REVIEW ARTICLE

Treatment for Ocular Adnexal Mucosa-Associated Lymphoid Tissue (OA-MALT) Lymphoma

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Abstract

Ocular adnexal mucosa-associated lymphoid tissue (OA-MALT) lymphoma is one of the B lymphoid malignancies that originates in the orbit and shows indolent progression with a predominantly localized stage. Radiotherapy appears to be recognized as the most common treatment for localized OA-MALT lymphoma. Surgical resection, eradication of *Chlamydia psittaci* (*C. psittaci*) based on the reports of the existence of *C. psittaci* DNA, and 'watchful waiting' are also selected in some cases. Systemic immunochemotherapies including anti-CD20 antibodies may be another option for advanced stages of OA-MALT lymphoma. However, due to the lower frequency of this disease and the difficulty of conducting large-scale clinical trials, no randomized, controlled trial evaluating these treatments has been reported. Therefore, the optimal treatment strategy for OA-MALT lymphoma has not been established. This review provides an update on treatments and discusses the appropriate treatment for OA-MALT lymphoma.

Keywords: ocular adnexal mucosa-associated lymphoid tissue (OA-MALT) lymphoma, treatment, watchful waiting, *Chlamydophilia psittaci* (*C. psittaci*)

Introduction

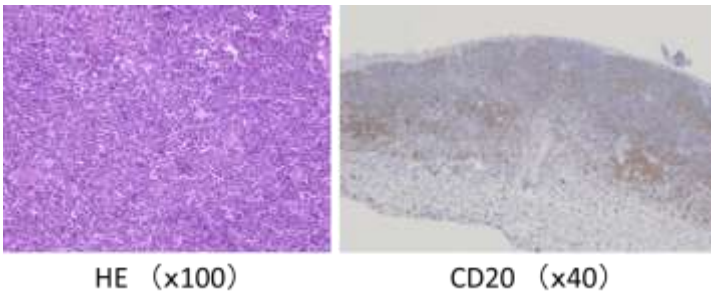
From 1986 to 1987, Sheibani and Cousar separated a tumor in which monocyte-like differentiation-prone B cells proliferated in a parafollicular (follicular marginal zone) from reactive lymphoid hyperplasia and proposed it as an independent tumor concept[1,2]. Later, this disease concept of marginal zone B-cell lymphoma came under the spotlight due to its relationship with chronic gastritis and low-grade gastric primary B-cell lymphoma[3]. In the 4th revised edition of the WHO classification, marginal zone B-cell lymphoma is classified into two categories, 'nodal' and 'extra-nodal' marginal zone B-cell lymphoma. Extranodal marginal zone B-cell lymphoma is currently understood as extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) lymphoma.

Marginal zone B-cell lymphoma is categorized as an indolent B-cell lymphoma that occurs on a background of chronic inflammation (allergic, autoimmune, or infectious diseases), such as Sjögren syndrome in salivary gland MALT lymphoma, Hashimoto thyroiditis in thyroid MALT lymphoma, *Helicobacter pylori* (*H. pylori*) infection in gastric MALT lymphoma, *Campylobacter jejuni* (*C. jejuni*) infection in small intestinal MALT lymphoma, *Borrelia burgdorferi* (*B. burgdorferi*) infection in cutaneous MALT lymphoma, and *Chlamydia psittaci* (*C. psittaci*) infection in ocular adnexal (OA) MALT lymphoma. The primary onset of MALT lymphoma is known to occur in the stomach (50%), salivary glands (14%), bronchial mucosa (14%), thyroid gland (4%), and mammary glands (4%). OA-MALT lymphoma occurs in ocular adnexa (orbital, lacrimal gland and sac, conjunctiva, and eyelids) with a frequency of about 10% to 15%, and it is recognized as the major lymphoma in the OA site.

OA-MALT lymphoma originates in the ocular appendages (Figure 1A, B), with a low frequency of metastasis, and treatment of this disease is considered to require strategies different from those of other lymphoid malignancies. However, due to the low frequency of this disease and the difficulty of conducting large-scale clinical trials, the optimal approach to the treatment of OA-MALT lymphoma has not been established. The treatment of OA-MALT lymphoma can be broadly divided into two strategies, local treatments and systemic treatments. The treatment should be selected based on the lesion site, stage, age, performance status (PS), clinical symptoms, adverse effects of treatment, and patient philosophy of life. Radiotherapy, surgical resection, and chemotherapies including monoclonal antibodies (immuno-chemotherapies) should be considered treatment options. Careful follow-up (so-called 'watchful waiting') can also be one of the clinical options. This review considers the treatment of primary OA-MALT lymphoma and discusses its appropriate treatment.

Figure 1. (A) Cases of ocular adnexal mucosa-associated lymphoid tissue (OA-MALT) lymphoma in the subconjunctiva and macroscopic findings. (B) Magnetic resonance (MR) imagings showing the primary site of OA-MALT lymphoma in orbital fat as tumors.

(A)



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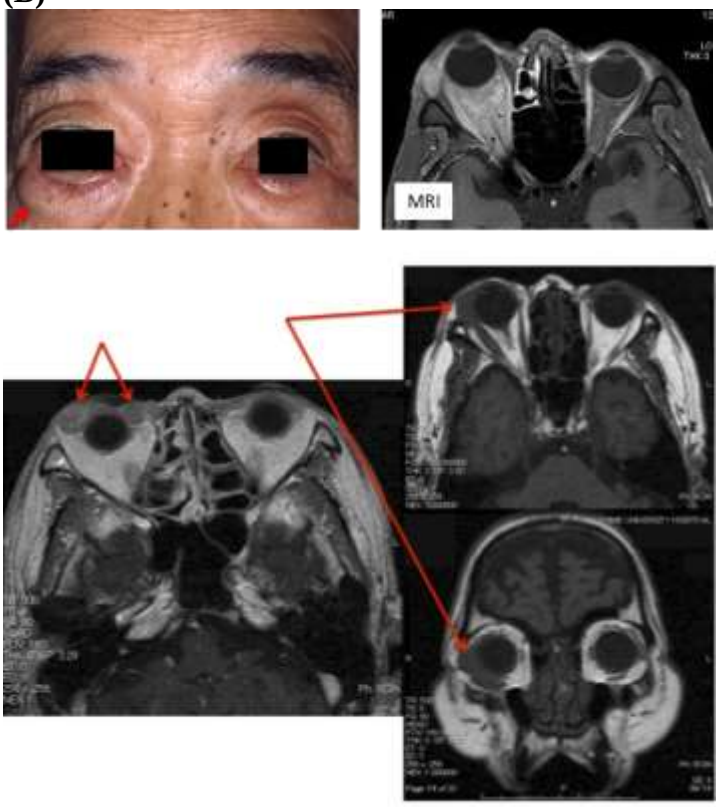


Treatment for localized OA-MALT lymphoma

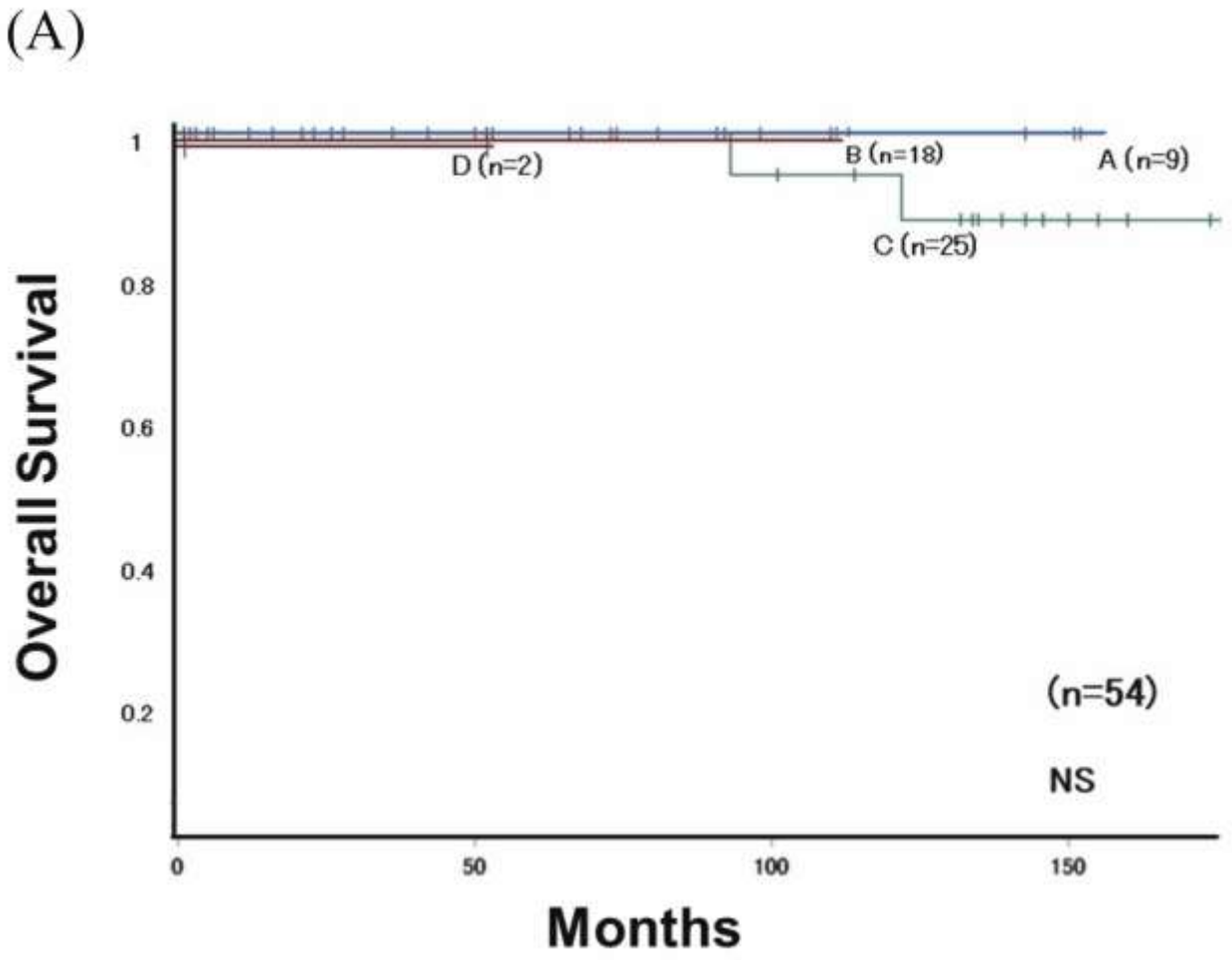
In the NCCN Guidelines (version 4.2021) for Treatment of Cancer by Type, OA-MALT lymphoma has not been described as an independent disease. In contrast, this lymphoma has been included independently in Nongastric MALT lymphoma (Noncutaneous) [4]. Localized MALT lymphomas that are the same as those in the stomach that are positive for *H. pylori* are treated with local treatment such as radiotherapy[5-8] and surgical resection[5,6]. Regardless of which treatment is selected, a good prognosis of MALT lymphomas has been reported with a 5-year overall survival (OS) of 90% and 10-year OS of 80%[5,6]. Careful follow-up (watchful waiting) is also an option for the patient without any symptoms. However, no randomized, controlled trial comparing the treatment options has been reported.

The same local treatments for MALT lymphomas could be selected for OA-MALT type, even if OA-MALT might be present in both orbits, because distant metastasis and progression of OA-MALT lymphoma are rarely the same as other MALT lymphomas,

and the prognosis is good no matter which treatment is selected[9]. Radiotherapy appears to be the most selected of the several local treatment options. We have recently reported treatment-associated outcomes of patients with localized OA-MALT lymphoma. We have performed a treatment-based data analysis of 54 cases of OA-MALT lymphoma with stage I or II after their accurate diagnosis. Their progression-free survivals at 5 years and 10 years were 100% and 100% with radiotherapy, 93% and 67% with immune-chemotherapies, and 92% and 82% with surgical resection, respectively (Figure 2-A, B), suggesting that radiotherapy might be the most promising treatment for localized OA-MALT[9].

In this review, the local treatments for localized OA-MALT lymphoma will each be described.

Figure 2. Overall (A) and progression-free (B) survival of OA-MALT lymphoma patients who were diagnosed with molecular/immunological methods in addition to pathological findings based on treatment strategies (n = 54). NS, not significant. (from reference #6)



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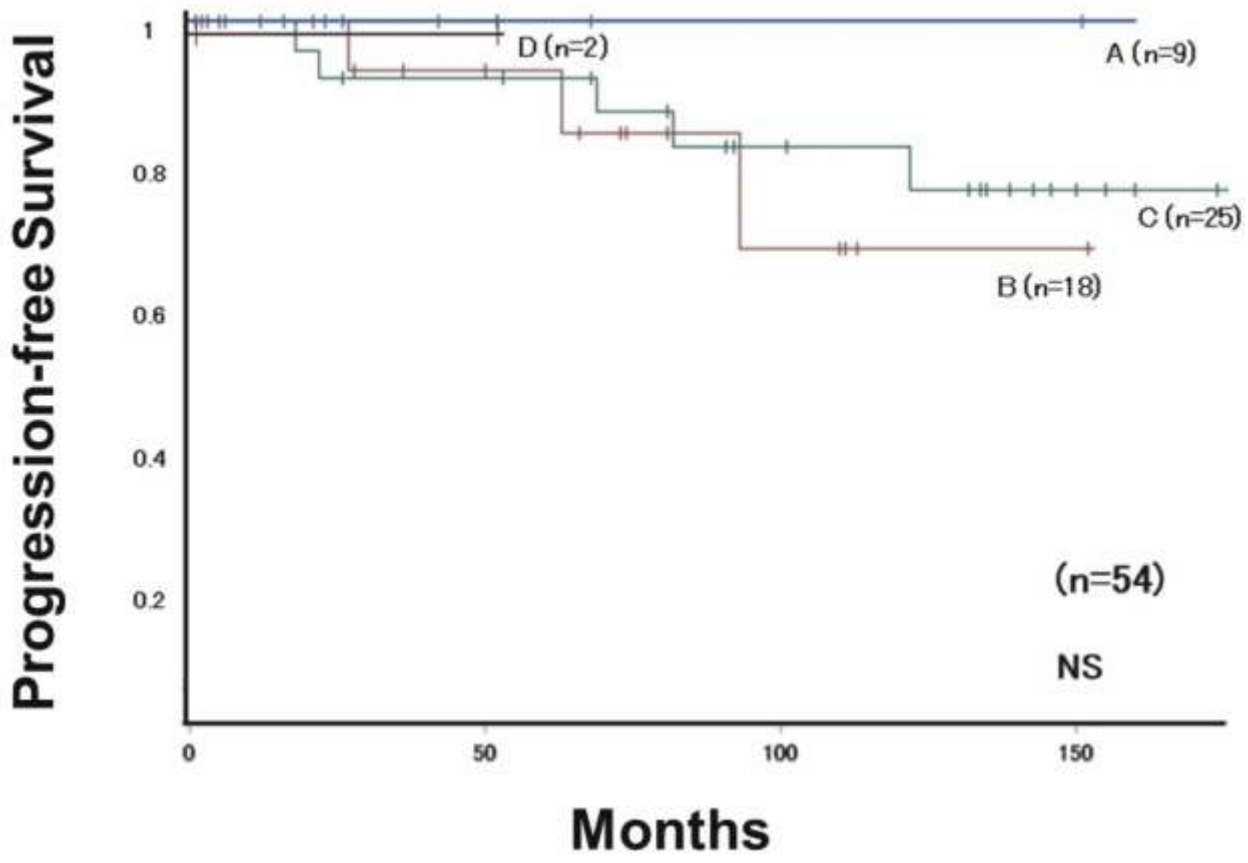


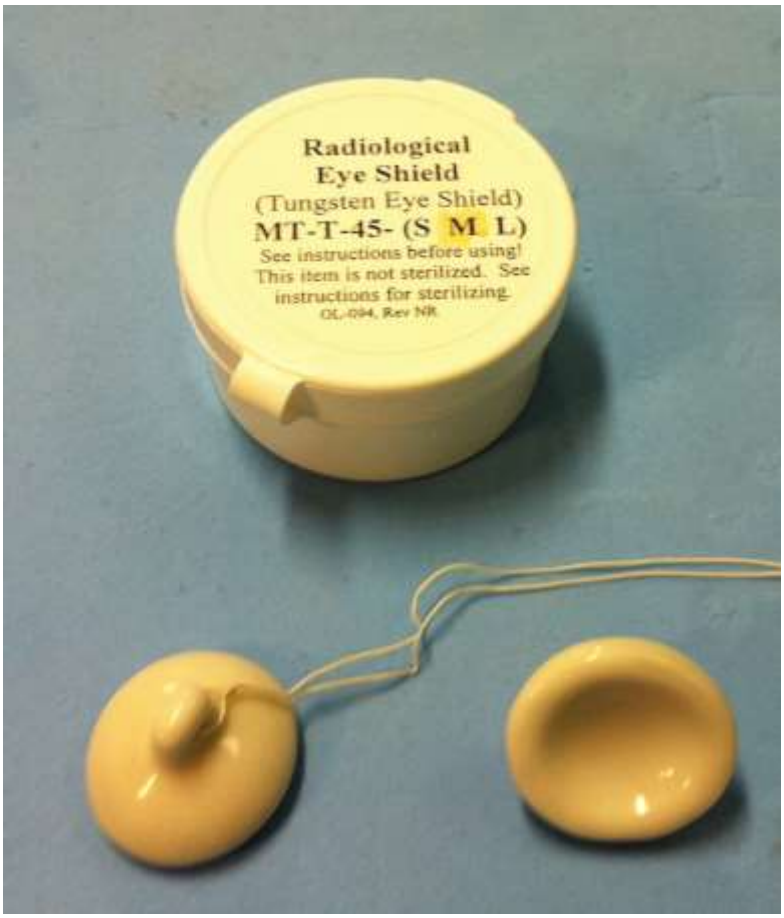
(% at risk)		(5 years)	(10 years)
A: radiotherapy	(n=9)	100%	100%
B: immuno-chemotherapy	(n=18)	93%	67%
C: surgical resection	(n=25)	92%	82%
D: watchful waiting	(n=2)	100%	-

1. Radiotherapy

MALT lymphoma is highly radiosensitive and can be well controlled by radiotherapy up to 35 Gy, with 25 Gy in most cases of ocular appendage onset and 30 Gy in other areas[7,10]. A total of 20-30 Gy treatment with 1.5-1.8 Gy fractions is optimal. When it exceeds 34 Gy, the frequency of retinal damage increases significantly[11], and it has been reported that cataracts occur in 30-50% and xerophthalmia in 20-40% with general radiotherapy[11]. Especially for cataracts, the hazard ratio was 3.47 ($p = 0.026$) at a dose less than 30 Gy, and 4.10 ($p = 0.008$) without lens protection[12]. In terms of local control, radiotherapy may be the best choice. However, this treatment requires careful attention to the eye (retina, lens, lacrimal glands, and so on) and a thorough explanation of adverse events. On the other hand, to minimize the effects of radiation on the eyeball, many facilities use an eye shield (Figure 3), but it is necessary to always consider recurrence or relapse in the area covered by the shield. According to reports of treatment with doses of 25 Gy or higher, 18 of 71 patients (25%)[7], 14 of 70 patients (20%)[13], 10 of 58 patients (17%)[14], and 9 of 73 patients (12%)[15] relapsed after

treatment. Recently reported ultra-low-dose (4 Gy) radiation treatment for early OA-MALT lymphoma has shown excellent therapeutic efficacy and tolerability without eye complications such as cataracts and dry eye[16]. However, the number of cases is small, and accurate assessment requires further study with larger sample sizes and long-term follow-up.

Figure 3. Radiological (tungsten) eye shields



2. Surgical resection

When the tumor is encapsulated and the complications would be acceptable, surgical resection should be considered in all cases of OA-MALT lymphoma. However, evaluation of the surgical treatment for this disease has not yet been reported. Surgical resection does not affect patient survival[9,17,18]. In a follow-up evaluation of 9 completely resected cases, 3 had recurrence within 10 years[17]. We have also had 36 surgically resected cases in the last 20 years, and 4 cases of orbital recurrence occurred in the 25 cases in whom long-term follow-up was possible[9]. For tumor in sites that make removal difficult, such as the orbits, surgical therapy cannot be superior to other local treatments, and it would only be indicated for OA-MALT lymphoma localized to the eyelid or conjunctiva.

3. 'Watchful waiting', and others

The 'watchful waiting' approach is also acceptable for the patient who does not have any symptoms or who has no residual tumor

after complete surgical resection for diagnosis. In those cases, it is necessary to pay sufficient attention to histological transformation clinically and pathologically. The 'watchful waiting' approach and corticosteroid monotherapy are also considered for elderly patients and patients with complications or poor performance status[17-19].

As another local treatment, local injection of anti-CD20 antibody (rituximab) into the orbit had been reported[20]. It is an intralesional injection treatment in which 5-15 mg of an undiluted solution of rituximab are repeatedly injected into the lesion site 1-2 times a week. However, the number of treated cases is small, evaluations of adverse effects are few, and the long-term therapeutic effect cannot be evaluated.

Treatment of advanced or recurrent OA-MALT lymphoma

Systemic chemotherapy is usually selected for advanced or recurrent patients for whom local treatment is not indicated. A strategy similar to that for indolent lymphoma should be adopted. Radiotherapy may be indicated for curative treatment of multiple sites (for example, bilateral orbital disease with no evidence of disease elsewhere) or palliative treatment for symptomatic tumors[4]. In cases with no symptoms and whose tumor volume is low, the patient should be considered for careful follow-up (watchful waiting). If the patient has any organ damage due to tumor compression or infiltration, immuno-chemotherapies combined with ant-CD20 antibodies should be considered. The complete response (CR) rate of rituximab monotherapy is up to approximately 75%[5]. However, many recurrences have been reported in cases given rituximab monotherapy for other MALT lymphomas, even after showing initial effectiveness, so that multidrug therapy including rituximab is usually given for advanced or recurrent OA-MALT lymphoma with any symptoms. Like indolent lymphomas, there are several reports of concomitant medications, such as COP (cyclophosphamide, vincristine, and prednisolone)[21,22], chlorambucil[23,24], fludarabine[25], cladribine[26-28], etc. These were all pilot studies of a small number of cases included in a retrospective analysis. Compared with rituximab or chlorambucil monotherapy, the combination of rituximab and chlorambucil showed superior remission rate, progression-free survival (PFS), and event-free survival (EFS), but the survival rate was not changed[29]. Ibritumomab tiuxetan was tested in a single group of 16 patients with marginal zone B cell lymphoma (MZBCL), and PFS was 47.6 months[30]. As for new drugs, studies of bortezomib[31], everolimus[32], and lenalidomide[33] have been reported (Table 1). As one option, CHOP chemotherapy containing anthracycline has been reported. However, anthracycline-containing regimens should not be considered appropriate as a front-line treatment because of their many toxicities. Therefore, systemic administration of these antitumor agents needs to be carefully considered for OA-MALT lymphoma even in the advanced or recurrent stage because of its extremely indolent clinical course. In contrast, corticosteroid monotherapy and the 'watchful waiting' approach continue to be considered indicated for elderly patients and patients with complications[17].

Treatment considering the onset factors in OA-MALT lymphoma

Previous reports have shown that chronic inflammation, which is mediated by autologous or exogenous antigen stimulation, triggers the development of MALT lymphoma. To date, Sjögren syndrome, Hashimoto thyroiditis, *H. pylori*, *C jejuni*, *B. burgdorferi*, *C. psittaci*[34], etc. have been reported. The only established treatment for MALT lymphoma is eradication therapy with antibiotics for *H. pylori*.

Table 1. Immuno-chemotherapies for MALT lymphoma

Object	Treatment	Effect	Reference
21 patients with OA-MALT lymphoma	cyclophosphamide, vincristine, and prednisolone (COP)	overall response rate: 100% (CR: 76.2%) DFS: 66.7% after a median follow-up of 58 months	18
33 patients with OA-MALT lymphoma	rituximab and COP	CR: 93.9% at 2 years PFS: 90.3±5.3%, OS: 100% at 4 years	19
33 patients with OA-MALT lymphoma	chlorambucil	CR: 79%, disease recurrence or relapse: 12% after a median follow-up of 26 months	20
8 patients with OA-MALT lymphoma, one with follicular lymphoma	chlorambucil and rituximab	CR: 89% PFS: 100% after a median follow-up of 25 months	21
31 patients with nongastrointestinal MALT lymphoma	20 patients: fludarabine and mitoxantrone, 11 patients: COP	CR: 100% after a median follow-up of 3 years 5-year OS: 100%, 5-year DFS: 85%	22
25 patients with MALT lymphoma	cladribine	CR: 84% DFS at 6.7 years: 68.5%	23
19 patients with gastric and 7 patients with extragastric MALT lymphoma	cladribine	CR: 84% (gastric; 100%, extragastric; 43%)	25
227 patients with MALT lymphoma	chlorambucil (n=113) vs chlorambucil plus rituximab (n=114)	CR: 65% vs 78% 5-year EFS: 50% vs 68% 5-year OS: 89% vs 89% after a median follow-up of 62 months	26
16 patients with nongastric MALT lymphoma	ibritumomab tiuxetan	CR: 50% 5-year OS: 71.8%, 5-year PFS: 40%	27
29 patients with relapsed/refractory MALT lymphoma	bortezomib	overall response rate: 48% (CR: 31%)	28
24 patients with relapsed/refractory MALT lymphoma	everolimus	overall response rate: 25% median PFS: 14 months after a median follow-up of 14.5 months	29
18 patients with MALT lymphoma	lenalidomide	overall response rate: 61% (CR: 33%)	30

Assuming that the onset of OA-MALT lymphoma is due to chlamydia infection (*C. psittaci*), eradication therapy using doxycycline (Phase II international clinical trial) was reported in 2012[35]. According to this report, the response rate to doxycycline monotherapy (200 mg daily for 3 weeks) was 65% (complete remission: 18% + partial remission: 47%). However, many cases of OA-MALT lymphoma with chlamydia negativity have been reported [36-46], which can be expected to have a high remission rate by initial treatment with radiotherapy, and it is necessary to be cautious about applying this result to clinical practice. Eradication therapy is less invasive and can be a useful option for localized OA-MALT lymphoma. However, this should be limited to elderly patients and patients with reduced physical fitness, and it should be given only after informed consent has been obtained.

Other causative agents such as *H. pylori* and HSV-1, -2, in addition to chlamydia infection, have been examined so far. However, treatments based on these infectious agents have not yet been established.

Conclusions

OA-MALT lymphoma is mainly localized and has a good prognosis, similar to other indolent lymphomas. Radiotherapy, surgical resection, and 'watchful waiting' are recommended as local treatments in the localized phase. When local treatment is not indicated or there is recurrence, immuno-chemotherapy with rituximab or a 'watchful waiting' approach should be considered, as for follicular lymphoma. Therapy with *C. psittaci* eradication cannot yet be evaluated. After careful consideration of lesion sites, stage, age, PS, adverse effects of the treatment, and patient philosophy of life, the treatment for OA-MALT lymphoma should be selected.

Acknowledgments

The authors appreciate the cooperation of the cancer center personnel at Ehime University Hospital.

Conflict of interest

The authors have no conflict of interest.

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