Oral Chlorambucil for Extranodal, Marginal Zone, B-Cell Lymphoma of Mucosa-Associated Lymphoid Tissue of the Orbit

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Purpose: To report the outcome of oral chlorambucil as a single treatment in patients with orbital mucosa-associated lymphoid tissue (MALT) lymphoma.

Design: Retrospective nonrandomized clinical study.

Participants: Thirty-three patients with isolated orbital MALT lymphoma.

Methods: Medical records of all patients with histology-verified orbital MALT lymphoma treated with oral chlorambucil at the Royal Melbourne Hospital were reviewed.

Main Outcome Measures: Complete clinical response, partial response, local relapse, systemic extension (distant relapse), and survival.

Results: Thirty-three patients (19 female; mean age, 69 years) participated in the study. Patients received an average of 4 courses of oral chlorambucil with a mean total dose of 600 mg. The lacrimal gland was the most frequent site of occurrence (24%), followed by the conjunctiva, eyelid, and superior orbit. Orbital mass, swelling, and diplopia were common presenting signs. Complete response was noted in 26 patients (79%). In 2 of the patients with complete clinical response, mild residual thickening was noted on follow-up orbital imaging studies. Four patients (12%) showed disease recurrence or relapse. Mean follow-up time was 32 (±20) months (range, 8 months–6 years; median, 26 months). None of the patients developed granulocytopenia secondary to chemotherapy, and none suffered significant nausea or vomiting. One patient with malignant transformation died 12 months after diagnosis and initial treatment.

Conclusions: Systemic chemotherapy with chlorambucil is a reasonable option in patients with orbital MALT lymphoma. It is associated with minimal to no side effects. Additionally, it may be well tolerated by elderly patients and also may treat subclinical disease elsewhere. *Ophthalmology 2006;113:1209–1213 © 2006 by the American Academy of Ophthalmology.*

Orbital lymphoma is most commonly a low-grade malignancy that follows a benign course. It accounts for 5% of all cases of extranodal non-Hodgkin's lymphoma.[1–5] Orbital lymphomas present as painless slowly enlarging lesions arising from the orbit, lacrimal gland, eyelid, and conjunctiva. Most patients have primary stage IE disease at initial diagnosis (involvement of a single extralymphatic organ or site), with 10% having prior lymphoma or more advanced stages.[6] Marginal zone B-cell lymphomas of the mucosa-associated lymphoid tissue (MALT) type comprise the majority of non-Hodgkin's lymphomas of the orbit. Mucosa-associated lymphoid tissue lymphomas have an indolent natural history, and excellent local control can be achieved by radiotherapy.[3,6–11] A local control rate of 98% to 100% and 75% distant relapse-free survival for stage IE orbital MALT have been described recently, with overall survival of 73% to 81% at 10 years and almost no deaths from lymphoma.[6,11]

Radiotherapy is a common treatment for low-grade disease but may be associated with ocular morbidity. Ocular manifestations after radiotherapy include dry eyes; other side effects such as cataract formation, retinal vasculopathy (rare), optic neuropathy, and orbital fat tissue atrophy are less common. Moreover, several studies have reported a high incidence of distant relapse after radiotherapy.[3,12–14] In addition, radiotherapy requires travel and attendance for multiple fraction treatment courses, which can be difficult for elderly patients; some centers have long waiting lists for therapy. For these reasons, for the past several years we have treated patients with stage IE orbital MALT lymphomas with oral chlorambucil as a single agent.

The purpose of the current study is to report the outcome of oral chlorambucil in patients with biopsy-proven stage IE orbital MALT lymphoma.

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Materials and Methods

The medical records of all patients with biopsy-proven orbital MALT lymphoma who were treated with oral chlorambucil from January 1995 to December 2004 at the Royal Victorian Eye and Ear Hospital and the Royal Melbourne Hospital were reviewed. Medical records from patients with evidence of lymphoma in other sites were excluded from the study. Local institutional review board approval was obtained to protect patients' confidentiality in this retrospective chart review.

Data regarding comprehensive eye examination, including visual acuity (VA), intraocular pressure, anterior segment and fundus examination, exophthalmos measurements, ocular motility, laterality, presenting sign, orbital imaging findings, treatment, and outcome were collected and analyzed. Complete clinical response was defined as no clinical evidence of orbital disease, with or without imaging evidence of residual stable orbital involvement. Partial response was defined as clinical and radiographic evidence of tumor shrinkage with residual tumor after treatment cycle.

Each treatment cycle consisted of 6 mg of oral chlorambucil 3 times daily, days 1 to 14, repeated on day 28 for 4 cycles depending on response. Frailer older patients received 4 mg 3 times daily. A complete blood count was obtained before and at the conclusion of each treatment cycle.

Staging included orbital imaging by computed tomography (CT) and/or magnetic resonance imaging for all patients, complete blood count, serum lactate dehydrogenase levels, and, for the majority of patients, a CT scan of the chest and abdomen. Bone marrow biopsies were not performed. Full blood count tests were repeated throughout the course of oral chemotherapy.

Tissue Samples

The histopathology of all cases was reviewed by one of the authors (PM). The cases were classified according to the World Health Organization classification of lymphomas using a combination of clinical, histological, immunophenotypic, and genetic features.

Molecular genetic testing for rearrangement of the immunoglobulin heavy chain was performed by polymerase chain reaction.

Statistical Analysis

Kaplan–Meier survival analysis was used to calculate cumulative survival in patients with disease relapse or patients with tumor-related death (disease-free survival); time was calculated from the date of diagnosis to the event of interest, which was death (from any cause), local relapse, systemic extension, or transformation. A nonparametric Wilcoxon Mann–Whitney test was used to calculate the difference in numeric variables (such as VA and age) between patients with complete response and patients with partial response to chemotherapy, and chi-square analysis and the Fisher exact test were used to calculate the difference in categorical variables between these groups.

Conversion of Snellen acuity to logarithm of the minimum angle of resolution values was performed. Statistical analysis was carried out using Excel 2003 (Microsoft Corp., Redmond, WA) and SPSS (version 13, SPSS, Inc., Chicago, IL).

Results

Thirty-three patients (19 female; mean age, 69±17 years) with biopsy-proven isolated orbital MALT lymphoma were included in the study. Demographics of the study population are summarized in Table 1.

Table 1. Demographics of 33 Patients with Histology-Ascertained Isolated Orbital Mucosa-Associated Lymphoid Tissue Lymphomas That Were Treated with Oral Chlorambucil as the Sole Treatment over a 10-Year Period (n = 33)

	Value (± SD) [Range]
Gender	
Male	14 (42%)
Female	19 (58%)
Age (yrs)	69 (±17) [36–100]
Presenting Sign	
Orbital mass	9 (49%)
Periorbital swelling	6 (18.2%)
Diplopia	5 (15.2%)
Proptosis	1 (3%)
Reduced visual acuity	1 (3%)
Tumor location	
Lacrimal gland	8 (24%)
Conjunctiva	7 (21%)
Eyelid	6 (18%)
Superior orbit	6 (18%)
Extraocular muscle	4 (12%)
Other	2 (6%)
Visual acuity	20/25 [20/15–20/80]
Follow-up (mos)	
Mean	32 (±20) [8–84]
Median	26

SD = standard deviation.

Tumor was diagnosed in the right orbit in 16 patients (49%). An orbital mass was the most common presenting sign (16 patients [49%]), followed by periorbital swelling, diplopia, proptosis, and reduced VA (Table 1). The lacrimal gland was the most common location of involvement (8 patients [24%]), followed by conjunctiva (7 patients), eyelid (6 patients), superior orbit, and extraocular muscles. Four patients (12%) had bilateral disease, of which 2 were conjunctival.

Patients received an average (± standard deviation) of 4 (±1.5) courses of oral chlorambucil (range, 2–8; median, 4], giving an average total dose of 600 (±260) (range, 300–1120 mg).

Twenty-six patients (79%) showed complete clinical response after oral chemotherapy; 2 of these patients (6%) had residual extraocular muscle thickening on imaging studies of the orbit. Partial response was noticed in 7 patients (21%), and these required additional surgery, radiotherapy, or combination chemotherapy. Patients who had a partial response to chemotherapy were similar in age, gender, dose of chlorambucil, tumor location, and laterality to patients with complete response (Table 2); they also received a similar total dose of chlorambucil ($P = 0.54$). With respect to orbital involvement, patients with partial response were more likely to have tumor involving the superior orbit or the lacrimal gland and to present with reduced VA or diplopia; however, these proportions were not statistically significant ($P = 0.085$).

One patient (3%) showed orbital recurrence after a mean follow-up time of 48 months; an additional 3 patients (9%) had extraorbital relapse in regional lymph nodes, parotid gland, and cheek after a mean follow-up of 28 months. One of these patients had transformed to diffuse B large cell lymphoma (Fig 1); this patient died 1 year after initial diagnosis after declining treatment for his relapse.

No hematological suppression was observed; the only side effect was occasional minimal nausea.

Table 2. Comparison of Demographics in Patients with Orbital Mucosa-Associated Lymphoid Tissue Lymphoma Who Were Treated with Oral Chlorambucil Achieving Complete Clinical Response, versus Patients Achieving Partial Response

	Complete Response (± SD) (n = 26)	Partial Response (± SD) (n = 7)	P*
Age (yrs)	68 (±18)	73 (±14)	NS
Gender			
Male	9 (35%)	5 (71%)	NS†
Female	17 (65%)	2 (29%)	
Visual acuity	20/28	20/25	NS
Chlorambucil			
No. of courses	4	4	
Total dose (mg)	570 (±284)	664 (±138)	NS
Follow-up (mos)	34 (±21)	25 (±19)	NS

NS = not significant ($P>0.05$); SD = standard deviation.
*Calculated using the nonparametric Wilcoxon Mann–Whitney test for small-group analysis.
†Calculated using χ^2.

Discussion

Orbital MALT lymphoma may comprise 8% to 30% of all extranodal non-Hodgkin's B-cell lymphoma. External beam radiotherapy generally has been accepted as a preferred treatment modality.[8,11,15–21] In this report, we present our results with single-agent oral chemotherapy in 33 patients with orbital MALT lymphoma. Oral chlorambucil in patients with stage IE orbital MALT lymphoma resulted in 79% complete response and 21% partial response. Distant relapse was noted in 3 patients, and an additional patient showed local orbital recurrence. One patient had malignant transformation to diffuse B large cell lymphoma; this patient died a year later after declining further chemotherapy.

Female predominance in our series is similar to that in other reports in the literature; however, our patients had a median age of 72 years (mean, 69), which is older than reported in the literature for all MALT lymphomas.[3,8,11,14,16,22–24] In addition, we saw a similar extent of bilateral disease (20%).[8,11,25] Tumor location differed in several studies of orbital MALT lymphomas, where conjunctiva and the retrobulbar space or orbital soft tissue involvement comprised nearly 75% of all patients; lacrimal gland involvement is described in 4% to 11% of these studies' populations.[8,11,21,26] However, our study and the authors of previous reports[8] found no difference in tumor location and patient characteristics between complete response and partial response to treatment.

In contrast to previous studies, which report higher rates of complete clinical response (up to 100%), we had only 79% complete response and a comparable relapse rate of 15%.[3,8,12,14] However, different studies found 25% to 50% extraorbital relapse 5 years after radiotherapy.[13,14,27] The distant relapse rate may be higher with increased follow-up, and usually occurs in extranodal mucosal sites where primary MALT lymphomas have been described.[6,11] Systemic chemotherapy may decrease distant relapse with long-term follow-up. Although excellent local control may be achieved with radiotherapy, the risk of relapse in distant extranodal sites remains significant[3,13,28,29]; therefore, it seems reasonable to consider initial chemotherapy. This has not been studied before.

Radiotherapy may be associated with long-term sequelae, which include cataract formation with a median toxic dose of 15 Gy. Lens opacities usually appear several years after treatment[21,30]; systematic use of lens shields appears to reduce the incidence of cataract formation greatly. Other complications such as subacute conjunctivitis, punctal stenosis, and cicatricial diplopia also have been

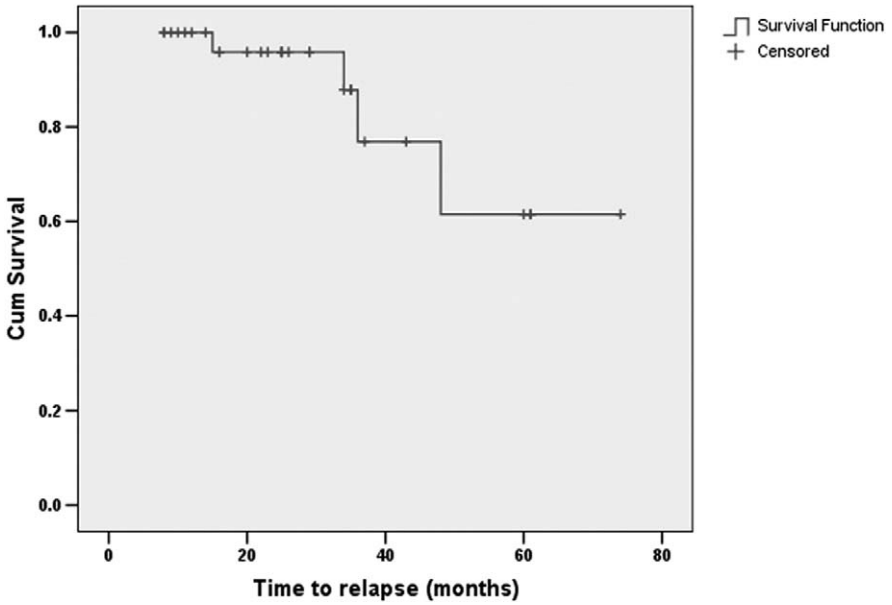

Figure 1. Kaplan–Meier survival curve describing freedom from local relapse (local control) or systemic (extraorbital) extension for 33 patients with localized orbital mucosa-associated lymphoid tissue lymphoma who were treated with oral chlorambucil as the only treatment. Cum = cumulative.

reported.[21] Severe dry-eye and microvascular retinopathy with possible visual loss may occur with doses higher than 34 to 40 Gy.[11,28] Chemotherapy and chlorambucil may be associated with systemic complications, including bone marrow suppression, thrombocytopenia, neutropenia, and infection; less commonly, chlorambucil may be associated with genitourinary, gastrointestinal, pulmonary, and dermatologic manifestations.[31–33] However, in the current study none of the patients developed systemic complications or significant side effects after oral chlorambucil.

Interestingly, previous studies reported that nearly 20% of patients with orbital MALT lymphoma have a more advanced stage at diagnosis with previous or concurrent systemic disease.[6,27] Although these studies may support the need for adequate staging evaluation of MALT lymphoma, it is important to realize that staging workup and treatment strategy is controversial and a consensus has not been reached. Others postulate that a complete staging evaluation including abdominal and chest CT scans and a bone marrow study are needed to select an adequate treatment modality.[21]

Other treatment modalities include surgery, with a general consensus that this should not be employed as the main treatment, and previous reports showing local relapse for all patients who received surgical resection alone.[21,23]

Chemotherapy, single agent or in combination, has been described in previous studies with good response.[31,32] Chemotherapy, in the form of mitoxantrone, chlorambucil, and prednisone, was found effective in extranodal marginal-zone B-cell lymphoma of MALT for advanced stage in 15 patients, with 8 (53%) achieving a complete response and 6 (40%) achieving a partial response; no tumor-associated death or disease relapse occurred after a median follow-up of 16 months. Only 1 patient in that group had orbital lymphoma; however, treatment was found to be effective and well tolerated irrespective of localization.[34] As in our study, subjective tolerance of chemotherapy was excellent, and no cases of nausea were encountered; however, the study reports that with prednisone 4 patients developed granulocytopenia or thrombocytopenia. Higher rates of complete response with chemotherapy are reported in gastric MALT lymphoma; however, these studies may have used multiple drug chemotherapy regimens.[31–33]

Given that the majority of MALT lymphoma cells express CD20, rituximab, a chimeric antibody directed against CD20, has been reported to have significant clinical activity, with a response rate of 73%.[22] The exact mechanism of action for rituximab remains unclear.[35–37] This therapy is often associated with infusion-related toxicity consisting of fevers, chills, and rigors, usually during the first infusion. This toxicity is usually self-limited and responds well to temporary interruption of the infusion and supportive care measures. Subsequent treatments with rituximab are generally well tolerated.[22]

Mucosa-associated lymphoid tissue lymphoma of conjunctival origin showed spontaneous regression of the tumor after biopsy with no additional treatment. Follow-up without radiation was suggested as an option for patients with MALT lymphoma of conjunctival origin.[38] However, although some conjunctival MALT lymphomas essentially may remain dormant without treatment, it is not clear whether distant relapse can occur with long-term follow-up in such patients. Finally, recent studies suggest *Chlamydia psittaci* as an etiologic factor for conjunctival MALT lymphoma, and showed regression of ocular adnexal lymphoma after *C. psittaci*–eradicating antibiotic therapy.[39,40]

Our study was limited by all the inherent weakness of any retrospective study. Longer follow-up may have altered the local relapse or systemic extension rate. However, in light of good local control, relatively low disease relapse, and no systemic side effects, we conclude that oral chlorambucil may be used as an alternative treatment for patients who do not wish to have radiation therapy or are not good candidates for stronger chemotherapy or radioimmunotherapy, even though it may be less effective at local control compared with radiation therapy. Future studies comparing chemotherapy and external beam radiation may provide more powerful evidence for the safety and efficacy of oral chlorambucil as a single agent in orbital MALT lymphoma.

References

1. Freeman C, Berg JW, Cutler SJ. Occurrence and prognosis of extranodal lymphomas. Cancer 1972;29:252–60.
2. Thieblemont C, Bastion Y, Berger F, et al. Mucosa-associated lymphoid tissue gastrointestinal and nongastrointestinal lymphoma behavior: analysis of 108 patients. J Clin Oncol 1997; 15:1624–30.
3. Tsang R, Gospodarowicz MK, Pintilie M, et al. Localized mucosa-associated lymphoid tissue lymphoma treated with radiation therapy has excellent clinical outcome. J Clin Oncol 2003;21:4157–64.
4. Nutting CM, Jenkins CD, Norton AJ, et al. Primary orbital lymphoma. Hematol J 2002;3:14–6.
5. Zinzani PL, Magagnoli M, Galieni P, et al. Nongastrointestinal low-grade mucosa-associated lymphoid tissue lymphoma: analysis of 75 patients. J Clin Oncol 1999;17:1254–8.
6. Fung CY, Tarbell NJ, Lucarelli MJ, et al. Ocular adnexal lymphoma: clinical behavior of distinct World Health Organization classification subtypes. Int J Radiat Oncol Biol Phys 2003;57:1382–91.
7. Bhatia S, Paulino AC, Buatti JM, et al. Curative radiotherapy for primary orbital lymphoma. Int J Radiat Oncol Biol Phys 2002;54:818–23.
8. Uno T, Isobe K, Shikama N, et al. Radiotherapy for extranodal, marginal zone, B-cell lymphoma of mucosa-associated lymphoid tissue originating in the ocular adnexa: a multiinstitutional, retrospective review of 50 patients. Cancer 2003;98: 865–71.
9. Bolek TW, Moyses HM, Marcus RB Jr, et al. Radiotherapy in the management of orbital lymphoma. Int J Radiat Oncol Biol Phys 1999;44:31–6.
10. Cahill M, Barnes C, Moriarty P, et al. Ocular adnexal lymphoma—comparison of MALT lymphoma with other histological types. Br J Ophthalmol 1999;83:742–7.
11. Le QT, Eulau SM, George TI, et al. Primary radiotherapy for localized orbital MALT lymphoma. Int J Radiat Oncol Biol Phys 2002;52:657–63.
12. Tsang RW, Gospodarowicz MK, Pintilie M, et al. Stage I and II MALT lymphoma: results of treatment with radiotherapy. Int J Radiat Oncol Biol Phys 2001;50:1258–64.
13. Wenzel C, Fiebiger W, Dieckmann K, et al. Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue of

the head and neck area: high rate of disease recurrence following local therapy. Cancer 2003;97:2236–41.
14. Hasegawa M, Kojima M, Shioya M, et al. Treatment results of radiotherapy for malignant lymphoma of the orbit and histopathologic review according to the WHO classification. Int J Radiat Oncol Biol Phys 2003;57:172–6.
15. Isaacson P, Wright DH. Malignant lymphoma of mucosa-associated lymphoid tissue: a distinctive type of B-cell lymphoma. Cancer 1983;52:1410–6.
16. Harris NL, Jaffe ES, Stein H, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood 1994; 84:1361–92.
17. Ye H, Liu H, Attygalle A, et al. Variable frequencies of t(11;18)(q21;q21) in MALT lymphomas of different sites: significant association with CagA strains of H pylori in gastric MALT lymphoma. Blood 2003;102:1012–8.
18. Wotherspoon AC, Finn TM, Isaacson PG. Trisomy 3 in low-grade B-cell lymphomas of mucosa-associated lymphoid tissue. Blood 1995;85:2000–4.
19. Du MQ, Peng H, Liu H, et al. BCL10 gene mutation in lymphoma. Blood 2000;95:3885–90.
20. Matteucci C, Galieni P, Leoncini L, et al. Typical genomic imbalances in primary MALT lymphoma of the orbit. J Pathol 2003;200:656–60.
21. Lee JL, Kim MK, Lee KH, et al. Extranodal marginal zone B-cell lymphomas of mucosa-associated lymphoid tissue-type of the orbit and ocular adnexa. Ann Hematol 2005;84: 13–8.
22. Conconi A, Martinelli G, Thieblemont C, et al. Clinical activity of rituximab in extranodal marginal zone B-cell lymphoma of MALT type. Blood 2003;102:2741–5.
23. Esik O, Ikeda H, Mukai K, Kaneko A. A retrospective analysis of different modalities for treatment of primary orbital non-Hodgkin's lymphomas. Radiother Oncol 1996; 38:13–8.
24. Horning S, Rosenberg SA. The natural history of initially untreated low-grade non-Hodgkin's lymphomas. N Engl J Med 1984;311:1471–5.
25. McNally L, Jakobiec FA, Knowles DM II. Clinical, morphologic, immunophenotypic, and molecular genetic analysis of bilateral ocular adnexal lymphoid neoplasms in 17 patients. Am J Ophthalmol 1987;103:555–68.
26. Wotherspoon A, Diss TC, Pan LX, et al. Primary low-grade B-cell lymphoma of the conjunctiva: a mucosa-associated lymphoid tissue type lymphoma. Histopathology 1993;23: 417–24.
27. Jenkins C, Rose GE, Bunce C, et al. Histological features of ocular adnexal lymphoma (REAL classification) and their association with patient morbidity and survival. Br J Ophthalmol 2000;84:907–13.
28. Pfeffer MR, Rabin T, Tsvang L, et al. Orbital lymphoma: is it necessary to treat the entire orbit? Int J Radiat Oncol Biol Phys 2004;60:527–30.
29. Zucca E, Conconi A, Pedrinis E, et al, International Extranodal Lymphoma Study Group (IELSG). Nongastric marginal zone B-cell lymphoma of mucosa-associated lymphoid tisse. Blood 2003;101:2489-95.
30. Henk JM, Whitelocke RA, Warrington AP, Bessell EM. Radiation dose to the lens and cataract formation. Int J Radiat Oncol Biol Phys 1993;25:815–20.
31. Hammel P, Haioun C, Chaumette MT, et al. Efficacy of single-agent chemotherapy in low-grade B-cell mucosa-associated lymphoid tissue lymphoma with prominent gastric expression. J Clin Oncol 1995;13:2524–9.
32. Jager G, Neumeister P, Brezinschek R, et al. Treatment of extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue type with cladribine: a phase II study. J Clin Oncol 2002;20:3872–7.
33. Manoharan A. Sustained remissions with long-term weekly chlorambucil maintenance therapy in patients with mucosa-associated lymphoid tissue lymphoma. Int J Hematol 2004; 79:472–3.
34. Wohrer S, Drach J, Hejna M, et al. Treatment of extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) with mitoxantrone, chlorambucil and prednisone (MCP). Ann Oncol 2003;14:1758–61.
35. Smith MR. Rituximab (monoclonal anti-CD20 antibody): mechanisms of action and resistance. Oncogene 2003;22:7359–68.
36. Eisenbeis CF, Caligiuri MA, Byrd JC. Rituximab: converging mechanisms of action in non-Hodgkin's lymphoma? Clin Cancer Res 2003;9:5810–2.
37. Esmaeli B, Murray JL, Ahmadi MA, et al. Immunotherapy for low-grade non-Hodgkin secondary lymphoma of the orbit. Arch Ophthalmol 2002;120:1225–7.
38. Matsuo T, Yoshino T. Long-term follow-up results of observation or radiation for conjunctival malignant lymphoma. Ophthalmology 2004;111:1233–7.
39. Ferreri AJ, Guidoboni M, Ponzoni M, et al. Evidence for an association between Chlamydia psittaci and ocular adnexal lymphomas. J Natl Cancer Inst 2004;96:586–94.
40. Ferreri AJ, Ponzoni M, Guidoboni M, et al. Regression of ocular adnexal lymphoma after Chlamydia psittaci-eradicating antibiotic therapy. J Clin Oncol 2005;23:5067–73.