검안 및 콘택트렌즈학회지 2019년 제18권 제3호
Ann Optom Contact Lens 2019;18(3):67-74
ISSN 2384-0919 (Print) · ISSN 2384-0927 (Online)

Original Article

Characteristics of Ocular Adnexal Mucosa-associated Lymphoid Tissue Lymphoma after First-line Chemotherapy: a 7-year Experience

Sung Eun Kim, MD[1*], Ji-Sun Paik, MD, PhD[2*], Suk-Woo Yang, MD, PhD[1]

Department of Ophthalmology, Catholic University Lymphoma Group, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea[1], Seoul, Korea
Department of Ophthalmology, Catholic University Lymphoma Group, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea[2], Seoul, Korea

Purpose: Ocular adnexal mucosa-associated lymphoid tissue lymphoma (OAML) is the most common primary orbital malignancy. While radiotherapy is the treatment of choice for limited stage tumors, chemotherapy is required to treat disseminated disease or those patients who cannot tolerate radiotherapy. In this study, we examined the characteristics of OAML and treatment responses after first-line chemotherapy.
Methods: Eighty patients with histopathologically confirmed OAML were treated with a combination of cyclophosphamide, vincristine, and prednisolone (CVP) with selective addition of rituximab (R-CVP) or the combination of cyclophosphamide, hydroxydaunorubicin, oncovine and prednisolone (CHOP). Radiation therapy or additional chemotherapy with different regimens was undertaken for chemotherapy failure cases.
Results: The most common site of lymphoma was orbit and 25 (31.3%) patients had bilateral disease at presentation. The tumor stage was IE in 39 (48.8%) patients, IIE in 18 (22.5%) patients, IIIE in 3 (3.8%) patients, and IVE in 20 (25%) patients. Twenty-eight (35%) patients had no ocular symptoms and the common symptoms were foreign body sensation, periorbital swelling, and proptosis. Overall response rate of 100% was achieved in all patients regardless of chemotherapy regimen: complete remission (CR) was observed in 93.5% of patients treated with R-CVP, 66.7% with CHOP, and 72.7% with CVP. After a median follow-up of 54 months, relapse occurred in five (6.2%) patients and three of these patients underwent radiation therapy while the other two patients received additional chemotherapy. All patients except for two patients had CR as the final response.
Conclusions: First-line chemotherapy is effective and well tolerated in patients with localized (stage 1) and advanced stage (≥ stage 2) OAML. R-CVP therapy can achieve a higher treatment response than CHOP or CVP therapy, as well as higher progression-free survival.
Ann Optom Contact Lens 2019;18(3):67-74

Key Words: Chemotherapy; Marginal zone B cell lymphoma; Ocular adnexal mucosa-associated lymphoid tissue lymphoma

INTRODUCTION

Ocular adnexal lymphomas (OALs) are lymphoproliferative neoplasms that involve conjunctiva, lacrimal gland, lacrimal sac, extraocular muscles, eyelids, and the orbit itself. OALs account for approximately 8% of extranodal non-Hodgkin's lymphomas and primary OALs are the most commonly encountered orbital malignancy, occurring in about 30-55% patients.[1,2] The majority of OALs are extranodal, marginal zone B cell lymphomas of mucosa-asso-

■ **Received:** 2019. 6. 14. ■ **Revised:** 2019. 8. 22.
■ **Accepted:** 2019. 9. 6.
■ Address reprint requests to **Suk-Woo Yang, MD, PhD**
Department of Ophthalmology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, #222 Banpo-daero, Seocho-gu, Seoul 06591, Korea
Tel: 82-2-2258-1188, Fax: 82-2-599-7405
E-mail: yswoph@hanmail.net

* Sung Eun Kim and Ji-Sun Paik contributed equally to this work as first authors.

ciated lymphoid tissue type (MALT).[3,4] Most MALT lymphomas are localized tumors that show an excellent response to radiation therapy;[5] chemotherapy is not widely used. However, limited-stage ocular adnexal MALT lymphomas (OAMLs) have been reported to have a recurrence rate of 25% following radiation therapy,[5] especially in patients who have lymphoma in both eyes or in whom the lymphoma has spread beyond the conjunctiva.[1,6,7] Disseminated relapses after radiation therapy have been reported in 17% of patients.[8] In contrast, patients with disseminated or high-grade OAML require chemotherapy for systemic control. Several researchers have studied the efficacy of first-line chemotherapy to treat ocular adnexal MALT lymphoma.[9-11] We have 7-years of experience with several chemotherapeutic modalities, including immunotherapy with rituximab as the first-line treatment for both low-grade and high-grade OAMLs. Rituximab as an immunotherapeutic agent has emerged as a promising treatment option because of its safe toxicity profile and good tolerability.[12,13] In this study, we sought to determine the characteristics of OAML and the efficacy of different kinds of chemotherapy in terms of outcomes such as recurrence rates and adverse events.

MATERIALS AND METHODS

1. Patients

From March 2009 to December 2016, 80 patients with pathologically diagnosed OAML who received R-CVP, CVP, or CHOP chemotherapy as frontline regimens were recruited for this retrospective study at Seoul St. Mary's Hospital. We obtained all clinical and pathologic data by medical record review, including gender, age, tumor stage, histological subtype, B symptoms, IPI score, lymph node and extranodal invasion, hematological examination, therapeutic regimen, and curative effect. A staging work-up that involved physical examination, review by an experienced ophthalmologist (S.W.Y), chest radiography, magnetic resonance imaging (MRI) of the orbit, computed tomography (CT) for the chest and abdomen, and bone marrow aspiration biopsy was performed. The institutional review board of the Catholic University of Korea approved the research protocol for data analysis.

2. Treatment

All 80 patients received a CVP/R-CVP or CHOP regimen with 6-8 cycles as an initial treatment (n = 46, R-CVP; n = 22, CVP; n = 12, CHOP). The chemotherapy regimen was chosen by the physicians based on their clinical judgement. CVP chemotherapy consisted of cyclophosphamide (750 mg/m^2) and vincristine (1.4 mg/m^2) on day 1 and prednisolone (60 mg/m^2) on days 1-5 every 21 days. Rituximab (375 mg/m^2) on day 1 was added to CVP chemotherapy (R-CVP chemotherapy). The CHOP regimen consisted of cyclophosphamide (750 mg/m^2), doxorubicin (50 mg/m^2), vincristine 1.4 mg/m^2 on day 1, and prednisone (100 mg/m^2) orally on days 1-5 every 21 days. Treatment cycles were repeated every three weeks in our outpatient clinic. After three and six cycles of chemotherapy, all patients underwent disease assessment by physical and or ophthalmologic examination along with radiologic findings including MRI or CT scans of the affected area.

After completion of three or six cycles of chemotherapy, all patients underwent treatment response assessments every 3 months for one year, followed by assessments every 4-6 months for three years, and then annually to identify local and systemic recurrence. Complete remission (CR) was defined as the disappearance of all evidence of disease partial remission (PR) as regression of measurable disease without new lesions; stable disease (SD) as the failure to attain CR, PR, or progressive disease (PD); relapse disease as any new site lesions; and PD as an increase > 50% of previously involved sites from the nadir status.

3. Statistical analysis

Overall response rates after chemotherapy or chemotherapy followed by either additional radiotherapy or another chemotherapy regimen in recurrent cases were evaluated in addition to progression-free survival (PFS) and significant adverse events.[14] PFS was measured from the start date of chemotherapy to the date of disease progression or relapse at the last follow-up visit. PFS curves were obtained using the Kaplan-Meier method and compared using the log-rank test. A p-value of <0.05 was considered to indicate statistical significance. Statistical analyses were carried out using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA).

RESULTS

1. Patient characteristics

The clinical characteristics of the study patients and disease are described in Table 1, 2. A total of 80 patients (42 men and 38 women) were included in the study. Median age of the patients was 49 years (range, 19-77 years). No patients had B symptoms and most patients (96.2%) had good performance status scores. Only two patients (2.5%) had elevated lactate dehydrogenase levels. Twenty-eight patients (35%) did not have any symptoms, 17 patients (21.3%) had foreign body sense, 14 patients (17.5%) had periorbital swelling, 12 patients (15%) had proptosis, and four patients (5%) had exophthalmos. The most common primary site of OAML was the orbit (n = 36), followed by the conjunctiva (n = 28), eyelid (n = 8), lacrimal gland (n = 4), lacrimal sac (n = 3), and orbital adnexa (n = 1). Twenty-five patients (31.3%) had bilateral disease at presentation. According to the Ann Arbor staging, 39 patients (48.8%) had stage IE disease, 18 patients (22.5%) had stage IIE disease, three patients (3.8%) had stage IIIE disease, and the remaining 20 patients (25%) had stage IVE disease. Chemotherapeutic treatment comprised R-CVP in 46 patients, CVP in 23 patients, and CHOP in 11 patients.

2. Treatment outcomes

Response to first-line chemotherapy in patients is shown in Table 3. All study patients were initially treated with chemotherapy and of those who received R-CVP, 43 patients (93.5%) achieved CR. All patients with Ann Arbor stage I or II had a CR after completion of chemotherapy, while one patient with stage III disease and two patients with stage IV disease achieved PR. After a median follow-up duration of 43 months, relapse was observed in three (7%) of the 43 CR patients and disease progression was found in one PR patient. A male PR patient with stage IV MALToma in the eyelids and tonsils with invasion to the bone marrow received eight cycles of R-CVP, but the disease was refractory to treatment. After five cycles of R-CVP, he developed chemotherapy-induced peripheral neuropathy and vincristine was withheld in the following three cycles of chemotherapy. At the end of eight cycles, disease evaluation showed negative conversion of lymphoma in the bone marrow but the ocular lesion was refractory

Table 1. Characteristics of 80 patients with ocular adnexal mucosa-associated lymphoid tissue lymphoma

Characteristic	Value
Age (years)	49.75 ± 12.50 (19-77)
Sex	
Male	42 (52.5)
Female	38 (47.5)
B symptoms	
No	80 (100.0)
Yes	0
Lactate dehydrogenase level	
Normal	78 (97.5)
Elevated	2 (2.5)
Ann Arbor stage	
IE	39 (48.8)
IIE	18 (22.5)
IIIE	3 (3.8)
IVE	20 (25.0)
Performance status	
0	77 (96.2)
1	3 (3.8)
Presenting symptoms	
No symptoms	28 (35.0)
Foreign body sense	17 (21.3)
Periorbital swelling	14 (17.5)
Proptosis	12 (15.0)
Exophthalmos	4 (5.0)
Visual impairment	3 (3.8)
Dryness	2 (2.5)
Anatomic location	
Orbit	36 (45.0)
Conjunctiva	28 (35.0)
Eyelid	8 (10.0)
Lacrimal gland	4 (5.0)
Lacrimal sac	3 (3.8)
Orbital adnexa	1 (1.2)
Tumor laterality	
Unilateral	55 (68.7)
Bilateral	25 (31.3)
IPI	
0	56 (70.0)
1	11 (13.8)
2	10 (12.5)
3	3 (3.7)
Chemotherapy	
R-CVP	46 (57.5)
CVP	22 (27.5)
CHOP	12 (15.0)

Values are presented as mean ± standard deviation (range) or number (%).
IPI = international prognostic index: R-CVP = rituximab, cyclophosphamide, vincristine, prednisolone; CVP = cyclophosphamide, vincristine, prednisolone; CHOP = cyclophosphamide, hydroxydaunorubicin, oncovine, prednisolone.

to treatment. Radiation therapy was given for both eyes. After one month, biopsy of the cervical lymph node showed diffuse large B-cell lymphoma (DLBCL) transformation and R-CHOP was given for three cycles. Then, rituximab-induced interstitial pneumonitis developed and steroid pulse therapy was given. Rituximab was withheld and the patient was treated with three cycles of CHOP. Despite additional chemotherapy, systemic relapse was found in the right palate, cervical lymph node, and nasal cavity and salvage chemotherapy was recommended. The patient refused further treatment and was lost to follow-up.

Among the remaining five patients that had a relapse or PD, four patients received additional radiotherapy and one patient received additional different chemotherapy. Eventually, all of these patients achieved a CR. Characteristics of patients with either relapse or PD who required additional treatment are summarized in Table 4.

Twenty-two patients were treated with CVP. Sixteen (72.7%) patients achieved a CR while the remaining six patients achieved a PR. Two patients relapsed; one patient with stage I disease had locally relapsed disease after a follow-up period of 31 months and the other one with stage IV disease was found to have disseminated disease in the kidney. This latter patient received additional chemotherapeutic treatment and his final response was a CR. The other six patients with a PR required additional radiotherapy and their final response was a CR at the end of radiotherapy.

Of the 12 patients treated with CHOP, eight (66.7%) achieved a CR and four (33.3%) achieved a PR. No relapse was found during the median follow-up period of 54 months in the CR patients. A 64-year-old female PR patient who initially had lymphoma in the lateral rectus muscle, lacrimal

Table 2. Comparison of demographic factors between the treatment groups

	R-CVP (n = 46)	CVP (n = 22)	CHOP (n = 12)
Age (years)			
Median (range)	52.5 (19-73)	52 (43-66)	46 (27-77)
Sex			
Male/female	26/20	10/12	6/6
Tumor laterality			
Unilateral	27 (58.7)	18 (81.8)	10 (83.3)
Bilateral	19 (41.3)	4 (18.2)	2 (16.7)
Ann Arbor stage			
IE	15 (32.6)	17 (77.3)	7 (58.3)
IIE	10 (21.7)	3 (13.6)	4 (33.3)
IIIE	3 (6.5)	0	0
IVE	18 (39.1)	2 (9.1)	1 (9.1)

Values are presented as number (%) unless otherwise indicated.
R-CVP = rituximab, cyclophosphamide, vincristine, prednisolone; CVP = cyclophosphamide, vincristine, prednisolone; CHOP = cyclophosphamide, hydroxydaunorubicin, oncovine, prednisolone.

Table 3. Response to first-line chemotherapy in patients with ocular adnexal mucosa-associated lymphoid tissue lymphoma: complete remission and relapse

Ann Arbor stage	R-CVP			CVP			CHOP		
	N	CR	Relapse	N	CR	Relapse	N	CR	Relapse
I	15	15	1	17	13	1	7	5	0
II	10	10	1	3	1	0	4	2	0
III	3	2	0	0	0	0	0	0	0
IV	18	16	1	2	2	1	1	1	0
Total	46	43	3	22	16	2	12	8	0

R-CVP = rituximab, cyclophosphamide, vincristine, prednisolone; CVP = cyclophosphamide, vincristine, prednisolone; CHOP = cyclophosphamide, hydroxydaunorubicin, oncovine, prednisolone; CR = complete remission.

gland, and deep orbit received additional orbital radiation and achieved complete remission for a follow-up period of 45 months. However, her lymphoma disseminated to the brain, and pathologic diagnosis confirmed diffuse DLBCL transformation. Her brain was then treated with radiation therapy. However, after 25 months, relapse of malignant lymphoma occurred in the brain and the patient had a drowsy mentality and dysarthria. Physicians decided that additional chemotherapy was impossible and supportive care was the final decision made.

Except for two patients described above, all patients treated with first-line chemotherapy alone or with additional radiotherapy or chemotherapy achieved a complete response, with a median PFS period of 53 months. PFS in the three chemotherapy groups is shown in the Kaplan-Meier plot in Fig. 1. Treatment with R-CVP resulted in a 5-year PFS rate of 69% compared to 67% and 47% in patients treated with CVP and CHOP, respectively. The PFS curves of groups who were treated with rituximab and those who were not were significantly different (p = 0.033). Moreover, when PFS was compared among the three chemotherapy regi-

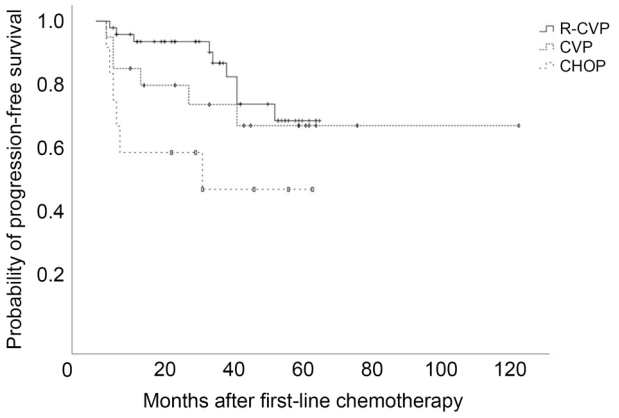

Figure 1. Kaplan-Meier plot of progression-free survival of patients with ocular adnexal mucosa-associated lymphoid tissue lymphoma treated with first-line chemotherapy. R-CVP = rituximab, cyclophosphamide, vincristine, prednisolone; CVP = cyclophosphamide, vincristine, prednisolone; CHOP = cyclophosphamide, hydroxydaunorubicin, oncovine, prednisolone.

Table 4. Characteristics of 18 patients with relapse or disease progression who required either radiation therapy or additional chemotherapy

Sex	Age (years)	Location of tumor	First-line CTx	Response to CTx	Pattern of relapse or disease progression	PFS (months)	Additional treatment	Final response
M	41	Orbit (right)	R-CVP	CR	Local	34	RTx	CR
F	42	Conjunctiva (both), bone marrow	R-CVP	CR	Local	41	RTx	CR
F	30	Lacrimal gland (both)	R-CVP	CR	Local	52	CTx	CR
M	49	Orbit (left)	R-CVP	PR	Local	6	RTx	CR
M	54	Conjunctiva, orbit (both)	R-CVP	PR	Local	4	RTx	CR
M	57	Eyelids (both), tonsils, bone marrow	R-CVP	PR	Nasal cavity, palatine, cervical lymph node (DLBCL)	11	RTx CTx	NE (f/u loss)
M	67	Orbit (right)	CVP	PR	Local	3	RTx	CR
M	46	Orbit (both)	CVP	PR	Local	6	RTx	CR
F	34	Conjunctiva (both)	CVP	PR	Local	13	RTx	CR
F	27	Conjunctiva (right)	CVP	CR	Local	41	RTx	CR
F	50	Conjunctiva (left)	CVP	PR	Local	27	RTx	CR
M	46	Eyelid (right)	CVP	CR	Kidney	38	CTx	CR
F	28	Conjunctiva (left)	CVP	PR	Local	5	RTx	CR
F	59	Conjunctiva (left)	CVP	PR	Local	5	RTx	CR
F	55	Lacrimal gland (right)	CHOP	PR	Local	5	RTx	CR
F	64	Lacrimal gland, rectus muscle, orbit (right)	CHOP	PR	Brain (DLBCL)	45	RTx	Progression
F	66	Orbit (right)	CHOP	PR	Local	7	RTx	CR
M	56	Orbit (right)	CHOP	PR	Local	4	RTx	CR

CTx = chemotherapy; PFS = progression-free survival; M = male; R-CVP = rituximab, cyclophosphamide, vincristine, prednisolone; CR = complete remission; RTx = radiotherapy; F = female; PR = partial remission; NE = not evaluable; CVP = cyclophosphamide, vincristine, prednisolone; CHOP = cyclophosphamide, hydroxydaunorubicin, oncovine and prednisolone; DLBCL = diffuse large B-cell lymphoma.

mens by Kaplan-Meier analysis, a statistically significant difference was found between the R-CVP group and CHOP group (p = 0.006), whereas there was no significant difference between the R-CVP group and CVP group or between the CVP group and CHOP group (p = 0.465 and p = 0.199, respectively).

3. Adverse events associated with chemotherapy

Adverse events associated with chemotherapy are summarized in Table 5. Hematologic complications were the main adverse events: grade 1 or 2 neutropenia, n = 39 (48.8%); grade 3 or 4 neutropenia, n = 5 (6.3%); grade 1 or 2 anemia, n = 16 (20.0%); grade 3 or 4 anemia, n = 4 (5.0%), grade 1 or 2 thrombocytopenia, n = 15 (18.8%); grade 3 or 4 thrombocytopenia, n = 6 (7.5%). Eleven patients had hepatotoxicity, but this was tolerable with conservative treatment. Seven patients had peripheral neuropathy and five patients had infection, including interstitial pneumonitis as mentioned above. As a late ophthalmologic complication, radiation retinopathy occurred in one patient with progressive disease who had additional radiotherapy.

DISCUSSION

Most ocular adnexal MALT lymphomas are limited stage and radiation therapy is the initial treatment of choice.[5] The response rate to radiation therapy is excellent, but relapses can occur, especially in those with both conjunctival lymphoma or with lymphoma beyond the conjunctiva.[6,7] Also, ophthalmologic complications can occur after radiation therapy in some patients, and dry eye syndrome is bothersome to patients.[15-19] Chemotherapy is the preferred treatment option in those who cannot receive radiotherapy or who have higher stage or disseminated disease. Our results show that first-line chemotherapy is an effective treatment modality for OAML. For initial work-up of OAML, systemic evaluation including bone marrow biopsy is required, because up to 15% of patients have systemic involvement at the time of diagnosis.[8] In the current study, 20% of patients were found to have disseminated disease with involvement of various sites including the parotid gland, stomach, mediastinum, bronchus, and kidney.

Most studied patients had lymphoma in the orbit, but among them only three patients had visual impairment. No patients had B symptoms and most patients had good performance status scores. Three patients had lymphoma involvement in the extraocular muscles, but they had no limitations in ocular movement.

Although OAMLs have a more favorable prognosis than other lymphoid proliferative diseases,[20] long-term follow-up has shown that local or systemic relapses do occur occasionally and there can be transformation to a more aggressive form. In this study, 18 patients had either relapse after a CR or disease progression after a PR despite systemic chemotherapy. Among these 18 patients, two patients were found to have DLBCL transformation as described previously. These were the only two patients who did not achieve a CR with additional treatment.

In our study, the pattern of relapse or disease progression was mainly local (83.3%) rather than systemic (16.7%). Previous retrospective research showed that the prognosis of OAML is different in conjunctival and non-conjunctival lesions as the response rate is high, but systemic involvement is low in conjunctival lymphoma compared to other orbital lesions such as those of the eyelids, lacrimal glands, and orbit. However, relapse rate was not found to differ according to the site of lymphoma involvement.[21] Another study showed that conjunctival lymphoma had a low rate of extra-orbital spread and lymphoma-related death compared to deep orbital lymphoma, lacrimal gland lymphoma, or eyelid

Table 5. Adverse events associated with first-line chemotherapy

Adverse event type	Grade	Patient
Hematologic complications		
Neutropenia	1, 2	39 (48.8)
	3, 4	5 (6.3)
Anemia	1, 2	16 (20.0)
	3, 4	4 (5.0)
Thrombocytopenia	1, 2	15 (18.8)
	3, 4	6 (7.5)
Nonhematologic complications		
Elevated ALT	× 3 times	9 (11.3)
	× 6 times	2 (2.5)
Paresthesia		7 (8.8)
Infection (pneumonitis, urinary tract infection)		5 (6.2)

Values are presented as number (%).
ALT = alanine aminotransferase.

lymphoma.[22] In our study, no significant difference was found in chemotherapy response rate according to the site of lymphoma involvement. However, all three patients with systemic relapse or disease progression initially had lymphoma in non-conjunctival lesions of the eyelids, lacrimal gland, and orbit.

Three types of chemotherapy regimens were reviewed retrospectively and significantly higher PFS was found in those patients who received R-CVP than the other two regimens. Rituximab is a chimeric mouse human monoclonal antibody to CD20 and CD20 antigens are expressed by all B cells. Rituximab has an effect on CD20-positive cells by activating complement-mediated lysis and antibody-dependent cell-mediated cytotoxicity,[23] in addition to activation of apoptosis and a direct antiproliferative effect.[24,25] In our study, 46 patients were treated with rituximab-containing chemotherapy and an increase in local control was observed compared to chemotherapy not involving rituximab.

Analysis of PFS according to chemotherapy regimen showed that the R-CVP group had the highest PFS while the CHOP group had the lowest PFS, and that this difference was statistically significant (p = 0.006). Although PFS was not significantly different between the CVP group and R-CVP group, a higher PFS was achieved with rituximab-containing treatment.

Based on our results and those of six other research groups (Table 6), 88.9% of patients with state IE and IV MALT lymphoma who received a rituximab-based chlorambucil regimen achieved a CR.[26] Interestingly, a CR was achieved in 67% of patients with stage IE MALT lymphoma who received a rituximab-only regimen.[13] These findings indicate that in addition to radiotherapy, a chemotherapy regimen containing rituximab is an effective treatment strategy for patients with localized or expanded MALT lymphoma.

Toxic effects associated with rituximab are minor, and include flu-like symptoms. Combination chemotherapy is associated with adverse events including hematologic complications (neutropenia, anemia, and thrombocytopenia) and non-hematologic complications (nausea, general weakness, hepatotoxicity, peripheral neuropathy, and systemic infections). Most hematologic complications can be addressed with appropriate management and patients generally recover well after chemotherapy. In this study, the most severe adverse event was rituximab-associated interstitial pneumonitis.

Table 6. Treatment outcome of first-line immunotherapy or chemotherapy in ocular adnexal mucosa-associated lymphoid tissue lymphoma

Study	Number of eyes	Stage	Regimen	Cycles	Response	FU period (median, months)	Survival (%)
Rigacci et al[26]	9 (MALT: 8; FL: 1)	IE: 8, IV: 1	Rituximab, chlorambucil	N/A	CR: 8 (88.9) PR: 1 (11.1)	13-41 (25)	
Song et al[9]	21	I-IIE	Cyclophosphamide, vincristin, prednisolone	6	CR: 16 (76.2) PR: 5 (23.5)	5-163 (52)	5-year PFS: 66
Tuncer et al[27]	11 (MALT: 10; FL: 1)	IE	Rituximab	6-8	CR: 4 (36) PR: 7 (64)	10-31 (31)	
Annibali et al[13]	6	IE	Rituximab	6	CR: 4 (67) PR: 2 (33)	8-34 (29)	
Esmaeli et al[28]	12 (MALT: 9; FL: 3)	IE: 11, IVE: 1	Rituximab, zevalin (Y-90 ibritumomab tiuxetan)	2	CR: 10 (83.3) PR: 2 (16.7)	6-44 (20)	
Ma et al[29]	20	I-IIE1	Total: 20 Chlorambucil: 5 Rituximab-based: 12 CHOP: 3	2-8	CR: 15 (75) CR: 4 (80) CR: 10 (83) CR: 1 (33.3)	-	5-year EFS: 94.4, 5-year OS: 100
Present study	80	I-IVE	Total: 80 R-CVP: 46 CVP: 22 CHOP: 12	6-8	CR: 67 (83.8) CR: 43 (93.5) CR: 16 (72.7) CR: 8 (66.7)	6-118 (42)	5 year PFS: 69 67 47

Values are presented as number (%).
FU = follow-up; MALT = mucosa-associated lymphoid tissue lymphoma; FL = follicular lymphoma; N/A = not applicable; CR = complete remission; PR = partial remission; PFS = progression-free survival; CHOP = cyclophosphamide, hydroxydaunorubicin, oncovine, prednisolone; EFS = event-free survival; OS = overall survival; R-CVP = rituximab, cyclophosphamide, vincristine, prednisolone; CVP = cyclophosphamide, vincristine, prednisolone.

The limitation of this study is that the chemotherapy regimen was selected by the physicians based on their clinical judgement and the patient's preference. Therefore, the selection bias could have affected the study results.

In conclusion, we demonstrated that first-line combination chemotherapy is an effective treatment option for both low-grade and high-grade OAML, and adverse events are generally well tolerated. Furthermore, rituximab is an effective adjunct to chemotherapy for OAML.

REFERENCES

1) Stefanovic A, Lossos IS. Extranodal marginal zone lymphoma of the ocular adnexa. Blood 2009;114:501-10.
2) Freeman C, Berg JW, Cutler SJ. Occurrence and prognosis of extranodal lymphomas. Cancer 1972;29:252-60.
3) Cho EY, Han JJ, Ree HJ, et al. Clinicopathologic analysis of ocular adnexal lymphomas: extranodal marginal zone b-cell lymphoma constitutes the vast majority of ocular lymphomas among Koreans and affects younger patients. Am J Hematol 2003;73:87-96.
4) Ferry JA, Fung CY, Zukerberg L, et al. Lymphoma of the ocular adnexa: a study of 353 cases. Am J Surg Pathol 2007;31:170-84.
5) 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.
6) Lee SE, Paik JS, Cho WK, et al. Feasibility of the TNM-based staging system of ocular adnexal extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma). Am J Hematol 2011;86:262-6.
7) Nam H, Ahn YC, Kim YD, et al. Prognostic significance of anatomic subsites: results of radiation therapy for 66 patients with localized orbital marginal zone B cell lymphoma. Radiother Oncol 2009;90:236-41.
8) Decaudin D, de Cremoux P, Vincent-Salomon A, et al. Ocular adnexal lymphoma: a review of clinicopathologic features and treatment options. Blood 2006;108:1451-60.
9) Song EK, Kim SY, Kim TM, et al. Efficacy of chemotherapy as a first-line treatment in ocular adnexal extranodal marginal zone B-cell lymphoma. Ann Oncol 2008;19:242-6.
10) Kim SY, Yang SW, Lee WS, et al. Frontline treatment with chemoimmunotherapy for limited-stage ocular adnexal MALT lymphoma with adverse factors: a phase II study. Oncotarget 2017;8:68583-90.
11) Paik JS, Cho WK, Lee SE, et al. Ophthalmologic outcomes after chemotherapy and/or radiotherapy in non-conjunctival ocular adnexal MALT lymphoma. Ann Hematol 2012;91:1393-401.
12) Sullivan TJ, Grimes D, Bunce I. Monoclonal antibody treatment of orbital lymphoma. Ophthalmic Plast Reconstr Surg 2004;20:103-6.
13) Annibali O, Chiodi F, Sarlo C, et al. Rituximab as single agent in primary MALT lymphoma of the ocular adnexa. Biomed Res Int 2015;2015:895105.
14) Klapan E, Meier P. Nonparametric estimation from incomplete observation. J Am Stat Assoc 1958;53:457-81.
15) Parsons JT, Bova FJ, Fitzgerald CR, et al. Severe dry-eye syndrome following external beam irradiation. Int J Radiat Oncol Biol Phys 1994;30:775-80.
16) Merriam GR Jr, Focht EF. A clinical study of radiation cataracts and the relationship to dose. Am J Roentgenol Radium Ther Nucl Med 1957;77:759-85.
17) Parsons JT, Fitzgerald CR, Hood CI, et al. The effects of irradiation on the eye and optic nerve. Int J Radiat Oncol Biol Phys 1983;9:609-22.
18) Letschert JG, González D, Oskam J, et al. Results of radiotherapy in patients with stage I orbital non-Hodgkin's lymphoma. Radiother Oncol 1991;22:36-44.
19) Bessell EM, Henk JM, Whitelocke RA, et al. Ocular morbidity after radiotherapy of orbital and conjunctival lymphoma. Eye (Lond) 1987;1(Pt 1):90-6.
20) White WL, Ferry JA, Harris NL, Grove AS Jr. Ocular adnexal lymphoma. A clinicopathologic study with identification of lymphomas of mucosa-associated lymphoid tissue type. Ophthalmology 1995;102:1994-2006.
21) Nam SW, Woo KI, Kim YD. Characteristics of primary extranodal marginal zone B-cell lymphoma in Korea: conjunctiva versus other ocular adnexa. Br J Ophthalmol 2018;102:502-8.
22) Jenkins C, Rose GE, Bunce C, et al. Clinical features associated with survival of patients with lymphoma of the ocular adnexa. Eye (Lond) 2003;17:809-20.
23) Reff ME, Carner K, Chambers KS, et al. Depletion of B cells in vivo by a chimeric mouse human monoclonal antibody to CD20. Blood 1994;83:435-45.
24) Pedersen I, Buhl A, Klausen P, et al. The chimeric anti-CD20 antibody rituximab induces apoptosis in B-cell chronic lymphocytic leukemia cells through a p38 mitogen activated protein-kinase-dependent mechanism. Blood 2002;99:1314-9.
25) Maloney D. The anti-tumor effect of monoclonal anti-CD20 antibody (mAb) therapy includes direct anti-proliferative activity and induction of apoptosis in CD20 positive non-Hodgkin's lymphoma (NHL) cell lines. Blood 1996;88:637a.
26) Rigacci L, Nassi L, Puccioni M, et al. Rituximab and chlorambucil as first-line treatment for low-grade ocular adnexal lymphomas. Ann Hematol 2007;86:565-8.
27) Tuncer S, Tanyildiz B, Basaran M, et al. Systemic rituximab immunotherapy in the management of primary ocular adnexal lymphoma: single institution experience. Curr Eye Res 2015;40:780-5.
28) Esmaeli B, McLaughlin P, Pro B, et al. Prospective trial of targeted radioimmunotherapy with Y-90 ibritumomab tiuxetan (Zevalin) for front-line treatment of early-stage extranodal indolent ocular adnexal lymphoma. Ann Oncol 2009;20:709-14.
29) Ma WL, Yao M, Liao SL, et al. Chemotherapy alone is an alternative treatment in treating localized primary ocular adnexal lymphomas. Oncotarget 2017;8:81329-42.