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ARTICLE

Feasibility of oral doxycycline as first-line therapy for conjunctival mucosa-associated lymphoid tissue lymphoma

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OBJECTIVES: To investigate the long-term outcomes of oral doxycycline as first-line treatment in patients with conjunctival extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma).
METHODS: In this case series, the medical records of 67 patients with conjunctival MALT lymphoma who received doxycycline as their primary treatment and were followed up for at least 5 years were retrospectively reviewed. Progression-free survival (PFS) was analysed at 3, 5, and 10 years after the initial doxycycline treatment. A Cox proportional hazards model was used to assess the independent risk factors for progression.
RESULTS: After the initial treatment, 25 patients (37.3%) achieved a complete response, 8 patients (11.9%) achieved a partial response, 30 patients (44.8%) showed stable disease, and 4 patients (6.0%) showed disease progression. The median PFS in all patients was 168 months, and the 3-, 5- and 10-year PFS rates for all patients were 70%, 65%, and 62%, respectively. No further progression was observed 6 years after the initial doxycycline treatment. Younger age and TNM stage T1c were significant risk factors for the time to progression in the multivariate Cox regression analysis ($p < 0.05$). Additional doxycycline (>2 cycles) showed no benefit. There were no serious adverse events associated with doxycycline therapy, and most patients were successfully salvaged by second-line treatments, including radiotherapy and chemotherapy.
CONCLUSION: In this case series, oral doxycycline treatment yielded acceptable long-term PFS with minimal complications. Especially in patients with stage T1a or T1b conjunctival MALT lymphoma, first-line doxycycline treatment could be considered under close monitoring for at least 6 years.

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INTRODUCTION

Ocular adnexal lymphoma (OAL), the most common primary orbital malignancy in adults, is a localised form of systemic lymphoma affecting the conjunctiva, orbit, lacrimal gland, and eyelids [1]. OAL encompasses heterogeneous groups of malignancies, among which extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) is the most frequent histologic subtype and accounts for 35–90% of all primary OALs [2, 3]. In the conjunctiva, MALT lymphoma is also the most common subtype and constitutes approximately 80% of conjunctival lymphomas [4, 5].

For the treatment of isolated conjunctival lymphoma, external beam radiation therapy (EBRT) is generally considered the gold standard treatment, while systemic immunotherapy with monoclonal antibodies plus/minus chemotherapeutic agents is occasionally selected in bilateral cases [5]. Although the local control rate and 10-year overall survival rates for ocular adnexa MALT lymphoma (OAML) treated with EBRT exceed 95% and 84%, respectively, chronic complications, including cataracts and dry eye, are common in up to 50% of patients, and even serious vision-threatening complications, such as retinopathy or corneal perforation,< can occur [6]. Systemic immunotherapy and/or chemotherapy may also cause serious systemic adverse events.

Considering that MALT lymphoma is a low-grade and indolent histological subtype with an excellent prognosis and that systemic involvement is extremely rare when it is confined to the conjunctiva, the choice of an alternative option for EBRT, immunotherapy or chemotherapy as a first-line treatment might be reasonable to avoid serious local and systemic complications. In line with this approach, oral doxycycline targeting *Chlamydia psittaci (Cp)*, similar to treatment targeting the association of gastrointestinal MALT lymphoma with *H. pylori* infection [7, 8], would be a safer and better tolerated alternative therapeutic option for indolent conjunctival lymphoma [9–12]. Chronic antigenic stimulation has been speculated to be a pivotal process associated with the pathogenesis of conjunctival MALT lymphoma, and microorganisms, including *Cp*, have been identified as causative factors [4–6]. *Cp* infection is known to be involved in the pathogenesis of OAML by inducing lymphoid proliferation and causing chromosomal aberration through genetic instability and oxidative damage to DNA [13–15]. However, the prevalence of *Cp* infection in patients with OAML varies greatly by geographic area,

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with high rates in North Italy (87%), Korea (79%), and Austria (54%), but is virtually absent in Japan, North China, Africa, and some regions of the United States [13, 15–19]. Therefore, it is rational that the use of doxycycline to resolve *Cp* infection be actively considered a first-line therapy for MALT lymphoma in countries with a high prevalence of *Cp* infection, including Korea.

In fact, the study group from the same institution, at which the current study was conducted, serially reported the viable efficacy of doxycycline as first-line therapy for OAML without causing serious systemic toxicities. The overall response rate after a median of 26.4 months of follow-up was 47%, and the 5-year progression-free survival (PFS) rate after a median of 40.5 months of follow-up was 60.9% [10, 12]. In particular, the study group found that tumour-node-metastasis (TNM) staging is an independent predictor of PFS and suggested that patients with OAML at the T1N0M0 stage are good candidates for doxycycline therapy [5, 12].

Since the treatment was recently introduced, there have been no long-term follow-up reports to provide a rationale for the use of doxycycline therapy as a first-line treatment in patients with conjunctival MALT lymphoma [10–12]. Accordingly, through a long-term follow-up surveillance of at least 5 years, we investigated the feasibility of oral doxycycline as a first-line therapy in patients with isolated conjunctival MALT lymphoma (T1N0M0 OAML).

MATERIALS AND METHODS

Study design and subjects

This study is a retrospective case series of patients who visited Seoul National University Hospital (SNUH) due to conjunctival MALT lymphoma and were treated with doxycycline as a first-line therapy between January 2001 and December 2020. This retrospective study was approved by the Institutional Review Board of SNUH (IRB No. H-1908-097-1055). All research was conducted following the tenets of the Declaration of Helsinki.

Patients were included based on the following criteria: (1) typical histological features of MALT lymphoma according to the World Health Organisation criteria [20, 21] as confirmed by specialised hematopathologists (when possible, *Cp* analyses were performed along with excisional biopsy); (2) primary tumour confined to the conjunctiva; (3) clearly measurable lesion on anterior segment photography at the time of doxycycline initiation; (4) doxycycline used as a first-line treatment; and (5) follow-up for longer than 5 years after the initial diagnosis. To confirm that the malignancy was confined to the conjunctiva only, the patient underwent a staging work-up, including an ophthalmic examination by experienced ophthalmologists, complete blood count, blood chemistry, chest radiograph, computed tomography (CT) and magnetic resonance imaging (MRI) of the orbit, CT of the chest and abdomen, and a bone marrow aspirate and biopsy. Each tumour was classified according to the seventh edition criteria of the American Joint Committee on Cancer (AJCC) for ocular adnexal lymphoma (OAL): T1a - involvement of bulbar conjunctiva only, T1b - involvement of palpebral conjunctiva and/or fornix and/or caruncle, T1c - involvement of both bulbar and nonbulbar conjunctiva without orbital involvement. (Table S1) [22].

The exclusion criteria were as follows: (1) follow-up of less than 5 years; (2) primary tumour involving structures other than the conjunctiva; and (3) insufficient medical records to assess tumour status and treatment response.

Initial doxycycline treatment

All patients were treated with initial single or double cycles of oral doxycycline at a dose of 100 mg twice a day for 3 weeks. Double-course therapy was assigned to patients with a residual mass or ocular discomfort who did not respond to single-course therapy, and a second cycle of doxycycline was administered after a 3-week drug-off period. The initial treatment response was evaluated 6 weeks after the initiation of doxycycline by ophthalmic examination, including anterior segment photography, orbital CT scan or orbital MRI.

Follow-up and additional treatment

After a visit to evaluate the initial doxycycline treatment, patients were followed up every 3 months for 2 years and every 6 months thereafter unless they were indicated for second-line therapy. During the follow-up period, an ophthalmic examination, including anterior segment photography, complete blood count, blood chemistry including lactate dehydrogenase (LDH), and radiologic examination (CT or MRI), were performed at every visit. Based on the ophthalmic or radiologic evaluation, the treatment response was assessed using the following modified international workshop criteria [23]: complete response (CR) is the complete disappearance of all detectable evidence of disease; partial remission (PR) is a 50% or more decrease and no new disease; progressive disease (PD) is a 50% or more increase of previously involved lesions from nadir or any new lesion; stable disease (SD) is the absence of CR, PR, and PD [24].

Second-line treatment was advised for PR patients with persistent eye-related symptoms or disease progression and for all SD and PD patients. After experienced oncologists provided a comprehensive explanation of the common natural course of the disease and the pros and cons of each treatment modality, second-line treatments using additional cycles of doxycycline, combination chemotherapy composed of cyclophosphamide, vincristine, and prednisolone, EBRT, or interferon-alpha eye drops were given to the patients who agreed to receive further treatment. If the tumour showed progression or did not sufficiently regress after the second-line treatment, salvage treatments, including doxycycline, EBRT, and chemotherapy, were additionally given.

Table 1. Patient characteristics.

Characteristics	
Age at diagnosis (years)	
Mean ± SD	43.0 ± 13.1
Range	21–71
Duration of follow-up (months)	
Mean ± SD	109.7 ± 34.0
Range	60–195
Gender	
Male, *n* (%)	20 (29.9%)
Female, *n* (%)	47 (70.1%)
B symptoms at diagnosis	
Yes, *n* (%)	1 (1.5%)
No, *n* (%)	66 (98.5%)
ECOG performance status score at diagnosis	
0–1, *n* (%)	67 (100%)
2–4, *n* (%)	0 (0%)
Chief complaint at diagnosis	
Mass, *n* (%)	34 (50.7%)
Conjunctival injection or irritation, *n* (%)	26 (38.8%)
Epiphora, *n* (%)	4 (6.0%)
Ptosis, *n* (%)	1 (1.5%)
Pain, *n* (%)	1 (1.5%)
No symptom, *n* (%)	1 (1.5%)
Laterality	
Unilateral, *n* (%)	35 (52.2%)
Bilateral, *n* (%)	32 (47.8%)
TNM stage	
T1aN0M0, *n* (%)	3 (4.5%)
T1bN0M0, *n* (%)	54 (80.6%)
T1cN0M0, *n* (%)	10 (14.9%)
Ki-67 proliferation index (%)	
Mean ± SD	5.8 ± 5.3

SD standard deviation, *ECOG* Eastern Cooperative Oncology Group.

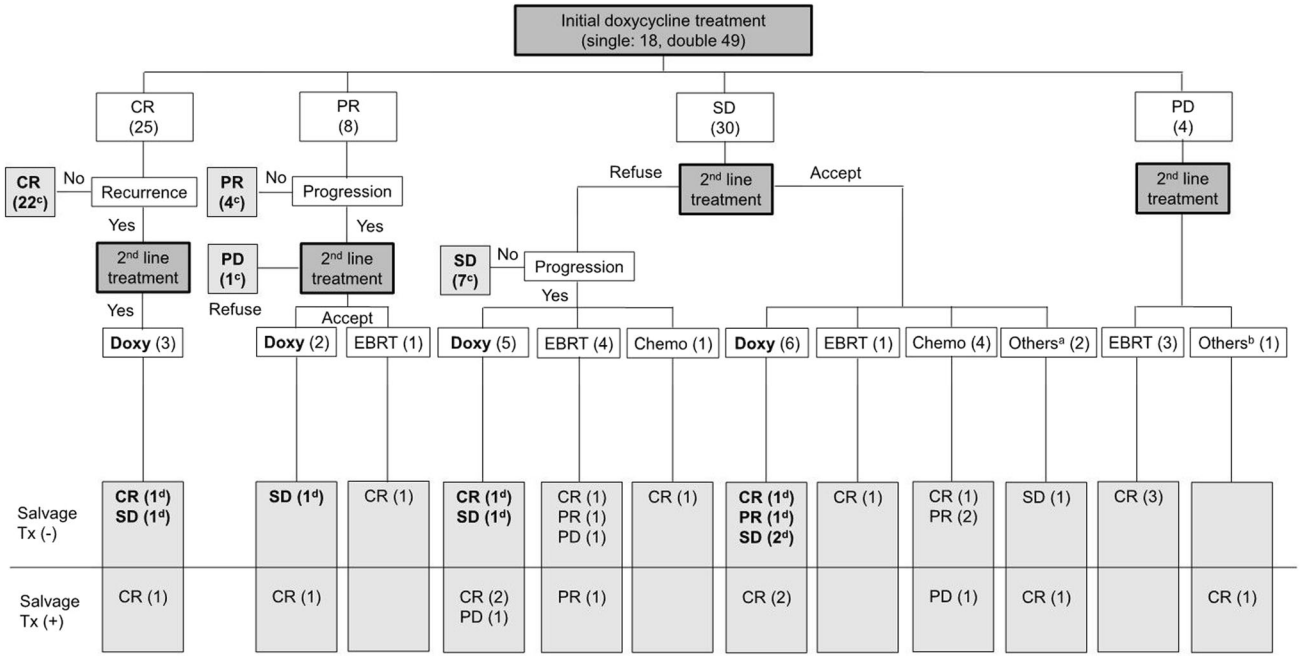

Fig. 1 Overall treatment sequence according to the response of first-line doxycycline therapy. CR complete response, PR partial remission, SD stable disease, PD progressive disease, Doxy doxycycline, Chemo chemotherapy, EBRT external beam radiation therapy, Tx treatment. [a]Interferon alpha eyedrops were used in 2 patients. [b]Patient who received cryotherapy during entropion repair surgery. [c]Patient who received only initial doxycycline treatment. [d]Patients who received doxycycline treatment only for both initial and second treatment.

Statistical analysis

All statistical analyses were performed using SPSS statistics software (version 26) (IBM Corp., Chicago, IL, USA). PFS was measured from the date of doxycycline initiation to the date of disease progression or censoring of patients at the date of the last follow-up. Survival curves for PFS were derived by the Kaplan–Meier method, and comparisons between the groups were made using the log-rank test. Univariate and multivariate analyses of PFS were performed using the Cox proportional hazards regression model. Two-sided $P < 0.05$ were considered statistically significant.

RESULTS

Demographic and clinical characteristics

One hundred and fourteen patients were pathologically confirmed as having primary ocular adnexal lymphoma and received doxycycline as the first-line treatment at SNUH. Among them, 21 patients were excluded due to a follow-up of less than 5 years, 18 patients were excluded because of extraconjunctival involvement of the tumours, and 8 patients were excluded due to lack of sufficient ophthalmic examination records. Ultimately, 67 patients were enrolled in this study, and all patients were Korean.

The demographic and clinical characteristics of the patients are summarised in Table 1. The mean age at onset was 43.0 years (range, 21–71 years), and the mean follow-up duration was 109.7 months (range, 60–195 months). Although there was a female predominance with a ratio of 2.35:1, there were no demographic differences based on gender (Table S2). All patients had an Eastern Cooperative Oncology Group performance status of 0–1, and only one patient had B symptoms (fever >38 °C, night sweats, and/or unintentional weight loss of >10% of the body weight over a period of up to 6 months) at diagnosis. Detection of a mass was the most common chief complaint at diagnosis ($n = 34$, 50.7%), followed by conjunctival injection or irritation ($n = 26$, 38.8%), epiphora ($n = 4$, 6.0%), and pain ($n = 1$, 1.5%). Thirty-two patients (47.8%) had bilateral involvement. According to the TNM staging, 3 patients (4.5%) were T1a, 54 (80.6%) were T1b, and 10 (14.9%) were T1c. The mean Ki-67 proliferation index was 5.8%. *Cp* analyses were conducted in 5 patients, and two (40%) of them tested positive.

Outcomes of initial doxycycline treatment

Figure 1 shows the overall treatment sequence of all the patients. For initial treatment, 49 patients (73.1%) received double cycles of doxycycline. After single or double cycles of initial doxycycline treatment, 25 patients (37.3%) achieved CR, 8 patients (11.9%) achieved PR, 30 patients (44.8%) showed SD, and the disease progressed in 4 patients (6.0%).

Secondary treatment outcomes by group classified based on initial treatment results

Tumours recurred in 3 of 25 patients who achieved CR after the initial doxycycline treatment. These three patients underwent an additional cycle of doxycycline therapy. One patient achieved CR again after two cycles of additional doxycycline, and two other patients showed SD after one cycle of additional doxycycline. One of these patients finally achieved CR after EBRT.

After the initial doxycycline treatment, tumours progressed in 4 of 8 PR patients. Among these 4 patients, one patient refused further treatment, one patient achieved CR after one cycle of EBRT, and the remaining 2 patients received additional doxycycline treatment as a second-line therapy. The disease became stable in one patient after two additional cycles of doxycycline, and the other patient showed progression after one cycle of doxycycline and therefore received two cycles of EBRT, which induced CR.

In the SD group, 17 patients refused additional treatment, but 10 showed progression and eventually accepted secondary treatment. The median time from initial doxycycline treatment to progression was 11.5 months (range 3–59), and the median time from progression detection to the start of second-line treatment was 2.5 days (range 0–240). Five patients received additional doxycycline, 4 patients received EBRT, 1 patient received chemotherapy, and 2 of these 10 patients progressed despite additional treatment. Of the 13 patients in the SD group who agreed to the second-line treatment after the initial

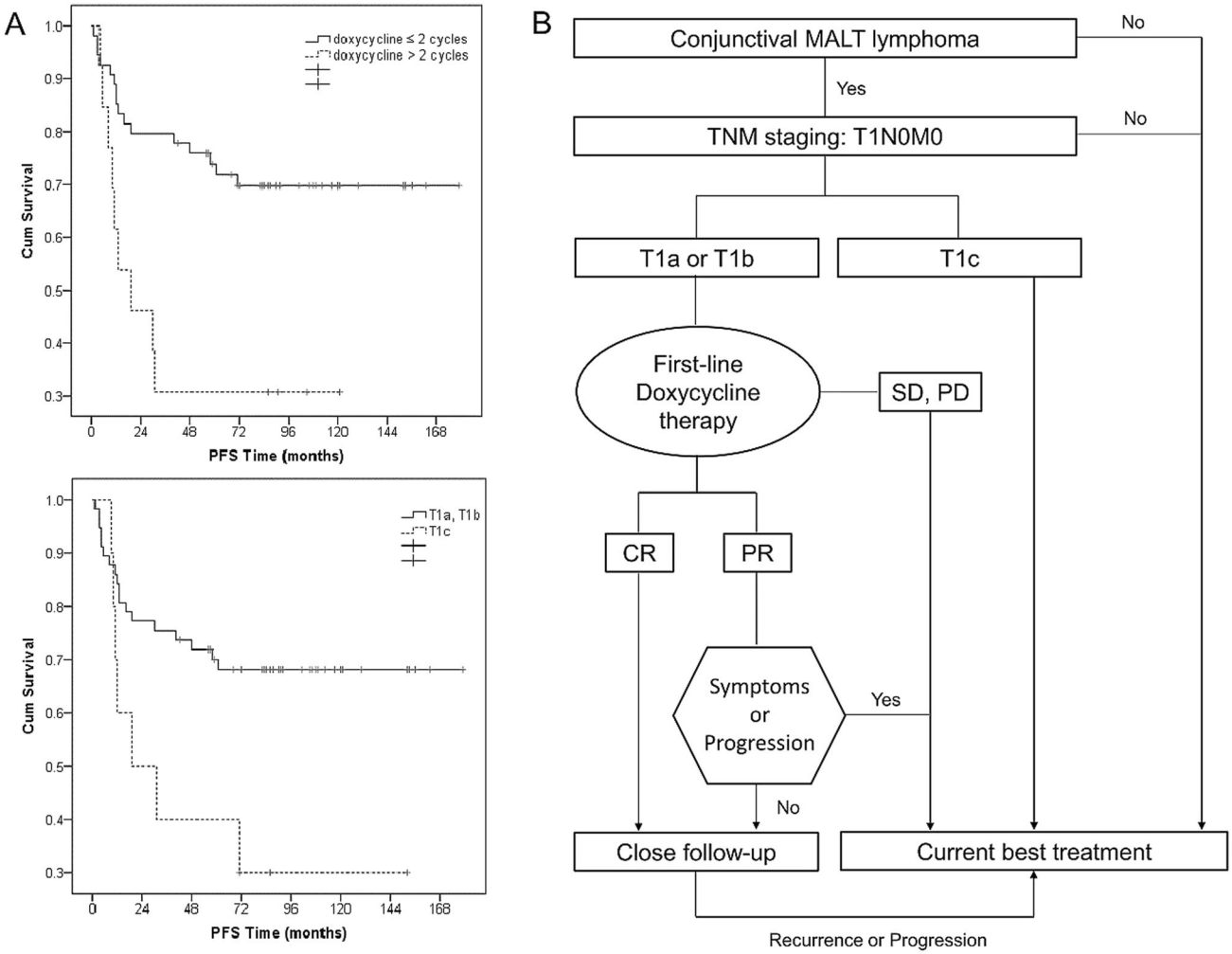

Fig. 2 Survival analyses and proposed treatment algorithm using doxycycline as first-line therapy. A The risk of disease progression significantly increases when more than 2 cycles of doxycycline treatment are required and in patients presenting with T1c stage disease. **B** First-line doxycycline therapy should be actively considered for patients with T1aN0M0 or T1bN0M0 stage disease, particularly in regions with a high prevalence of Cp infection or when Cp DNA is positively identified in the excised specimen or conjunctival swab. These patients should be closely monitored according to the prescribed schedule, unless there is an evident recurrence after a Complete Response or progression following a Partial Response. PFS progression-free survival, Cum Survival cumulative survival, MALT mucosa-associated lymphoid tissue, CR complete response, PR partial remission, SD stable disease, PD progressive disease.

doxycycline treatment, 6 received additional doxycycline, 1 received EBRT, 4 received chemotherapy, and 2 received interferon-alpha eye drops. Only one of these patients eventually progressed despite additional treatment.

Four patients who exhibited PD after the initial doxycycline treatment received second-line treatment. Three patients achieved CR after one cycle of EBRT. The remaining patient achieved CR after surgical excision and cryotherapy but showed recurrence and underwent one cycle of EBRT to achieve CR again (Fig. 1 and Fig. S1).

Frequency of use of each treatment modality in all patients

Out of 67 patients, sixteen (23.9%) received additional doxycycline as a second-line treatment (Fig. 1). Including salvage treatments, 15 patients (22.4%) received 1 cycle, 39 (58.2%) received 2 cycles, 8 (11.9%) received 3 cycles, 4 (6.0%) received 4 cycles, and 1 patient received 9 cycles of doxycycline. There were no serious adverse events related to the administration of doxycycline. Overall, 43 (64.2%) patients received doxycycline treatment alone, eighteen (26.9%) patients received at least one cycle of EBRT, and 6 (9.0%) patients received at least one cycle of chemotherapy. Only one patient received a combination of doxycycline, chemotherapy and EBRT (Fig. S2).

Survival analysis and predictive factors

All patients were alive until the last follow-up. The median PFS in all the patients was 168 months (range, 1–179 months). The 3-, 5- and 10-year PFS rates for all the patients were 70%, 65% and 62%, respectively. There was no additional progression after 71 months. Patients who required more than 2 cycles of doxycycline treatment had an increased risk of progression compared with patients who received 1 or 2 cycles of doxycycline ($p = 0.003$). Patients with TNM stage T1c disease showed a significantly increased risk of progression compared with patients with stage T1a and T1b disease ($p = 0.021$) (Fig. 2A).

Regarding clinical predictors of PFS, age (hazard ratio [HR], 0.967; 95% confidence interval [CI], 0.937–0.998; $p = 0.033$) and T1c stage (HR, 2.681; 95% CI: 1.115–6.449; $p = 0.022$) were significantly associated with time to progression in the univariate Cox proportional hazards regression analysis. Male sex, bilateral involvement of the tumour, high Ki-67 proliferation index and positive anti-HCV antibody also tended to show associations with

Table 2. Univariate and multivariate Cox proportional hazards regression analysis of the progression free survival.

Factors	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age	**0.967**	**0.937–0.998**	**0.033**	**0.968**	**0.938–1.000**	**0.048**
Sex (male vs female)	0.546	0.245–1.218	0.134			
Laterality (unilateral vs bilateral)	1.795	0.806–3.998	0.126			
T stage (T1a/b vs T1c)	**2.681**	**1.115–6.449**	**0.022**	**2.533**	**1.052–6.098**	**0.038**
Ki-67 (<5% vs ≥5%)	1.871	0.674–5.197	0.222			
Serum LDH level (<225 U/L vs ≥225 U/L)	1.209	0.411–3.554	0.730			
HBV (HBsAg negative vs positive)	0.045	0.000–211.601	0.472			
HCV (Anti-HCV negative vs positive)	3.374	0.745–15.292	0.115			
Lymphocytosis (ALC < 1900 vs ≥1900)	1.308	0.534–3.202	0.557			
Neutrophilia (ANC < 3299 vs ≥3299)	0.911	0.379–2.189	0.834			
NLR (<1.6426 vs ≥1.6426)	1.361	0.564–3.285	0.491			

HR hazard ratio, *CI* confidence interval, *LDH* lactate dehydrogenase, *ALC* absolute lymphocyte count, *ANC* absolute neutrophil count, *NLR* neutrophil to lymphocyte ratio.
Bold entries denote statistically significant values.

progression-free survival. In the multivariate analysis, age (HR: 0.968; 95% CI: 0.938–1.000; $p = 0.048$) and T1c stage (HR: 2.533; 95% CI: 1.052–6.098; $p = 0.038$) were significantly associated with time to progression (Table 2).

DISCUSSION

In this study, based on long-term follow-up, we investigated the feasibility of doxycycline therapy as a first-line treatment for patients with MALT lymphoma confined to the conjunctiva. Among 67 patients who received oral doxycycline as an initial treatment, no mortality was observed during the mean follow-up duration of 109.7 months. CR and PR were 49.2% after the initial one or two cycles of doxycycline treatment. Approximately two-thirds (64.2%) of patients received doxycycline treatment alone, and most of the remaining patients were successfully salvaged by other treatments. The median PFS was 168 months (range, 1–179 months), and the 3-, 5- and 10-year PFS rates were 70%, 65% and 62%, respectively. Stage T1c was significantly associated with an increased risk of progression. There were no serious complications associated with the oral administration of doxycycline.

According to the results of a previous study [12], we only enrolled patients with stage T1N0M0 OAML (conjunctival MALT lymphoma) in this study. The mean age at diagnosis was 43.0 years, 47 of 67 (70.1%) patients were female, and 32 of 67 (47.8%) patients had bilateral disease. These findings correspond well to the characteristics (young age onset, female predilection, and higher rate of bilateral cases) of conjunctival MALT lymphoma compared with other OAMLs in Korean patients described elsewhere [25–28].

Primary treatment with oral doxycycline in patients with OAML has shown an acceptable 5-year PFS rate of 58% on average without compromising salvage treatment in two of the largest previous studies [11, 12]. Moreover, the PFS in patients with T1N0M0 stage disease was significantly better than that in patients with more advanced stages [12], and *Cp* eradication was associated with an improved response rate and 5-year PFS [11]. In this study, the clinical outcome of doxycycline as a first-line treatment showed complete tumour regression in 25 patients and partial tumour regression in 8 patients, with an overall initial response rate of 49.2%, which was very similar to that in a previous report from the same institution [12]. The median PFS in all the patients was 168 months, and the 5- and 10-year PFS rates were 65% and 62%, respectively. The 5-year PFS was slightly higher than that in previous studies [11, 12], which is thought to be because we included only patients with T1N0M0 stage disease. There were no serious adverse events associated with doxycycline therapy, and most patients were successfully salvaged by the current best treatment modalities, including EBRT and chemotherapy, after recurrence or progression from CR and PR or doxycycline failure. Interestingly, some patients progressed after 5 years, but no further progression was observed after 6 years regardless of treatment. Our results solidify the prospect of using doxycycline as a first-line therapy for patients with conjunctival MALT lymphoma without compromising salvage treatment after progression or doxycycline failure.

Regarding clinical risk factors for PFS, multivariate Cox proportional hazards regression analysis revealed that T1c stage was an independent predictor for poorer PFS than T1a/b stage. This is a notable finding from this study, which implies that a first-line treatment modality should be considered separately according to T1a/b or T1c stage despite the same T1N0M0 tumours. As in a previous report, sex, laterality, serum LDH level, lymphocytosis and neutrophilia were not significantly associated with PFS [12]. Notably, among 67 patients, 32 (53.1%) showed bilateral involvement. However, there was no significant difference between patients with unilateral involvement and those with bilateral involvement in either the Kaplan–Meier survival analysis (Long-rank test, $p = 0.144$) or the univariate Cox proportional hazards regression analysis ($p = 0.126$). This contrasts with most other diseases, where involvement of bilateral or multiple lesions is associated with a worse prognosis. Our results provided another new insight that 3 or more administrations of doxycycline posed no additional benefit for patients who required more than 2 cycles of doxycycline treatment. Therefore, it is recommended to use doxycycline a maximum of two times only as an initial treatment and to consider other treatments for cases of recurrence after CR, a regrowing mass after PR, or doxycycline-resistant SD or PD cases.

This study has some limitations. First, *Cp* DNA was not evaluated from all the excised tissues or conjunctival swabs. Unfortunately, a formal process for *Cp* analysis has not been established in our hospital. From 2006 to 2008, we could only perform the test using the excised conjunctival tissues under a laboratory setting, which showed 60% (15 out of 25) *Cp* positivity in conjunctival MALT lymphoma specimens. Among them, only 5 patients met the inclusion criteria for our study, and the number was too small to

draw a concrete conclusion. Although it has been documented in previous reports that the *Cp* infection rate in Korea is as high as 60-79% and that *Cp* positivity is not associated with doxycycline response [10, 16], Ferrari et al. reported that successful *Cp* eradication was associated with outcomes and that there was no clinical benefit of doxycycline in patients with *Cp*-negative OAML [11]. As Ferrari et al. also reported that *Cp* DNA detection can be easily performed with a noninvasive method such as a conjunctival swab [11], *Cp* DNA detection should be considered in conjunctival MALT lymphoma in future research. Second, various second and salvage treatments were implemented according to the preferences of physicians, the choice of individual patients and the results of previous treatments. In future clinical protocols, there should be standardised second and salvage treatment after initial doxycycline treatment.

In conclusion, when used together with appropriate salvage treatment, up to 2 cycles of oral doxycycline treatment can be used as a first-line treatment for T1a and T1b stage conjunctival MALT lymphoma, especially in patients from countries with a high *Cp* prevalence or with confirmed *Cp* DNA (Fig. 2B). Although conjunctival MALT lymphoma has a benign nature, it may continue to progress in some patients, so at least 6 years of follow-up is needed.

SUMMARY

What was known before

- For the treatment of conjunctival extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma), external beam radiation therapy can achieve excellent tumour control. However, various long-term ocular complications, such as cataracts, dry eye disease, corneal ulceration, and retinopathy are common. Eradication of Chlamydia psittaci (Cp), known to be involved in the pathogenesis of MALT lymphoma, has shown acceptable results without compromising salvage treatment in previous studies.

What this study adds

- Oral doxycycline treatment, when used together with appropriate salvage treatment, demonstrated acceptable long-term progression-free survival with minimal complications, especially in patients with stage T1a and T1b conjunctival MALT lymphoma. As no further progression was observed after 6 years, a minimum follow-up period of 6 years is recommended.

DATA AVAILABILITY

All data relevant to the study are included in the article or uploaded as supplementary information.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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