Clinical Characteristics of 95 Patients With Ocular Adnexal and Uveal Lymphoma: Treatment Outcomes in Extranodal Marginal Zone Subtype

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Abstract

Involved-field radiotherapy (IFRT) is effective for unilateral ocular adnexal lymphoma (OAL) but treatment for higher stages is unclear. We retrospectively evaluated 95 patients with OAL and report the characteristics and outcomes. Progression was more likely with rituximab than IFRT, but systemic progression was more likely with IFRT. IFRT remains the standard for localized OAL, but rituximab might have a role in higher stage OAL.

Background: Lymphoma rarely presents in the ocular adnexa but is usually extranodal marginal zone (ENMZ) lymphoma when it does. Involved-field radiotherapy (IFRT) is the standard of care for unilateral disease, but the optimal management of more extensive disease is unclear. **Patients and Methods:** We retrospectively evaluated the clinical characteristics and outcomes of 95 patients with ocular adnexal lymphoma (OAL) or uveal lymphoma treated or diagnosed at our institution. All patients identified were included in the risk factor analysis for progression-free survival (PFS). The initial treatment-related outcomes were assessed for ENMZ OAL only (n = 62). **Results:** With a median follow-up of 32 months, significant risk factors for PFS after initial treatment were age (hazard ratio, 1.33; 95% confidence interval, 1.02-1.74), female gender (hazard ratio, 2.04; 95% confidence interval, 1.04-4.00), and a history of lymphoma (hazard ratio, 2.31; 95% confidence interval, 1.12-4.78). In ENMZ, IFRT was associated with improved PFS (median, 5.4 years; $P < .001$). Progression occurred in 7 of 39 (23%), with 6 of the 7 (86%) at systemic sites. Single-agent rituximab was typically used for bilateral ocular or systemic presentations of ENMZ OAL. Progression occurred in 7 of 11 (64%), with no progression at systemic sites. All progression events in those initially treated with rituximab occurred in the ocular adnexa. **Conclusion:** The results of the present study have confirmed IFRT as the standard for unilateral ENMZ OAL. Single-agent rituximab was an effective agent for bilateral ocular or systemic ENMZ OAL, particularly for systemic control, but ocular progression should be closely monitored. Combined modality therapy should be studied further in bilateral and systemic ENMZ OAL.

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Introduction

The ocular adnexa, defined as the eyelids, conjunctiva, lacrimal apparatus, muscles, and other connective tissue in the orbit, are a rare site of lymphoma, representing ≤ 8% of extranodal presentations of non-Hodgkin lymphoma.[1] Ocular adnexal lymphoma (OAL) often presents as unilateral or bilateral ocular-only disease (60%-80%), although OAL can also have concurrent systemic involvement (15%-20%).[2,3] Bilateral disease will be seen in 10% to 15% of ocular-only presentations.[4] The ocular adnexa can also be a site of relapse in otherwise systemic lymphomas.[2,5,6] Indolent subtypes of non-Hodgkin lymphoma represents 80% to 85% of primary OALs,[2,4] with extranodal marginal zone (ENMZ) of the mucosa-associated

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lymphoid tissue (MALT) type occurring in 45% to 55% of primary OALs.[2,4] Follicular lymphoma (FL) is the next most common histologic type, representing 23% of primary OALs.[4] The uvea is also a common site of concurrent OAL and is often of the ENMZ subtype.[7] Uveal lymphomas will also behave similarly to ENMZ OALs.[7]

Involved-field radiotherapy (IFRT) has been evaluated in single-institution series.[8-13] A complete response occurred in 90% to 100%, with relapse in < 20% during a 5-year average follow-up period.[8-10] However, these series mostly evaluated unilateral stage IE ENMZ OAL, and other studies have demonstrated that bilateral or systemic presentations of OAL have a greater risk of progression and lymphoma-related death.[3,14] This suggests that systemic therapy could be useful for bilateral or systemic OAL. Furthermore, the use of rituximab as a single agent in ENMZ lymphoma of the MALT type at other anatomic sites has shown a promising response rate of 73%, with a duration of response of 10.3 months[15-17]; however, few small case reports of single-agent rituximab in OAL have been published.[8,18-22]

We present a retrospective description and risk assessment of patients with any type and presentation of lymphoma occurring in the ocular adnexa or uvea evaluated at the Cleveland Clinic. Treatment-related outcomes were reviewed for ENMZ OAL only. After 2005, our institution adopted a treatment algorithm according to the disease presentation: those with unilateral ENMZ OAL were treated with IFRT and those with bilateral or systemic ENMZ OAL were treated with single-agent rituximab. We hypothesized that systemic therapy with single-agent rituximab would be useful in bilateral or systemic presentations of ENMZ OAL.

Patients and Methods

Patient Selection

After approval by our institutional review board, the study population was identified by screening the clinic lists of lymphoma oncologists and ophthalmic oncologists at the Cleveland Clinic from January 2004 to January 2013. Patients with lymphoma occurring in the ocular adnexa or uvea were selected if they had been evaluated in that period and had lymphoma diagnosed after 1995. Lymphoma involving the uvea was also included, because uveal lymphoma is frequently ENMZ lymphoma, often seen in concert with other masses in the ocular adnexa, and behaves similarly to ENMZ OAL.[7,23-25] Diagnostic biopsy was typically performed on the ocular adnexal disease site; however, in the presence of concurrent systemic involvement, biopsy specimens from other involved sites were obtained. Cases in which the diagnostic biopsy had been performed at outside institutions were routinely reviewed by pathologists at the Cleveland Clinic. Lymphomas were classified according to the standard classification schema at diagnosis. A pathologic review according to the 2008 update of the World Health Organization classification[26] was not possible owing to unavailable tissue, either because of outside biopsy or small biopsy specimens with insufficient tissue remaining after the primary diagnosis. For reference, 7 patients were classified before 2001, 31 were classified between 2001 and 2007, and 58 were classified from 2008 onward. The outcomes were updated in April 2013.

The staging evaluations included history, physical examination, and computed tomography (CT) of the chest, abdomen, and pelvis (91.6% of evaluable patients). Ocular imaging with either magnetic resonance imaging of the orbits (48.8%) or CT of the brain or orbits (39.5%), or both (11.6%), was also routinely performed. A complete bilateral ophthalmologic examination was performed on all patients, including an assessment of the best-corrected visual acuity, intraocular pressure, pupillary responses, external examination, slit lamp examination, and dilated fundus examination. Bilateral B-scan ultrasonography and slit lamp and fundus photography were also routinely performed. Lumbar puncture was performed in only 8 patients (8.4%), and central nervous system involvement by lymphoma was detected in only 1 patient. Bone marrow aspiration and biopsy was performed in 33.7% of patients and was involved by lymphoma in 7 of the 32 patients evaluated. Systemic involvement was defined as any disease, nodal or extranodal, occurring outside the ocular adnexa in concert with disease in the ocular adnexa. Bilateral ocular-only involvement was defined as disease identified in bilateral ocular adnexa or uvea without other systemic involvement at diagnosis.

Statistical Analysis

The clinical characteristics and outcomes were collected and managed in the research electronic data capture (REDCap) database hosted at the Cleveland Clinic.[27] Statistical analyses were performed using SAS software (SAS Institute, Cary, NC). All statistical tests were 2-sided, and $P < .05$ indicated statistical significance.

Three outcomes were assessed: overall survival (OS), progression, and progression-free survival (PFS). Events corresponding to PFS and OS were progression or all-cause mortality and all-cause mortality, respectively. Outcomes were calculated from the date of diagnosis until the date of the first event or the date of the last follow-up examination. To determine the natural history of ocular involvement, the date of ocular adnexal involvement was considered the date of diagnosis for those with a history of lymphoma. Disease progression was recorded as the date when additional therapy was initiated. Thus, patients with a partial response (PR), or who were observed, were considered to have progressive disease if they required additional therapy. Cox proportional hazards analysis was used to identify univariate prognostic factors for OS and PFS. Stepwise Cox analysis with a variable entry criterion of $P < .10$ and a variable retention criterion of $P < .05$ was used to identify the multivariate prognostic factors for PFS. Multivariate analysis could not be done for OS, because only 9 patients had died. The Cox results are presented as the hazard ratio (HR) and 95% confidence interval (CI). Age at diagnosis (as a continuous variable, per 10-year increase), gender, previous autoimmune or inflammatory disease, a history of lymphoma, a history of other malignancy, pathologic diagnosis (ENMZ vs. all others), bilateral ocular disease, and ocular disease site were analyzed as potential prognostic factors.

In the patients with ENMZ lymphoma, treatment-related outcomes were estimated using the Kaplan-Meier method. Outcomes were compared among treatments using the log-rank test; for treatment-related analyses, the outcomes were calculated relative to the treatment start date rather than the diagnosis date.

Results

Patient Characteristics, Histologic Diagnosis, and History

The patient characteristics are listed in Table 1. Ninety-five consecutive patients, newly diagnosed with lymphoma involving

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