefore remains controversial. Based on the available treatment data, no definite treatment recommendations can be given.

In a recent international effort coordinated by the IPCG, a retrospective case series of 81 patients with isolated PIOL was assembled from 15 centers in seven countries. Twenty-one patients received local (ocular) treatment alone, ie, intraocular methotrexate (n = 6), ocular radiation (n = 14), or both modalities (n = 1). Systemic chemotherapy alone was administered in 20, and a combination of chemotherapy and radiotherapy in 32 patients (five patients received no treatment, and details remained unknown in three). PFS and OS were 29.6 months and 57 months, respectively, and were unaffected by the choice of therapy. Nineteen patients (58%) died of CNS disease. Patients treated with ocular therapy alone did not have an increased risk of brain relapse ($p = 0.6$). The authors concluded that the best initial therapy in patients with isolated PIOL should be limited to local treatments to minimize systemic toxicity (Grimm, Pulido, Jahnke et al 2006).

A similar retrospective case series of 225 (164 evaluable) PIOL patients with concomitant parenchymal brain involvement was assembled from 15 centers in eight countries by the IPCG. Local ocular therapy (mainly radiation) in conjunction with treatment for cerebral disease was given to 92 patients, and PCNSL therapy without local ocular treatment to 72 patients. PFS and OS were 18.7 months and 33.1 months, respectively. The cause of death in 71% of patients was PCNSL progression or relapse. Patients treated with a combination of focal ocular therapy and specific PCNSL therapy had significantly longer PFS (19 months vs 14.2 months, $p = 0.008$). Since patients who received more aggressive ocular treatment had an improved PFS, it was concluded that the optimal initial therapy in patients with concomitant PIOL and PCNSL should include intraocular chemotherapy or ocular radiotherapy (Grimm, Pulido, Omuro et al 2006).

The importance of systemic chemotherapy for cerebral disease control in PIOL was emphasized in several studies. In one trial with 22 PIOL patients, among them 21 with concomitant brain disease, disease control was longer in PIOL patients whose treatment included systemic chemotherapy as compared to patients treated with radiotherapy alone, and ocular disease control was best for patients treated with a combination of systemic chemotherapy and ocular radiation (Ferreri et al 2002). A median OS of only 16 months in patients treated with chemotherapy not able to penetrate the blood-brain barrier has been reported in an Australian study (Hoffman et al 2003), this being in contrast to a median OS of 39 months in patients with isolated PIOL and 24 months in patients with PIOL secondary to CNS disease predominantly treated with blood-brain barrier-crossing chemotherapy (Hormigo et al 2004). In the latter study, patients whose ocular disease was identified and treated before CNS progression had a significantly improved survival, thus underscoring the need for CNS disease control and rapid diagnosis of PIOL. In a trial with 19 PIOL and three secondary IOL patients, median PFS was 12 months for patients treated with systemic therapy, but only 5.5 months after local therapy. Cerebral relapse occurred in six of nine patients after local therapy, but only in one of 13 patients after systemic chemotherapy; a second patient developed a systemic relapse (Jahnke, Korfel et al 2006).

Conclusions and future directions

Several questions in the diagnosis and management of PIOL still remain open, eg, regarding PIOL pathogenesis, prognostic factors, the optimal methotrexate dose in high-dose methotrexate-based regimens, and the timing and necessity of radiation. Animal models offer the opportunity to study various aspects of pathology, pathogenesis and treatment in PIOL (Chan et al 2005; Li et al 2006). There is no consensus on the optimal treatment of PIOL, and prognosis remains poor despite recent advances in diagnosis and treatment. Recent studies favor the use of systemic high-dose methotrexate-based chemotherapy in conjunction with local ocular treatment as first-line management for patients with concomitant PIOL and PCNSL. For patients with isolated PIOL, the current trend has shifted towards the first-line use of local treatment modalities. Future treatment strategies for PIOL/PCNSL could include intravenous rituximab that has already proven efficient in PCNSL and systemic lymphoma (Rubenstein et al 2003; Enting et al 2004; Wong et al 2004; Feugier et al 2005). The usefulness of intravitreal rituximab administration is under investigation (Kim et al 2006). Based on its efficacy in systemic lymphomas (Nowakowski et al 2006), radioimmunotherapy may be an interesting option in the future treatment of PIOL/PCNSL. Since dose intensity is important for the outcome of PCNSL patients (Kraemer et al 2001) and because of favorable neurocognitive outcomes (McAllister et al 2000), the approach of intraarterial chemotherapy in conjunction with osmotic blood-brain barrier disruption deserves further investigation. The role of high-dose chemotherapy followed by stem cell support should be further investigated in relapsed PIOL/PCNSL, and future studies should possibly be extended to first-line treatment of younger patients.

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