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Ocular and Adnexal Lymphoma

Second Edition

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Series Editor

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Preface

Ocular and adnexal lymphomas are rare and diverse; hence their diagnosis and treatment usually require special expertise. Increasingly, the care of such a patient is provided by a multidisciplinary team comprising ocular oncologists, general oncologists, pathologists, radiation oncologists, and other specialists. The field of lymphoma is advancing rapidly because of accelerating progress in tumor biology, pharmacology, and the advent of targeted therapies. For all these reasons, we felt that there was scope for a new edition of the monograph regarding ocular and adnexal lymphoma.

To harmonize the terminology across this monograph the editors have taken the liberty of labeling vitreo-retinal lymphoma as PCNSL-O as the preferred term to emphasize that it is an ocular variant or subset of primary CNS lymphoma (PCNSL). Those with concurrent CNS and ocular disease may be labeled as PCNSL-CNS/O in contrast to patients with CNS only involvement (PCNSL-CNS) at presentation. This monograph, a conjoint effort of ocular oncologists, general oncologists, and pathologists, comprises 11 chapters covering molecular pathology, clinical features, and treatment. It is our sincere hope that this monograph will provide a useful resource for providing appropriate care to our patients.

Hyderabad, Telangana, India — Vishal R. Raval
Palo Alto, CA, USA — Prithvi Mruthyunjaya
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1 Primary Central Nervous System Lymphoma: Terminology and Outcome Measures

Arun D. Singh and Vishal R. Raval

Introduction

Central nervous system (CNS) is rarely affected by lymphoma, either as a primary site or as secondary site with prior non-CNS involvement [1]. In either case, diffuse large B cell lymphoma (DLBCL) is the most frequent variant [2]. Other less common subtypes include Burkitt lymphoma, mantle cell lymphoma, and anaplastic large cell lymphoma [3]. Histologic subtypes of lymphoma that most frequently affect ocular adnexa such as extranodal marginal zone lymphoma, follicular lymphoma, lymphoplasmacytic lymphoma, and chronic lymphocytic leukemia/small lymphocytic lymphoma rarely affect the CNS [3].

Terminology

To a large extent, vitreoretinal lymphoma mimics the pattern of CNS lymphoma. However, there is a lack of consensus regarding appropriate terminology for primary CNS lymphoma (PCNSL) involving the ocular compartment. Historically CNS lymphoma involving the eye was described as reticulum cell sarcoma [4] and microgliomatosis [5]. In the last two decades, terminology such as intraocular lymphoma (IOL) has been introduced [6]. However, this term is confusing as it does not differentiate lymphoma involving such as the retina and vitreous (high grade DLBCL subtype) from lymphoma involving the uveal tract (low grade extranodal marginal zone lymphoma) [7]. Vitreoretinal lymphoma (VRL) is the most commonly used term in the literature; however, it implies that the disease originates in the eye [8].

We suggest PCNSL-O as the preferred term to emphasize that it is an ocular variant or subset of PCNSL [9, 10]. Those with concurrent CNS and ocular disease may be labeled as (PCNSL-CNS/O) in contrast to patients with CNS only involvement (PCNSL-CNS) at presentation.

PCNSL is a subtype of non-Hodgkin lymphoma confined to the CNS compartments. As per the 2017 World Health Organization classification of hematopoietic and lymphoid tumors [11], PCNSL is classified as primary DLBCL of the CNS. The CNS compartments include the brain (deep cortical regions, periventricular regions, and basal ganglia), spinal cord, meninges, and eyes [12]. The involvement of the eye and other CNS compartments varies as ophthalmic manifestations can precede, occur simultaneously with or follow disease in other CNS sites.

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Sixty percent to 90% of patients with ocular involvement ultimately involve other CNS compartments, while 20% of patients with PCNSL present with concurrent ocular involvement [13, 14]. The median interval between the progression of lymphoma from the eye to other CNS compartments and vice versa varies over a follow-up of 8–29 months [12, 13, 15]. The overall prognosis of ocular involved PCNSL is also poor, because of CNS involvement with 5-year survival rates between 25% and 40% [16].

Secondary vitreoretinal lymphoma also follows pattern similar to that of secondary CNS lymphoma with DLBCL being the predominant lymphoma subtypes identified by retinal biopsy [17, 18]. Uncommon vitreoretinal involvement in the setting of cutaneous peripheral T-cell lymphoma, the NK-T cell lymphoma and adult T-cell lymphoma/leukemia and CNS T-cell lymphoma has also been reported [19–23].

Outcomes

Currently, the management of PCNSL-O is focused on local ocular control, given insufficient evidence that ocular treatment decreases progression to CNS [10, 24]. Despite achieving high rates of local ocular control with intravitreal agents including methotrexate [25] and rituximab [10, 26].

Additional secondary and tertiary outcome measures of progression-free survival (PFS) and overall survival (OS), respectively, should also be reported.

Primary Outcome

Assessment of local treatment response in the eye and CNS compartments is the primary outcome measure. Local treatment response can be assessed using terminology and criteria proposed by International PCNSL Collaborative Group for standardization of baseline evaluation and response criteria for primary CNS lymphoma [27].

- Complete response (CR); no evidence of residual disease within the anterior eye chamber, vitreous cavity, or retina
- Partial response (PR): 50% or greater reduction in ocular disease
- Progressive disease (PD): 25% increase of ocular manifestations compared to pretreatment assessment

Two additional concepts specific to PCNSL-O need special mention

- Relapse in local ocular disease or recurrence after a defined period of CR. This is not synonymous as progression of lymphoma into CNS compartment and it is preferable not to include such cases with compartmental progression for reporting of progression-free survival (PFS)
- Minimal residual disease (MRD) concept of subclinical tumor burden is used frequently in the management of leukemias [28]. A similar concept of MRD in treatment and staging of vitreoretinal lymphoma is recommended [29] as most of the patients at the end of treatment are left with residual vitreous opacities/debris which seems to be clinically nonactive. However, without sure knowledge of the origin of those opacities, it is not entirely correct to label such a patient as a complete response (CR). Therefore, at minimum ophthalmologists should document the presence or absence of all vitreous opacities using a graded scale.

Secondary Outcome: Progression-Free Survival (PFS)

Given that PCNSL-O is a subset of PCNSL [9] with a strong propensity to progress to the CNS, treatment effectiveness should not be evaluated solely in terms of local ocular response [10]. Most retrospective studies have defined PFS as time from onset of symptoms [30] or diagnosis to progression or relapse/death [31–34]. PFS defined in this way results in heterogeneous outcomes such as local relapse, progression, and death making results among studies non-comparable. The lack of well-defined outcome measures, particularly related to progression, further hampers valid comparisons between published studies [10].