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International Central Nervous System and Ocular Lymphoma Workshop: Recommendations for the Future

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CNS and Ocular Lymphoma Workshop Group

Abstract

Purpose—To bring together multidisciplinary experts to discuss primary central nervous system lymphoma (PCNSL) and primary intraocular lymphoma (PIOL).

Methods—NIH campus workshop discussion focusing on future work in both clinical and basic lymphoma research.

Results—The discussion lead to recommendations on elucidating disease pathobiology, improving diagnostic accuracy and sensitivity, and novel therapeutic strategies.

Conclusions—Approaches which have been successfully applied to other neoplasms, such as microarray, may be applied to improve diagnostic accuracy and sensitivity of PCNSL and PIOL and should be systematically incorporated into clinical trials of both. Development of animal models of PCNSL and PIOL may be useful in understanding the unique ocular and CNS milieu. Disease detection by radiological, nuclear medicine, molecular and flow cytometric approaches should be systematically studied to improve early diagnosis, accurate staging, and response evaluation. Improved therapy remains the ultimate goal. Efforts in these arenas should be coordinated on a national and international level.

Keywords

Intraocular lymphoma; imaging; masquerade syndrome; microarray

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INTRODUCTION

Primary intraocular lymphoma (PIOL) is a rare malignancy that falls into the category of masquerade syndrome. This syndrome defines a group of diseases or disorders with manifestations of intraocular inflammation and is frequently misdiagnosed as chronic uveitis. There are two main distinct forms of intraocular lymphoma. One originates from outside the central nervous system (CNS) and metastasizes to the eye, whereas the other one falls within the continuum of primary CNS lymphoma (PCNSL). Hence, when PCNSL initially involves the retina, it is called primary intraocular lymphoma (PIOL).[1] PCNSL has an annual frequency of 1,000 cases in the United States, and has tripled over the past two decades.[2,3] The incidence of PCNSL is 4–5 per 1,000 person-years among patients with AIDS and 0.3% per 100,000 persons-years in immuno-competent patients.[4,5] Up to 25% of PCNSL present in the eye at the time of diagnosis, so that there are at least 100 new cases of PIOL yearly in the United States. PIOL and PC-NSL typically affect an older population with a median age in the late 50s and 60s, and a slight male predominance.[1,6,7]

PIOL typically presents as a posterior uveitis and patients complain of floaters and a mild decrease in vision. The disease is bilateral in at least 80% of the cases. The findings upon examination include keratitic precipitates on the posterior cornea and a mild inflammatory process in the front of the eye. The vitreous frequently has many cells that appear in sheets. The retina typically has lesions that can be seen either by indirect ophthalmoscopy or with fluorescein angiography.[8] A rather typical clinical finding is preservation of visual acuity out of proportion to the amount of inflammatory disease. The staging evaluation centers around the CNS since involvement of the CNS is common and systemic spread is rare; when systemic spread does occur, it is a late finding. The workup typically includes an MRI, lumbar tap, and usually a vitrectomy. The diagnosis is based on the cytology of the specimen taken from the eye if no malignant cells are found in the CSF. The vitreous sample frequently consists of normal reactive lymphocytes and large atypical lymphoid cells which are often in the minority. Cytologically, the malignant cells are large malignant B-cells with scanty basophilic cytoplasm, large nuclei, and prominent nucleoli that typically express CD19, CD20, and CD22. Other characteristics include a high IL-10/IL-6 ratio in the vitreous and an immunoglobulin heavy-chain gene rearrangement.[1,9] The Laboratory of Immunology/National Eye Institute (LI/NEI) has developed procedures that aid in diagnosis, including methods for maintaining cellular viability, immunocytopathology, cytokine analysis,[9] and molecular markers (immunoglobulin heavy-chain gene rearrangements).[7,8]

Therapy for PIOL is problematic in part because the primary focus has been on local control. Initial approaches centered on radiotherapy, but this had a minimal effect on extending survival and was associated with the possible development of radiation retinopathy. Methotrexate is also used to treat PIOL, both systemically as well as by intraocular injection, but rarely if ever offers curative potential.[10–12] Hence, new strategies that preserve visual function while recognizing the need for potentially curative approaches in the CNS, where the disease is frequently found, should be the focus for treatment of PIOL.

MATERIALS AND METHODS

It was felt that the best way to further the discussion in order to move research forward regarding this disorder was to have a conference to discuss this rare entity. The goal was to develop strategies for the future. The first was to bring basic and clinical researchers together to discuss primary CNS and intraocular lymphoma. The goal was to develop a roadmap for further research and therapy. This meeting took place on September 13 and 14, 2004, on the NIH campus in Bethesda, MD, USA. The meeting was divided into various sections. Each was devoted to specific areas pertaining to lymphoma. One person was asked to present an overview

of the subject at hand and to finish with points that needed to be discussed. Facilitators then helped the discussion which was based on the questions and those additional ones posed by the group. There was a recorder for each session. At the end of the sessions on the second day, the leader of each group reviewed the points and recommendations which were then discussed by the whole group.

RESULTS

Below are the recommendations of the group dividing the challenges into three areas: Mechanisms and Models, Diagnostic Approaches, and Therapy. These were generated over the two-day period.

Mechanisms and Models

The natural history of PIOL/PCNSL suggests that these tumors possess cellular mechanisms that are distinct from other diffuse large B-cell lymphomas (DLBCL). Indeed, it is known that systemic DLBCL are comprised of at least three molecular subtypes termed germinal center B cell (GCB), activated B cell (ABC), and primary mediastinal B cell (PMBL).[13–15] In addition to molecular differences, these subtypes exhibit differences in clinical outcome and presentation. Likewise, the confinement of PIOL/PCNSL to the CNS for most of their natural history suggests a unique pathobiology that reflects dependence on the CNS microenvironment and/or trafficking signals. Comparative microarray, proteomics, and genomic studies with systemic DL-BCL subtypes as well as normal B cells isolated from the CNS may provide insight into the pathobiology of PIOL/PCNSL. It should also not go unnoticed that CNS involvement by systemic DLBCL is associated with extranodal spread and may provide an understanding of specific growth requirements within the CNS compartment.[16] For example, does PIOL/PCNSL possess different chemokine or lymphokine receptors or other receptors that differentiate them from systemic DLBCL? The development of animal model(s) may also assist in elucidating the biology of the ocular and CNS microenvironment. Techniques for the development of cell lines from PIOL are a first step. Basic questions of why these cells have an affinity to particular cells in the eye, such as the retinal pigment epithelium, also need to be addressed.

The pathobiology of treatment response should be addressed. It is unclear if the low cure rate of PIOL/PCNSL is related to drug penetration through the blood-brain barrier and/or to higher apoptotic thresholds. Indeed, some of the most effective drugs in systemic DLBCL, such as anthracyclines, have low CNS penetration and are either omitted from treatment regimens or if not, likely achieve subtherapeutic concentrations.[17] Much is known about drug resistance in systemic DLBCL and molecular approaches should be employed to detect mechanisms in PCNSL/PIOL.[14]

Diagnostic Approaches

Current diagnostic approaches are suboptimal. The clinical signs of the ocular disease have yet to be clearly defined, and standard guidelines for diagnosis and staging have only recently been established.[18] It has been suggested that a diagnostic scoring system be devised to assist in the diagnosis of PIOL. More sensitive technologies are needed to diagnose and follow CNS disease. The use of routine MRI imaging with altered T1-weighted + T2 + fat and flair suppression parameters should be fully evaluated and standardized. Other modalities such as infrared (Tau imaging) should be analyzed as well. Currently available techniques for the detection of low volume disease should be exploited and routinely employed for early discovery of PIOL cells in the eye. While classical cytology remains the ‘gold standard’, its detection sensitivity is relatively low compared to flow cytometry and molecular techniques.[16, 19] Indeed, a panoply of molecular testing can be done with cells obtained from the vitreous

and cerebral spinal fluid such as gene rearrangement studies, proteomic screening, as well as searching for mutations whether germ line or somatic. Lymphokine determinations should become routine. The preparation of the vitreous for pathologic evaluation and molecular studies needs to be standardized. There was a strong feeling that while standard 3-port vitrectomies can be performed in Western countries, the proper preparation of the vitreous sample for the diagnosis of PCNSL cannot. It was also noted that corticosteroid treatment may obscure the diagnosis after vitrectomy because of cytolytic effects on tumor cells, highlighting the need to consider PIOL early in the differential diagnosis of masquerade syndrome.[15,16] The handling and subsequent analysis of the specimen is particularly critical. In general, malignant cells comprise the minority of cells and are often necrotic. An initial core vitreous specimen of 1–2 cc should be placed in cell culture media and immediately processed for cytology, flow cytometry, immunocytopathology,[20] cytokine analysis,[21] and molecular markers.[1]

Therapy

Current therapies are not curative in the majority of patients with PIOL/PCNSL, although advances have been made in quality-of-life measures and overall survival. The barriers to cure are likely to be multifactorial, but can be reasonably ascribed in part to the older median age of the patient population, where treatment is less well tolerated, and to drug penetration through the blood-brain barrier. Unfortunately, little is known about the relative treatment sensitivity of PCNSL compared to systemic DLBCL.[22] In the latter diseases, treatment failure has been associated with high tumor proliferation, p53 mutations, and overexpression of the anti-apoptotic protein, Bcl-2, that reflect growth rate and apoptotic sensitivity.[23,24] More recently, the ABC DL-BCL subtype, which is associated with overexpression of NFκB and Bcl-2 has been linked by some to treatment failure with standard CHOP chemotherapy.[14] Interestingly, some studies suggest that PCNSL may be derived from germinal center B cells, which by the standards of systemic GCB DLBCL, would suggest relatively good treatment sensitivity.[25] Other studies have investigated apoptotic proteins and tumor proliferation in PCNSL and found that tumor proliferation rates and Bcl-2 expression are similar to those found in systemic DLBCL.[22,23] However, the expression of these biomarkers that have not been related to clinical outcome of PCNSL have not been evaluated in a systemic manner.

Recent treatment approaches in systemic DLBCL have yielded potential cure rates in up to 80% of the patients.[26] Such advances should theoretically be within reach of PIOL/PCNSL. In this regard, an important advance over the past decade is the move away from whole brain radiation as the mainstay of treatment to the use of systemic combination chemotherapy.[27] Indeed, experience in PCNSL confirms the essential palliative nature of whole brain radiation as well as its high rate of long-term toxicity.[25] Important lessons can be learned from the chemotherapy of systemic DLBCL. Foremost is the observation that cure requires combination chemotherapy. Of course, the rational selection of agents for the treatment of PCNSL is dependent on the penetration of the blood-brain barrier.[28] This biology has driven the selection of systemic chemotherapy for PCNSL. While the ability of high-dose methotrexate to achieve reasonable therapeutic levels in the CNS has led to its common use, there is little clinical or theoretical evidence to support its curative potential as a single agent. Indeed, basic precepts would advise its combination with other classes of agents such as alkylating and tubulin-binding agents and topoisomerase II inhibitors.[27,29] Recent studies have shown promising results with combination chemotherapy in younger patients with a plateau in time-to-treatment failure in the range of 60%, suggesting potential cure.[27]

Rituximab, a monoclonal antibody against the CD20 antigen present on virtually all PCNSL tumors, represents the most important advance in the treatment of DLBCL over the past 30 years. The addition of rituximab to standard CHOP chemotherapy in older patients with systemic DLBCL has yielded improvements in progression-free survival of 24%.[30] Although

rituximab penetrates the CNS poorly, with 0.1% of the systemic concentration, it can achieve therapeutic concentrations as judged by single agent activity against CNS DLBCL.[31,32] Furthermore, its prolonged half-life can result in relatively stable, albeit low, levels over time. Studies are also investigating its safety for intrathecal administration.[33,34] Such observations lay the ground work for its integration into regimens for PCNSL, which are currently ongoing.[35]

An important consideration for any treatment approach is its risk benefit and clinical goal. The older median age of PIOL/PCNSL patients constrains the use of more aggressive and toxic treatments and may lead to a decision to pursue palliative approaches. However, it is important to recognize that in the absence of such constraints, the clinician should strive for curative approaches. This is a particularly important concept for PIOL, where local treatment approaches are virtually always palliative. Hence, we recommend that patients with PIOL always be evaluated by an expert in PCNSL and receive appropriate evaluation for CNS spread.[18] Indeed, even in the absence of demonstrable CNS spread at the time of PIOL presentation, the high likelihood of subsequent CNS disease suggests a need for systemic treatment from the outset. Of course, such decisions must be based on the patients overall medical condition and expectations.

In addition to discussions surrounding the best use of systemic therapy versus local therapy versus radiation, several new therapeutic approaches were enunciated during the meeting. In addition to systemic and local anti-CD20 therapy, some of the local therapies that need to be considered include: protein kinase inhibitors, siRNA, anti-angiogenic agents, anti-adhesion molecule therapy, anti-CD22 constructs, and anti-IL-10 therapy. Because such strategies need to be evaluated through well-conceived clinical studies, and these diseases are relatively rare, there is a need for a PIOL/PCNSL clinical consortium for their study.

WAYS OF CONTINUING THE MOMENTUM

There was a strong feeling that an infrastructure needs to be put in place to make significant progress in understanding this disease. There is a need to foster collaborations. Existing cancer networks in the United States and Europe have no ophthalmologic representation. Awareness of this tumor could be increased dramatically in the cancer community with the active participation of ophthalmologists. Websites could be used to foster and exchange ideas. There is a need for an information database and grants that would support work on this disorder by being multidisciplinary and multinational. An additional approach in the United States would be the establishment of ‘Centers of Excellence’ so that the majority of patients would be seen and treated in these centers. Beyond the ‘Centers of Excellence’, networks of researchers could be established (coordinated by the NEI and NCI) to study key aspects of the disease such as the elucidation of basic mechanisms, diagnostics, and therapy. These networks would be responsible for follow-up to the next meetings. There was a consensus that the NEI and NCI should consider developing a comprehensive initiative to create an infrastructure to support such studies.

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AppendixCNS and Ocular Lymphoma Workshop Group

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