Treatment of mucosa-associated lymphoid tissue-type ocular adnexal lymphoma

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New data have recently been reported in ocular adnexal lymphomas (OALs), particularly of mucosa-associated lymphoid tissue (MALT)-type, regarding their biological characteristics and therapeutic management. A possible association between OAL and *Chlamydia psittaci* infection has suggested new mechanisms of lymphomagenesis and opened the way for specific targeted treatment. Similarly, the place of rituximab monoclonal antibody therapy and more conventional chemotherapy, as well as a 'wait-and-see' policy in few clearly defined situations, must be defined in relation to the standard treatment option consisting of radiotherapy for low-grade lymphomas. The aims of this review are therefore to present the various treatment modalities and to discuss the place of each modality in the management of ophthalmologic lymphomas. *Anti-Cancer Drugs* 19:673–680 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Lymphoproliferations of the eye, including intraocular and ocular adnexal non-Hodgkin's lymphoma (NHL), constitute a heterogeneous group of neoplasms that represents less than 1% of all NHLs [1] and 5–15% of all extranodal sites [2]. First described in 1952 [3], they are the most frequent malignant tumors of the eye and ocular adnexae, representing up to 55% of all orbital tumors in the Florida cancer registry [4]. The positive diagnosis of OAL must be based on histologic examination of a sufficient tumor sample obtained by surgical biopsy, sufficiently large to allow rigorous definition of the lymphoproliferative disease according to the World Health Organization classification [5]. Therefore, a very large majority of reported OALs correspond with the B-cell type and 80% of B-cell lymphomas are low grade, with a high incidence of marginal zone B-cell lymphoma or mucosa-associated lymphoid tissue (MALT)-type lymphomas, reported in about 50% of patients. The other two most representative histopathologic subtypes are lymphoplasmocytic and follicular lymphomas. Finally, about 15% of diffuse large B-cell lymphomas have been observed.

Ocular adnexal lymphoma (OAL) is frequently responsible for symptoms, but only minor complaints that can delay specialist consultation. In a large single-center series, we showed that the presenting symptoms were ophthalmologic in 91% of patients, namely pink conjunctival mass (Fig. 1a) or conjunctival hyperemia in 32% of patients, exophthalmia in 27% of patients, orbital and/or palpebral mass (Fig. 1b) in 19% of cases, decreased visual acuity and ptosis in 6% of patients, and diplopia in 2% of patients [6]. Lacrimal gland and intraorbital sites are the most frequent ophthalmologic sites, observed in about 50% of all patients. Conjunctival sites are observed in one-third of the cases and almost always consist of low-grade NHL (96% of cases). Eyelid involvement is observed in 0–44% of patients in the various published series, with a mean of about 10%. Finally, bilateral OAL involvement is observed in 7–24% of patients, as illustrated in Fig. 1b [7]. The male/female sex ratio is often less than 1 and the median age is about 65 years. Very few series have reported any information about the presence of nodal involvement at diagnosis, which ranges between 0 and 24%. Stage IV disease, observed in at least 15% of the selected patients, is reported in the majority of the series, with about 5–10% of bone marrow involvement [7].

Very few studies have conducted multivariate Cox analysis to evaluate prognostic factors of disease-free survival and overall survival. Various pejorative prognostic factors have been identified: (i) high-grade subtype lymphomas [7], and non-MALT-type lymphomas [8,9]. In particular, MALT-type lymphoma was not found to have any prognostic impact [6,10,11] except in one series [12]; (ii) advanced disease [7] and (iii) age from 60 to 64 years [7]. In our experience, the survival of patients with low-grade OAL is significantly better than that of patients with high-grade OAL [6]. The outcome of lymphoma patients with OAL involvement at diagnosis therefore

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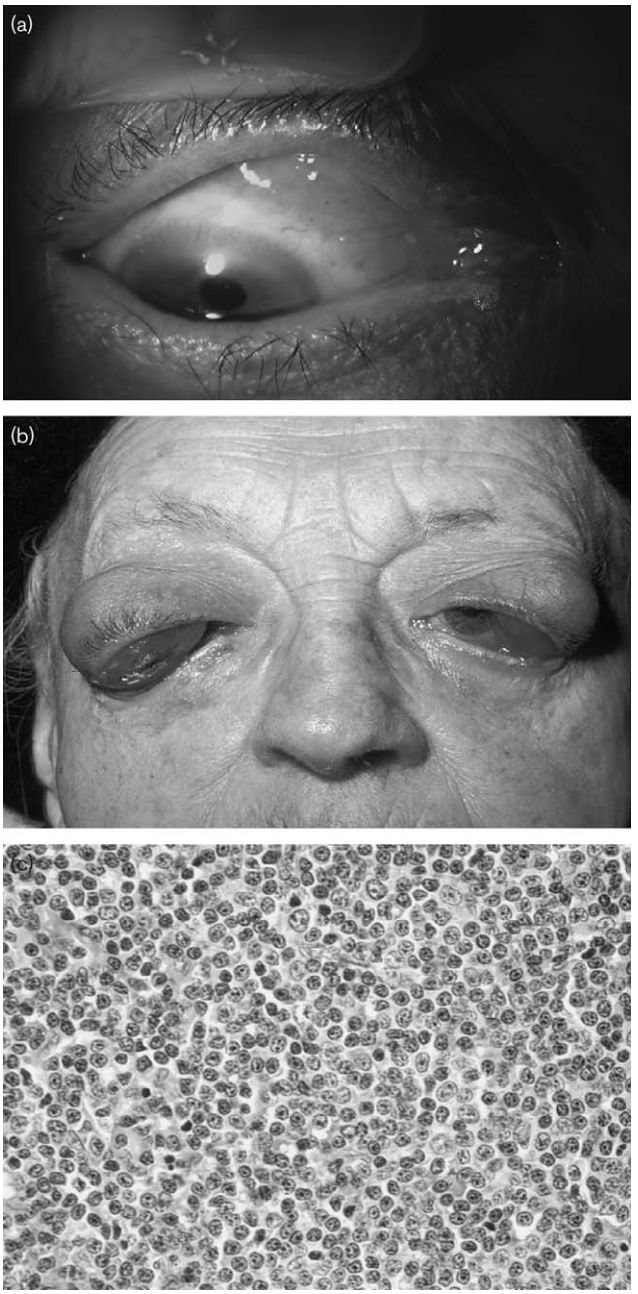
Fig. 1



Pink conjunctival mass (a), and bilateral (b) orbital mass revealing ocular adnexal lymphoma. (c) Mucosa-associated lymphoid tissue-type lymphoma constituted by a proliferation of tumor cells composed primarily of small cells.

does not differ from that observed for nodal NHL, namely better survival in low-grade cases without stabilization of the survival curves, and an OS of about 50% for the high-grade group. This clearly illustrates the absence of any real prognostic impact of initial OAL involvement.

As radiotherapy has been the standard treatment for low-grade ophthalmologic lymphomas, other treatment options, such as single-agent or combination chemotherapy regimens, anti-CD20 monoclonal antibody therapy, and anti-*Chlamydia psittaci* antibiotic therapy, may constitute promising alternatives to external beam irradiation and its potential toxicity. In contrast, a 'wait-and-see' policy has been proposed in few well-defined situations. We will first review all of the data concerning these various treatment modalities and will then discuss the place of each modality in the management of ophthalmologic lymphoma.

Treatment of mucosa-associated lymphoid tissue-type ocular adnexal lymphoma

Treatment decision criteria

The treatment of OAL depends on various criteria that must be defined in the initial assessment of the disease, namely (i) the histopathologic subtype of lymphoma, according to the World Health Organization classification [5]; (ii) extension of the disease, inside and beyond the periocular region; (iii) prognostic factors related to the patient and to the disease; and (iv) the impact of the OAL on the eye(s) and visual function. This illustrates the importance of a multidisciplinary approach to OAL by a team composed of hematologists, radiotherapists, and ophthalmologists. As this review focuses on MALT-type OAL, the treatment of high-grade diffuse large B-cell lymphomas will not be described. Disease extension should be defined by a staging work-up performed at the diagnosis of malignant lymphoma including a personal or family medical history and clinical examination with the determination of performance status according to the Eastern Cooperative Oncology Group classification [13] and a search for B symptoms and nodal or extra nodal (nonperiocular) peripheral sites. Staging of the disease is completed by blood count, erythrocyte sedimentation rate, liver and renal function tests, serum protein electrophoresis, serum lactate dehydrogenase and β2-microglobulin determination, chest radiography, computed tomography scans, bone marrow biopsy, and fiberoptic gastroscopy. The staging classification is performed according to the Ann Arbor classification [14]. This staging work-up will therefore define the prognostic factors of the disease, which constitute the third set of criteria involved in the treatment decision. Ophthalmologic assessment must evaluate the impact of the tumor on visual function. Examination consists of complete bilateral ophthalmologic examination including visual acuity, description of functional complaints, diplopia, visual blurring, evaluation of eye movements, slit lamp examination with anterior chamber examination, determination of intraocular pressure, and examination of the conjunctiva as well as ocular fundus examination to detect any extraocular compression by the tumor. Finally, tumor extension is evaluated by intraorbital magnetic resonance imaging.

Radiotherapy of mucosa-associated lymphoid tissue-type ocular adnexal lymphoma

Radiotherapy is clearly the treatment modality for which immediate and long-term efficacy and toxicity have been most extensively reported, as shown in Table 1 [6,10,15–33]. However, in the majority of the reported series, no distinction was made between MALT-type and non-MALT-type lymphoma patients, or between low-grade and high-grade lymphoma cases, or between radiotherapy alone or combined radiotherapy and chemotherapy, making it difficult to interpret the final results. However, regardless of the histologic subtype of lymphoma, and particularly MALT-type lymphomas [10,25,29–31], radiotherapy induces a very high rate of control of ophthalmologic sites with local control rates ranging from 92 to 100%, and a local recurrence rate ranging between 0 and 22%. The very high local control of the disease by radiotherapy is well illustrated by the study of Charlotte *et al.* [30] describing five local relapses in patients treated with chemotherapy alone and no relapse in patients treated by a combination of chemotherapy and radiotherapy. Disseminated recurrences after radiotherapy have been reported in 4–20% of patients. In contrast with these very good results, radiotherapy is associated with a certain toxicity. Immediate and mostly moderate cutaneous or conjunctival reactions may be observed, followed by late complications such as constant cataract, or xerophthalmia, and rare ischemic retinopathy, glaucoma or xerophthalmia-induced corneal ulceration [17,19,21,22,24,26–32]. In particular, retinal disorders are correlated with irradiation dose, as the risk of grade 2–3 retinopathy is 4% in patients treated with 30 Gy versus 40% in patients treated with 36–40 Gy ($P = 0.006$) [31].

Table 1 Radiotherapy for MALT-type ocular adnexal lymphoma

References	*n*	MALT-type (%)	Local control (%)	Local relapse (%)	Disseminated relapse (%)
[15]	112	/	100	0	15
[16]	14	/	86	7	/
[17]	30	/	94	0	20
[18]	25	/	100	8	20
[19]	20	/	100	0	11
[12]	17	/	100	0	/
[21]	14	/	100	14	/
[22]	38	/	100	3	50
[20]	20	/	100	15	/
[23]	48	60	98	2	/
[24]	52	29	100	0	13
[25]	31	100	100	0	16
[26]	20	/	100	0	6
[27]	28	71	100	5[b]	20[b]
[28]	90	/	100	3	20
[29]	50	100	92	6	6
[10]	30	100	97	7	20
[6]	107	36	90	5	/
[31]	42	100	100	10	10
[30]	23	100	100	22[a]	4
[32]	62	89	100	0	7
[33]	48	100	100	6	/

[a]All five local relapses occurred in patients who did not receive initial radiotherapy.
[b]For the 20 MALT-type OAL patients.
MALT, mucosa-associated lymphoid tissue; OAL, ocular adnexal lymphoma.

Chemotherapy of mucosa-associated lymphoid tissue-type ocular adnexal lymphomas

In most reported series, patients were predominantly treated with radiotherapy alone and only a small proportion were treated with radiotherapy plus chemotherapy or chemotherapy alone. For low-grade lymphoma, treatment consisted of single-agent chemotherapy such as chlorambucil or combined chemotherapy regimens such as cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like protocols. A number of studies have reported series of MALT-type and/or non-MALT-type OAL patients treated with chemotherapy alone or in combination with other modalities, but very few publications have reported the response rates obtained with this treatment in MALT-type lymphoma patients, as shown in Table 2 [6,30,32,34–36]. Overall, in a very heterogeneous population of 47 MALT-type OAL patients, the overall response rate (ORR) was very high (98%) with 94% of complete remissions. In contrast, in a small series of 32 cases including 26 MALT-type lymphomas (81%), Sasai *et al.* [37] observed no significant difference in cause-specific or overall survival rates for MALT-type lymphoma patients treated with radiotherapy alone or exclusive single-agent or combination chemotherapy. These series therefore do not clearly define the optimal chemotherapy regimen in MALT-type OAL patients. However, one recent publication should be specifically mentioned. Rigacci *et al.* [36] treated nine low-grade OAL patients (including eight MALT-type lymphomas) with a combination of chlorambucil and rituximab and reported an overall response rate of 100%

Table 2 Chemotherapy for MALT-type ocular adnexal lymphoma

References	Number of MALT-type OAL (%)	Treatments and responses of MALT-type OAL
[6]	52 (36)	Three low-grade cases: CT alone. Two CR and one PR.
[34]	37 (100)	Three cases: CT alone (CHOP). Three CR.
[30]	23 (61)	23 cases: three CT alone (CHOP), eight CT (CHOP) + RT, 11 S + chlorambucil, one S + chlorambucil + RT. 23 CR (100%).
[32]	55 (89)	Seven stages II–IV cases: one R-CVP, two R-CVP + RT, four chlorambucil + RT. Six CR (86%).
[35]	15 (47)	Two cases: CT alone. Two CR.
[36]	8 (89)	Nine cases (eight MALT-type): chlorambucil + rituximab. eight CR (89%) and 1 PR
Total	/	47 cases: 44 CR (94%) and two PR (4%).

CR, complete remission; CT, chemotherapy; MALT, mucosa-associated lymphoid tissue; OAL, ocular adnexal lymphoma; PR, partial remission; RT, radiotherapy; S, surgical excision.

and no relapse after a median follow-up of 25 months. A treatment combining chlorambucil and rituximab could therefore be proposed as a possible alternative to radiotherapy, but still requires long-term follow-up evaluation.

Immunotherapy of mucosa-associated lymphoid tissue-type ocular adnexal lymphoma

Immunotherapy of MALT-type OAL includes interferon-α and rituximab, but very few data have been published concerning these two modalities. Blasi *et al.* [38] reported five patients with conjunctival MALT-type lymphoma treated with 1 500 000 IU of interferon-α injected subconjunctivally inside the lesion, three times a week for 4 weeks. Complete response was obtained in all patients, and four patients did not show any signs of local recurrence with a median follow-up of 21 months (range: 12–36 months), and one patient developed recurrence after 11 months with systemic progression of the lymphoma. Similarly, very few data have been reported on patients with OAL treated by rituximab. Rituximab is a chimeric anti-CD20 monoclonal antibody [39] that has been extensively used in the treatment of B-cell NHL, alone or in combination with chemotherapy. Various effector mechanisms for rituximab have been reported: (i) complement-dependent cytolysis [40], (ii) antibody-dependent cell-mediated cytotoxicity [40], (iii) mAb-triggered induction of B-cell apoptosis [41,42], (iv) inhibition of cell proliferation [43], and (v) a synergistic effect with cytotoxic agents [43,44] and interferon-α [45]. Rituximab combined with combination chemotherapy regimens induces a significant benefit compared with chemotherapy alone in terms of response rates, progression-free survival, and overall survival in follicular [46–49] and diffuse large B-cell lymphomas [50–52]. As shown in Table 3, in relapsed MALT-type lymphoma patients, rituximab induces overall and complete response rates in 74 and 38% of cases, respectively [53–63]. Sixteen patients with ocular adnexal MALT-type lymphoma received anti-CD20 antibody therapy, with s ix complete (37%) and four partial remissions (ORR of 62%) [56,57,59,62]. Finally, as previously mentioned, rituximab combined with chlorambucil-induced high response rates in a small cohort of MALT-type OAL patients [36]. In light of these very preliminary data, the place of rituximab in the treatment of ophthalmologic lymphomas therefore needs to be more extensively evaluated.

Surgical excision and 'wait-and-see' policy

Surgical biopsy, which is the first step in the management of OAL as for other histologic subtypes of lymphoma, can comprise apparent complete excision of the tumor, particularly in the case of lacrimal gland tumors, in which encapsulated lesions can be entirely removed. In all cases in which complete surgical excision is suspected, accurate staging of the disease must be performed by orbital MRI or computed tomography to detect any residual mass. Several publications have reported a few patients with MALT-type OAL in whom no complementary treatment, and particularly no radiotherapy, was performed after surgical excision and for whom the outcome was clearly defined [9,11,34,35,64]. Among the 34 reported cases of MALT-type OAL, 11 developed local recurrence at the initial ophthalmologic site (32%), one at the contralateral initial ophthalmologic site, and four patients developed disseminated extraophthalmologic disease (12%). Very few of these studies indicated that local relapse occurred more frequently after simple surgical excision than after radiotherapy [9,12]. More recently, Matsuo *et al.* [65] reported a series of eight patients with MALT-type lymphoma without complementary treatment after surgical biopsy, seven of whom presented spontaneous tumor regression in 1 to 5 years. However, some of these cases received local corticosteroid or anti-intracellular bacterial antibiotic therapy. Finally, Tanimoto *et al.* [66] evaluated the long-term results of no initial therapy for 36 patients with localized MALT-type OAL. They showed that 69% of patients did not require any treatment with a median follow-up of 7.1 years and that 6% died from progressive lymphoma. These data therefore indicate that further investigations are required to clearly evaluate a 'wait-and-see policy' after complete surgical excision of MALT-type OAL.

Table 3 Rituximab for MALT-type ocular adnexal lymphoma

References	Number of NHL (number of OAL)	Percentage of ORR (% CR)	Follow-up
[53]	34 extranodal MALT-type NHL (three OAL)	74 (44)	Median response duration: 10.5 months
[54]	9 advanced extranodal MALT-type NHL	56 (33)	/
[55]	Gastric MALT-type NHL	One CR	No recurrence after 24 months
[56]	Two conjunctival MALT-type OAL	100 (50)	No recurrence after 30 and 32 months
[57]	2 MALT-type OAL	2 CR	No recurrence after 48 months
[58]	One pulmonary MALT-type NHL	One PR	No progression after 19 months
[59]	Eight MALT-type OAL	62 (37)	Median time to progression 5 months
[60]	26 gastric MALT-type NHL	77 (46)	Two recurrences after 33 months
[61]	One conjunctival OAL	One CR	/
[62]	One MALT-type OAL	One PR	No progression after 9 months
[63]	One gastric MALT-type NHL	One CR	/
Total MALT-type NHL	86	74 (39)	/
Total MALT-type OAL	17	65 (41)	/

CR, complete remission; MALT, mucosa-associated lymphoid tissue; OAL, ocular adnexal lymphoma; ORR, overall response rate; PR, partial remission.

Anti-*Chlamydia psittaci* antibiotic therapy

A new therapeutic approach to OAL, particularly conjunctival NHL, has recently been proposed: anti-*C. psittaci* antibiotic therapy. As already mentioned in this review, Ferreri *et al.* [67,68] demonstrated an association between *C. psittaci* and OALs. Twenty-seven patients with *C. psittaci*-positive MALT-type OALs were treated by *C. psittaci*-eradicating antibiotic therapy (doxycycline) [68]. Objective responses were observed in 13 patients (48%) with six complete remissions (22%), and chlamydial DNA was no longer detectable in peripheral blood mononuclear cells of all four positive evaluable patients. The median response time ranged between 3 and 31 months, and the 2-year failure-free survival was 66%. All these findings were corroborated by a reported combination of adult inclusion conjunctivitis and MALT-type lymphoma in a young patient [69], and by a series of three patients treated with antibiotic therapy with two complete remissions and one partial response [70]. Inversely, Grünberger *et al.* [71] did not find any therapeutic effect of 'blind' antibiotic treatment in 11 MALT-type OAL patients.

However, two main reports do not support a role of *C. psittaci* in OAL. First, Ferreri *et al.* reported an overall response rate of 38% in *C. psittaci*-negative OAL, suggesting a non-*C. psittaci* eradication mechanism in tumor regression. Second, since the first report by Ferreri *et al.*, several other series have been reported, as shown in Table 4, with very heterogeneous data [32,67,72–84]. As the prevalence of *C. psittaci* infection in OAL samples was 22% in a series of 465 tumor biopsy samples. In contrast, the detection of *C. psittaci* infection is very low in nonadnexal orbital lymphomas (6%) and benign intraorbital lesions (5%). However, the prevalence of *C. psittaci* infection in OAL is very heterogeneous, ranging from 0 to 80%. Concordant results were observed in Japanese patients [73,76,82] and nonconcordant data were reported for patients from the USA [8,32,72,78], the Netherlands [32,72], and Italy, where the results are particularly discordant [67,72,75]. One hypothesis for this apparent discrepancy could be differences among the various reported series in terms of the material and tools used for DNA extraction. However, comparison of the methodologies used to detect *C. psittaci* DNA in tumor samples shows similar procedures and seems to exclude methodology-related variability of the results. Another hypothesis for this apparent discrepancy could be a heterogeneous epidemiologic distribution of *C. psittaci* infection in the world. This important question needs to be evaluated by international crossover studies to confirm the association between *C. psittaci* infection andOAL. Owing to the small number of treated patients and the heterogeneous results regarding the association between *C. psittaci* and OAL, anti-chlamydia antibiotic therapy cannot be considered to be standard treatment for OAL at present. However, this association between *C. psittaci* infection and these lymphomas is very impressive in view of the clearly established association between gastric MALT-type lymphomas and *Helicobacter pylori* infection [85]. In light of these findings, urgent biological studies and therapeutic trials are therefore justified to clarify this situation.

Table 4 Association between *Chlamydia psittaci* and ocular adnexal lymphoma

References	Countries	OAL (%)	Non-OAL (%)	Benign lesions (%)
[67]	Italy	32/40 (80)	/	3/46 (7)
[72]	United Kingdom	5/40 (12.5)	/	4/40 (10)
	Germany	9/28 (32)	/	1/9 (11)
	The Netherlands	8/24 (33)	/	/
	Italy	2/21 (9.5)	/	/
	China	6/57 (10.5)	/	0/2 (0)
	East USA	6/25 (24)	/	/
[73]	Japan	0/21 (0)	/	0/3 (0)
[74]	France	1/16 (6)	0/10 (0)	0/10 (0)
[75]	Italy	11/27 (41)	/	/
[76]	Japan	0/21 (0)	/	/
[77]	The Netherlands	0/20 (0)	/	/
[32]	South USA	0/57 (0)	/	0/2 (0)
[78]	West USA	0/11 (0)	0/1 (0)	0/5 (0)
[79]	Cuba	2/26 (8)	3/20 (15)	0/20 (0)
[80]	Germany	0/22 (0)	0/18 (0)	/
[81]	USA	0/30 (0)	/	/
[82]	Japan	0/23 (0)	/	/
[83]	Korea	26/33 (78)	/	5/21 (23)
[84]	USA	0/28 (0)	0/16 (0)	0/5 (0)
Total	/	102/525 (19)	3/41 (7)	10/114 (9)

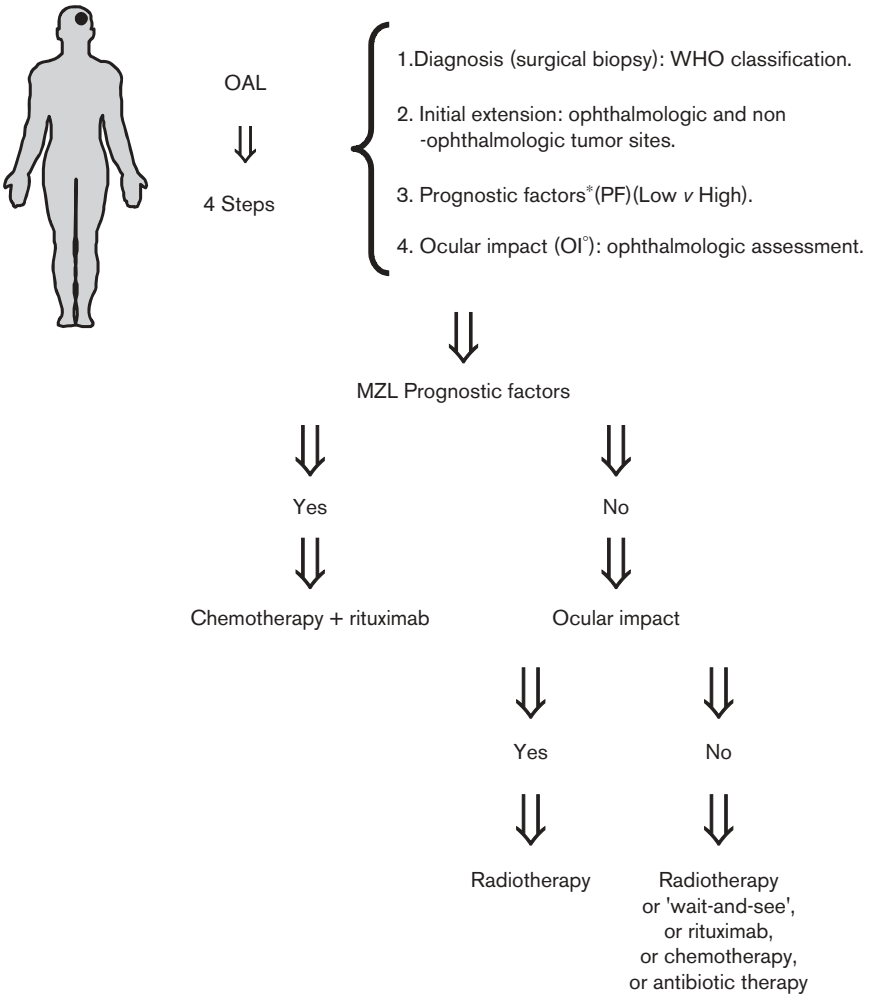
OAL, ocular adnexal lymphoma.

Which treatment for mucosa-associated lymphoid tissue-type ocular adnexal lymphoma?

After presenting the various treatment modalities, we will now discuss the place of each modality in the management of MALT-type ophthalmologic lymphoma and propose several guidelines that represent the author's approach, as shown in Fig. 2. This figure describes the elements that must be evaluated at the time of the initial diagnosis: histopathologic subtype of lymphoma, extension of the disease, prognostic factors related to the patient and to the disease, and the ocular impact of the ophthalmologic lymphoma, as well as new treatment modalities. The proposed treatment guidelines are therefore as follows:

1. In the case of pejorative prognostic factors of marginal zone lymphomas, such as age above 60 years [86] or 70 years [87], performance status greater than 1 [88,89], nodal involvement [88], advanced stage [88], low hemoglobin level [86,88,90], elevated serum lactate dehydrogenase level [89,90], serum albumin level lower than 35 g/l [89,90], low platelet count lower than 100×10^9/l [87], and elevated lymphocyte count higher than 16×10^9/l [87], or high Follicular Lymphoma International Prognostic index as defined earlier for follicular lymphomas [91], treatment should consist of a combination of rituximab and chemotherapy

Fig. 2



Management of mucosa-associated lymphoid tissue-type ocular adnexal lymphoma (OAL). *Prognostic factors include age above 60 years or 70 years, performance status (PS) greater than 1, nodal involvement, advanced stage, low hemoglobin level, elevated serum lactate dehydrogenase level, serum albumin level lower than 35 g/l, platelet count lower than 100×10^9/l, and elevated lymphocyte count higher than 16×10^9/l, or high Follicular Lymphoma International Prognostic index as previously defined for follicular lymphomas.

(chlorambucil, cyclophosphamide, vincristine, prednisone, or CHOP).

2. In the absence of pejorative prognostic factors of marginal zone lymphomas but in the presence of visual impairment because of the lymphomatous mass, radiotherapy of the ophthalmologic site should be proposed.
3. In the absence of pejorative prognostic factors of marginal zone lymphomas and in the absence of visual impairment, various treatment options can be proposed, such as radiotherapy, single-agent chemotherapy, immunotherapy with anti-CD20 monoclonal antibody, antibiotic therapy, such as anti-*C. psittaci* antibiotic therapy, and a 'wait-and-see' policy. However, in this type of situation, the place of each of these modalities needs to be clearly evaluated by multicenter prospective studies.

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