Primary CNS lymphoma with intraocular involvement

International PCNSL Collaborative Group Report

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ABSTRACT

Objective: To describe the demographics, diagnostic details, therapeutic management, and outcome in patients with primary CNS lymphoma (PCNSL) with ocular involvement.

Methods: A retrospective study of 221 patients was assembled from 16 centers in seven countries. Only HIV-negative, immunocompetent patients with brain and ocular lymphoma were included; none had systemic lymphoma.

Results: Median age at diagnosis was 60. Fifty-seven percent were women. Median Eastern Cooperative Oncology Group performance status was 2. Ocular disturbance and behavioral/cognitive changes were the most common presenting symptoms. Diagnosis of lymphoma was made by brain biopsy (147), vitrectomy (65), or CSF cytology (11). Diagnosis of intraocular lymphoma was made by vitrectomy/choroidal/retinal biopsy (90) or clinical ophthalmic examination (141). CSF cytology was positive in 23%. Treatment information was available for 176 patients. A total of 102 received dedicated ocular therapy (ocular radiotherapy 79, intravitreal methotrexate 22, and both 1) in addition to treatment for their brain lymphoma. Sixty-nine percent progressed at a median of 13 months; sites of progression included brain 52%, eyes 19%, brain and eyes 12%, and systemic 2%. Patients treated with local ocular therapy did not have a statistically significant decreased risk of failing in the eyes ($p = 0.7$). Median progression free survival and overall survival for the entire cohort were 18 and 31 months.

Conclusion: This is the largest reported series of primary CNS lymphoma (PCNSL) with intraocular involvement. Progression free and overall survival was similar to that reported with PCNSL. Dedicated ocular therapy improved disease control but did not affect overall survival.

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GLOSSARY

ECOG = Eastern Cooperative Oncology Group; **IPCG** = International Primary Central Nervous System Lymphoma Collaborative Group; **IT** = intrathecal chemotherapy; **MTX** = methotrexate; **PCNSL** = primary CNS lymphoma; **PFS** = progression-free survival; **RT** = radiotherapy; **WBRT** = whole brain radiotherapy.

Intraocular lymphoma is a rare subset of primary CNS lymphoma (PCNSL) that usually involves the retina, the vitreous, or the optic nerve head. It is a high grade, malignant tumor, usually of large B-cell histology. Intraocular lymphoma occurs in isolation or more commonly, in association with parenchymal brain lymphoma. It should be distinguished from systemic lymphoma with involvement of the orbit. It has been estimated that 15% to 25% of patients with PCNSL will have ocular dissemination at diagnosis, and thus represents a small fraction of

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patients with a rare disease.¹ Because it is so rare, the natural history and optimal treatment of PCNSL with ocular dissemination at diagnosis is unknown.

The International Primary Central Nervous System Lymphoma Collaborative Group (IPCG) is a multidisciplinary group from North America, Europe, Australia, and New Zealand established in 2002 under the sponsorship of the International Extranodal Lymphoma Study Group. Given its rarity, parenchymal brain lymphoma with ocular dissemination at diagnosis was identified as an area for which collaborative work could further our understanding of the disease.²

METHODS A retrospective chart review was conducted at 16 participating IPCG centers from seven countries to collect information on HIV seronegative, immunocompetent patients with intraocular lymphoma diagnosed between 1977 and 2005; patients with systemic lymphoma at diagnosis were excluded. Histologic diagnosis was reviewed at each participating institution by an experienced hematopathologist. Patient characteristics, diagnosis, treatment, site and date of progression, salvage treatment, treatment-related toxicity, and survival were obtained. The identified patients were divided into two groups: those with brain lymphoma and ocular dissemination reported here, and those with isolated ocular lymphoma who were reported previously.³ Local Institutional Review Board or Ethics Board approval was obtained by each participating center.

Progression-free survival (PFS) and overall survival were calculated from date of ocular lymphoma diagnosis to date of first progression, or death. Surviving patients were censored at date of last follow-up. Survival curves were drawn using the Kaplan-Meier product-limit method,⁴ and comparisons were examined by the log-rank test. Analysis of discrete variables was performed using the χ^2 method with Yates correction for expected values less than 5. Potential prognostic factors (age, performance status, gender) and treatment modalities were evaluated by Cox proportional-hazard analyses. Multivariate analyses were performed to identify variables that were independent predictors of outcome. Factors with $p \leq 0.1$ in the univariate analyses were entered as candidate variables and multivariate analyses were performed in a stepwise fashion. Calculations were performed using STATA version 8.0 (Stata Corporation, College Station, TX). Given the descriptive nature of this analysis, there were no a priori power estimates.

RESULTS Clinical features. A total of 221 patients were identified (table 1). All patients had lymphoma involving the eyes and brain parenchyma at diagnosis; patients with primary intraocular lymphoma with leptomeningeal dissemination were reported separately.³ The median age at diagnosis was 60 years (range: 16–82); 57% were women. The median Eastern Cooperative Oncology Group performance status was 2. Twelve patients had a prior unrelated malignancy: the site of origin included breast (3),

Table 1 Patient characteristics		
	No. of patients	%*
Total	221	
Age, y		
Median	60	
Range	16–82	
Female	126	57
ECOG performance status		
Median	2	
0–1	132	60
2	44	20
3–4	42	19
Not specified	3	1
Prior malignancy	12/122	10
Initial symptoms		
Ocular symptoms	137	62
Isolated ocular symptoms	7	3
Behavioral/cognitive change	59	27
Hemiparesis	32	14
Headache	32	14
Aphasia	25	11
Seizure	11	5
Ataxia	9	4
Visual field deficit	4	2
Not specified/other	66	29
Diagnostic procedure		
Brain biopsy	138	62
Vitreotomy	55	25
CSF cytology	9	4
Vitreotomy, brain biopsy	8	4
Vitreotomy, CSF cytology	1	0.4
Vitreotomy, CSF cytology, brain biopsy	1	0.4
Not specified	9	4
Diagnosed with vitrectomy or CSF	78	33
Ocular lymphoma diagnosis		
Vitreotomy/choroid/retinal biopsy	90	41
Slit lamp/ophthalmic examination	131	59

*Percentage based on number of positive cases divided by number of cases with available information.
ECOG = Eastern Cooperative Oncology Group.

basal cell of skin (1), myeloma (1), chronic lymphocytic lymphoma (1), transitional cell carcinoma of the bladder (1), melanoma (1), colon (1), and not specified (3).

The average duration of symptoms prior to diagnosis was 3 months (range: <1 to 48 months). Presenting symptoms included ocular complaints 137 (62%), behavioral/cognitive changes 59 (27%),

hemiparesis 32 (14%), headache 32 (14%), aphasia 25 (11%), seizure 11 (5%), ataxia 9 (4%), visual field deficit 4 (2%), and other 49. Seven patients presented with isolated ocular symptoms. Ocular symptoms were defined as blurred vision, floaters, or decreased visual acuity. Data regarding the incidence of bilateral vs unilateral ocular involvement were unavailable.

All patients had a histologic diagnosis of lymphoma; specific histologic subtypes included large B-cell (161), T-cell (5), and subtype not specified (55). Initial histologic diagnosis was made by brain biopsy (147), vitrectomy (65), or CSF cytology (11); in 10 patients more than one site was credited as the source of initial diagnostic material and in 9 the specific site of diagnostic material was not available. Intraocular dissemination of lymphoma was diagnosed by biopsy of the vitreous, choroid, or retina in 90; clinical assessment with slit lamp or detailed ophthalmologic examination confirmed the diagnosis of ocular dissemination in the remaining 131. In addition, a number of additional tests were performed to further document ocular involvement, including flow cytometry (14), IL-10 assay (6), PCR analysis of the vitrectomy specimen (3), and ocular ultrasound (2). A total of 151 patients had a staging lumbar puncture performed which revealed positive CSF cytology in 35 patients (23%).

Therapeutic management. Detailed treatment information was available for 176 patients and is summarized in table 2. A total of 141 patients received either systemic or intraocular steroids; however, the response to steroids was rarely evaluated. The initial treatment approach was categorized by whether a patient received dedicated ocular therapy defined as ocular radiotherapy or intraocular chemotherapy.

A total of 102 patients received dedicated ocular therapy in addition to treatment for their brain lymphoma; the median age of this group was 58 years and median ECOG was 1. Dedicated ocular therapy consisted of ocular radiotherapy in 79, intraocular methotrexate in 22, and both modalities in 1. Systemic chemotherapy was methotrexate-based in 84%. Eleven patients received non-methotrexate-based regimens including CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), high dose cytarabine (HDAC), or ifosfamide. Sixty-three patients were treated with whole brain radiotherapy (WBRT).

Seventy-four patients did not receive any dedicated ocular therapy; the median age of this group was 61 years and median ECOG was 1. In these patients treatment included methotrexate-based chemotherapy (52) and other systemic chemotherapeutic regimens (15) including CHOP, HDAC, or

Table 2 Treatment summary	
	No. of patients
Total	221
Focal ocular therapy +/- CNS lymphoma treatment	102
Ocular RT alone	6
Ocular MTX alone	1
Ocular MTX + chemotherapy + WBRT	2
Ocular MTX + chemotherapy + IT	11
Ocular MTX + chemotherapy	6
Ocular MTX + IT	2
Ocular RT + chemotherapy + WBRT + IT	24
Ocular RT + chemotherapy + WBRT	19
Ocular RT + chemotherapy + IT	2
Ocular RT + chemotherapy	10
Ocular RT + WBRT	16
Ocular RT + WBRT + IT	2
Ocular MTX + ocular RT + chemotherapy	1
CNS lymphoma treatment, no focal ocular therapy	74
Chemotherapy + WBRT + IT	5
Chemotherapy + WBRT	13
Chemotherapy + IT	20
Chemotherapy	29
WBRT + IT	1
WBRT	6
No treatment	3
Treatment unknown/incomplete	42

MTX = methotrexate; WBRT = whole brain radiotherapy; RT = radiotherapy; IT = intrathecal chemotherapy.

ifosfamide. Twenty-five received WBRT. Three patients received no definitive treatment and treatment details were unavailable in 42.

Outcome. Median PFS and overall survival for the entire cohort were 18 and 31 months (figure 1). Median PFS was prolonged in patients who received dedicated ocular therapy at 19 months as compared to 15 months in those who did not receive dedicated ocular therapy ($p = 0.01$, figure 2). However, the initial treatment approach did not impact overall survival (figure 3). Similarly, multivariate analysis identified receipt of dedicated focal therapy as the only factor predictive of PFS ($p = 0.01$, HR = 1.69, 95% CI 1.12, 2.54) while only age was predictive of overall survival ($p < 0.0005$, HR = 1.04, 95% CI 1.02, 1.05). At last follow-up, seventy-one patients remain alive with a median follow-up of surviving patients of 36 months. The causes of death include PCNSL in 107, toxicity in 12, unrelated in 8, and unknown in 23.

Figure 1 Kaplan-Meier curve showing progression free (dashed line) and overall survival (solid line) for all 221 patients with primary CNS lymphoma with intraocular involvement

A total of 153 patients (69%) progressed a median of 13 months (range: 0.5–81) after initial therapy. Sites of progression included brain in 79 patients (52%), eyes in 29 (19%), brain and eyes in 19 (12%), systemic in 3 (2%), meninges in 2 (1%), brain and meninges in 2 (1%), eyes and meninges in 2 (1%), spinal cord in 1 (0.7%), brain, eyes, and systemic in 1 (0.7%), brain, eyes, and meninges in 1 (0.7%), and unknown in 14 (9%). Risk of progression and pattern of failure was not effected by the initial therapeutic approach; those patients who did not receive dedicated ocular therapy did not have a statistically significant increased risk of ocular recurrence ($p = 0.7$).

DISCUSSION It has been estimated that 15% to 25% of patients with PCNSL will have intraocular involvement at diagnosis⁵; however, the prognostic and clinical impact of intraocular dissemination is unknown. Most reported series only include a handful of patients with PCNSL with ocular dissemination

tion; eligibility for clinical trial participation among this subset of patients is variable. This report represents the largest series of patients with PCNSL with parenchymal brain lymphoma and ocular dissemination assembled to date.

More than one-third of the patients in our series did not complain of ocular symptoms at diagnosis. This demonstrates the importance of a complete staging evaluation including a slit lamp and detailed ophthalmic examination in all patients with newly diagnosed PCNSL. Failure to diagnose and assess intraocular lymphoma may result in a reservoir of persistent active disease if disregarded. Furthermore, approximately 40% of patients were diagnosed on the basis of vitrectomy or ocular biopsy and could potentially have avoided intracranial biopsy and its associated risks.^{6,7} Flow cytometry and analysis of cytokine levels in the vitreous may help to confirm the diagnosis in patients with suspicious but inconclusive cytology.²

An obvious hypothesis about the clinical impact of PCNSL that has disseminated to the intraocular compartment at diagnosis is that the prognosis would be worse than that of patients with isolated brain disease. Worse prognosis, if seen, could be attributed to increased disease burden, lymphoma involving a compartment that is difficult to treat, or a more aggressive histology associated with more widespread disease dissemination. However, our series suggests that the natural history of patients with PCNSL with ocular dissemination is similar to those patients with isolated parenchymal brain lymphoma. Twenty-three percent of those tested in our series had a positive CSF cytology at diagnosis which is similar to 26% from a prospective study of patients with PCNSL.⁸ The average age is identical to that reported in most large PCNSL series and the patient outcomes largely match those described for PCNSL with an average survival of approximately 3 years.^{9–14} Furthermore, two recent large efforts to define independent prognostic variables failed to identify ocular dissemination as an independent risk factor.^{15,16}

Optimal management of patients with PCNSL who have ocular dissemination at diagnosis is not clear. Eradication of ocular lymphoma is critical to eliminate the eye as a reservoir of untreated disease that increases the risk of recurrence. A wide range of treatment modalities have described efficacy against intraocular lymphoma including high-dose systemic methotrexate (8 g/m²), myeloablative chemotherapy with autologous peripheral blood progenitor support, direct intraocular administration of chemotherapy and immunotherapy and ocular radiotherapy; however, most have been described in small series of patients.^{17–20} In this series, the incorporation of therapy directed specifically at the eye, defined as ocular

Figure 2 Kaplan-Meier curve showing progression free survival for patients treated with (dashed line) and without (solid line) dedicated ocular therapy in addition to treatment for their brain disease

Figure 3 Kaplan-Meier curve showing overall survival for patients treated with (dashed line) and without (solid line) dedicated ocular therapy in addition to treatment for their brain disease

radiotherapy or intraocular chemotherapy, resulted in prolonged disease control but did not impact survival or risk of recurrent ocular lymphoma. Specific treatment recommendations cannot be derived from our series; however, it seems appropriate to suggest that patients with PCNSL with ocular dissemination receive specific therapy with known efficacy against intraocular lymphoma.

This study has several limitations. Our data were based on retrospective information abstracted from the medical records by the submitting physician; complete demographic and treatment details were not available for all patients. Individual patient charts were not available for data verification by the primary authors. Patient evaluation and management were heterogeneous across the participating institutions; while this accurately reflects the varied approach to intraocular lymphoma in academic and community practices, this heterogeneity limits our ability to perform detailed analyses. Unknown confounding variables may have influenced treatment selection. Further, this study was largely conducted at tertiary care centers and cases submitted likely reflect a referral or selection bias. Central review of pathology was not performed; however, all centers submitting cases have expert lymphoma pathologists who reviewed or confirmed the diagnosis on submitted cases.

Ocular dissemination of lymphoma is a common finding among patients with a new diagnosis of PCNSL. Early recognition of ocular involvement may facilitate the diagnosis of PCNSL and obviate the need for brain biopsy in some patients. As there is no clear prognostic impact related to ocular dissemination, it seems reasonable to include these patients in prospective clinical trials for PCNSL. Specific therapy directed against the ocular compartment may prolong disease control.

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