LITERATURE REVIEW

CHEMOTHERAPY COMPARED WITH RADIOTHERAPY AS THE FIRST-LINE THERAPY OF EXTRANODAL MARGINAL ZONE LYMPHOMA: A REVIEW

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ABSTRACT

Objective: *To compare the efficacy and safety between chemotherapy and radiotherapy as the main therapy of Extranodal Marginal Zone Lymphoma (EMZL).*

Method: *Literature searching was conducted using PubMed, ScienceDirect, Google Scholar, ProQuest, and SpringerLink. All studies that met the inclusion and exclusion criteria were categorized based on the level of evidence. The data of demographic of the patients, staging of disease, type of treatments, and outcomes of this review including the number of local control rate, disease-free survival rate, overall survival rate, dosage, adverse drug reaction, complication and recurrence and/or relapses were also reported.*

Result: *From ten article, both radiotherapy and chemotherapy as the first-line treatment have high complete remission rate. Local control (complete remission) of chemotherapy group ranged from 56,25%-93,9%, while in radiotherapy group ranged from 70%-100%. Overal survival rate ranged from 92%-100% for chemotherapy group and 90,4%-100% for radiotherapy group. The most complication of the radiotherapy group were cataract formation, while the chemotherapy group showed systemic complications (hematologic or non-hematologic). The most relapse cases were shown in radiotherapy group.*

Conclusion: *Radiotherapy and chemotherapy showed high local control rates and survival outcomes especially in the early stages of extranodal marginal zone lymphoma (EMZL). Radiotherapy had a relatively higher incidence of ophthalmic complications that could interfere with patient's quality of life. Therefore chemotherapy could be considered especially in younger patients.*

Keywords: *Extranodal Marginal Zone Lympoma, Chemotherapy, Radioterapy,*

INTRODUCTION

Ocular adnexal lymphoma (OAL) is the most frequent malignancies in the ocular region in adults. It accounts for 2% of all lymphomas and 50% of eye malignancies.[1] The most common subtype of primary OAL are extranodal marginal zone lymphoma/ EMZL (66%), followed by follicular lymphoma (16%) and diffuse large B cell lymphoma (10%).[2] In RSCM Kirana, from 2016-2019, OAL found in 86 patients, with 82% of OAL are EMZL types.

EMZL is a low-grade variant of B-cell non-Hodgkins lymphoma (NHL) that originates from extranodal tissue of the gastrointestinal tract, thyroid, lung, salivary gland, lacrimal

gland, orbit, and conjunctiva. It generally develops after the fourth decade of life (peak age about 65 years) and have a female prevalence (male/ female = 1/1.5).[3] EMZL is rarely symptomatic in the early phase of the disease. Majority of cases (85%-90%) present with localized disease (stage I).[4] Therefore, the prognosis is generally favorable, with high percentages of local control rates, prolonged disease-free intervals and low lymphoma-related mortality rates.[5]

Various treatment modalities are available for the management of EMZL, including surgical resection, radiotherapy, single-agent or combination chemotherapy, and immunotherapy with monoclonal antibodies.[6] Radiation is the treatment of choice for the majority of patients with EMZL. However, radiotherapy is notorious with ophthalmic complications that affects patients' quality of life, especially considering the patient's age.[4] In the other hand, chemotherapy has tolerable local toxicity profile, but the practical recommendations are still limited.[5] The aim of this review is to evaluate the efficacy and safety of chemotherapy as the main therapy of EMZL, in comparison with radiotherapy.

METHODS

Literature searching was conducted using five online databases (PubMed, ScienceDirect, Google Scholar, ProQuest, and SpringerLink). Keywords "Ocular Adnexal Lymphoma", "radiotherapy", and "chemotherapy" were used. Inclusion criteria were all interventional or observational studies that reported the efficacy of treatment and local control rate, with or without disease-free survival rates and overall survival rates of radiotherapy or chemotherapy as treatment for EMZL. Studies not written in English, animal subjects, single case reports, systemic lymphomas, disease treated concomitantly with multiple medications or with treatments other than sole radiotherapy or chemotherapy, and inaccessible journal were excluded. The reported data were patients demographic, staging of disease, type of treatments, and outcomes including the number of local control rate, disease-free survival rate, overall survival rate, dosage,adverse drug reaction, complication and recurrence and/or relapses that represent efficacy and safety of therapy.

RESULTS

After selection process and detailed evaluation, ten articles were eligible to be reviewed in this study All of them were retrospective study and have evidence level III. Three studies compared radiotherapy and chemotherapy as the first-line therapy. Three studies used

chemotherapy only as the main therapy, while the other four used radiotherapy as the main therapy.

Most of the subjects in the studies were in stage I, regardless of their initial presenting anatomic location (Table 1). The age of subjects ranged from 18-100 years old with no gender predominance. The minimum time frame in the studies was 5 years, given the long follow-up needed to really see the overall survival rate. However, one study from Paik et al had the shortest follow-up time, which is 20 months.[7]

The chemotherapy used in the studies are combination of cyclophosphamide, doxorubicin, and prednisone (CHOP), combination of cyclophosphamide, vincristine, and prednisone (CVP), both with or without addition of rituximab (R-CHOP/ R-CVP). Two studies by Ma et al and Simon et al also used low dose of cyclophosphamide or chlorambucil as the primary treatment for the stage I disease include in their studies.[8,9] In adition, studies that used radiotherapy as the first-line therapy had similar dosage and regimen. The baseline characteristic between studies was summarized in Table 1.

Table 2 showed clinical outcomes and effectiveness of treatment modalities including local control, disease-free survival, and overall survival. Both radiotherapy and chemotherapy as the first-line treatment had high complete remission rate, except one study from Paik et al. Seven out of sixteen patients from the chemotherapy group still retained lesions after complete therapy.[7] Those seven patients subsequently received adjuvant radiotherapy and finally achieved complete response. Another interested study was from Simon et al They used low-dose oral chlorambucil as the primary treatment instead of CVP or CHOP to treat stage IE patients. The results were quite satisfactory with no complications noted during the follow-up.[9] Radiotherapy group also showed high local control rate, with complete remission rate ranging from 70%-100%.

Survival outcomes in this review used several parameter. Most of the studies included the overall survival rate in 3-13 years, depending on the follow-up period time. Studies that didn't include overall survival rate as one of the outcomes had short period of follow-up, such as Paik et al and Simon et al, that roughly had median follow-up time of 20.5 and 26 months, respectively.[7,9]

The most complications of the radiotherapy group were ophthalmic complications (localized) such as cataract formation (Table 2). Meanwhile, the chemotherapy group showed hematologic or non-hematologic complications (systemic). Systemic complications from the chemotherapy group were well manage with conservative treatments and none lasted more than three months.

Table1. Baseline Characteristics of Reviewed Studies

No	Author, Year, Level of Evidence, Time Frame	Subjects, Gender (M/F)	Lymphoma Subtypes (n)	Location of Tumor(n)	Staging of Disease	Median age (range)	Median follow-up (range)	Treatment (n)	Dose and Regimen of Therapy
					Comparative study				
1	Jeon et al[15] 2018 III January 2004-April2015	208 83/125	MALT203 (100%)	Conjunctiva (119) Orbit (59) Lacrimal ducts and glands (16) Eyelid (21) Bilateral:48	Ann Arbor: I/IE177 II9 III 2 IV 20	46 (18-85)	70 months (3.2-182)	RT(117) CT(86) CVP:19 R-CVP:39 CHOP:14 R-CHOP:14	RT:median 26 Gy (range24-32Gy) 1x1.8-2 Gy 5x/week CT: 1) CVP/R-CVP: cyclophosphamide 750mg/m^2 and vincristine (1.4mg/m$^{2)}$ on day 1 and prednisolone 60mg/m^2 on days 1 to 5 every 21 days with/ without rituximab (375mg/m$^{2)}$ on day 1. 2) CHOP/R-CHOP: cyclophosphamide (750mg/m2), doxorubicin (50 mg/m2), vincristine 1.4 mg/m2 on day 1, and prednisone (100 mg/m2) orally on days 1 to 5 every 21 days with/without rituximab (375mg/m2) on day 1.
2	Ma et al[8] 2016 III 1990-2015	107 58/49	MALT93 (87%) DLBCL MALT5(5%) DLBCL9 (8%)	Orbital(49) Conjunctiva(42) Lacrimal gland (16)	I-IIE 191 IIE2-IV 16	57 (22-102) 65.5 (29-84)	54.7 months	RT(34) CT(26) Low dosealkylating chemotherapy: 8 CHOP:5 R-CHOP:13	RT: median dose: 40Gy (range 30-50 Gy in daily fractions of 1.8-2.0 Gy CT: 2-8 cycles 1) Daily low-dose cyclophosphamide or chlorambucil with/ without rituximab (375mg/m2 of rituximab administered every 3–4 week) 2) CHOP-based regimens (the dose of doxorubicin was lowered or omitted on the basis of the attending physicians' judgment) 3) R-CHOP based chemotherapy (CHOP plus 375mg/m2 of rituximab administered every 3–4 week)
3	Paik et al[7] 2012 III March 2004-May2010	24 12/12	MALT 24 (100%)	Orbit(5) Lacrimal gland(7) Eyelid(10) Retrobulbar (3) Lacrimal sac (1)	IE19 IIE1 IIIE1 IVE3	52.5 (29-91)	20.5 months(13-72)	RT(8) CT (16)CHOP/R-CHOP(4) CVP(5)	RT: range30–40 Gy (mean 34.58±5.87 Gy), in daily fractions of 1.8–2.0 Gy. CT: 6-8 cycles, every 3 weeks 1) CVP/R-CVP: cyclophosphamide (750mg/m^2, IV>30 min] on day 1, vincristine [1.4 mg/m^2 (max 2 mg) IV, bolus) on day 1, and oral prednisone (60 mg/m^2) on days 1–5 with/without Rituximab (375mg/m^2, IV) 2) CHOP/R-CHOP: cyclophosphamide (750 mg/m^2 IV >30 min) on day 1, adriamycin (50mg/m^2 IV) on day 1, vincristine (1.4 mg/m^2 (max 2 mg IV bolus) on day 1, and oral prednisone (60 mg) on days1–5 with/ without Rituximab (375mg/m^2, IV)

					Maintherapy: Chemotherapy (CT)				
4	Kim et al[13] 2017 III July 2011-August2014	33 21/12	MALT33 (100%)	Conjuntiva (12) Orbit(13) Eyelid(5) Lacrimal gland(3)	IE33	49 (19-74)	50.6 months (7.4-62.8 months)	CT(33)	Every 21 days with six cycles of rituximab (375 mg/m2), cyclophosphamide (750mg/m2), and vincristine (1.4mg/m2) on day 1 and prednisolone (60 mg/m2) on days 1–5, which was followed by 2 cycles of rituximab (375mg/m2) every 21days
5	Simon et al[9] 2006 III January 1995-December 2004	33 14/19	MALT33 (100%)	Lacrimal gland (8); Conjunctiva (7); Eyelid 6; Orbit 6; Extraocular muscle 4; Other 2	IE33	72 (36-100)	26months (8-72)	CT(33)	6 mg of oral chlorambucil 3x/ daily, days 1 to 14, repeated on day 28 for 4 cycles (average) depending on response. Frailer older patients received 4 mg, 3x/ daily.
6	Song et al[11] 2007 III 1990-2004	21 15/6	MALT21 (100%)	Orbit 8 Conjunctiva 6 Eyelid 5 Lacrimal gland 2	IE19 IIE2	59 (29-79)	58months (5-163)	CT(21)	CT: 6 cycles, every 3 weeks CVP: cyclophosphamide (1000mg/m2 IV >30 min) on day 1, vincristine [1.5 mg/m^2 (maximum 2 mg) IV bolus) on day 1, and oral prednisolone (40mg/m^2) on day 1–10.
					Maintherapy: Radiotherapy (RT)				
7	Goda et al[10] 2011 III January 1989-December 2007	89 37/52	MALT89 (100%)	Conjunctiva 59 Lacrimal apparatus 20 Softtissue 10	IE:89	56.4 (23.6-92.4)	5.9years (1-16years)	RT(89)	RT: 25-30 Gy in 10 fractions over 2 weeks
8	Lim et al[14] 2011 III October 1997-January 2009	95 57/38	MALT95 (100%)	Conjunctiva 62 Orbit 15 Eyelid 13 Lacrimal gland 5	IAE83 IAEE7 IIIAE3 IVA2	44 (21-80)	NA	RT(95)	RT: range 30.6-45z.0 Gy, 5days/ week with 180 Gy/ fraction
9	Niwa et al[12] 2020 III 2006-2016	81 42/39	MALT81 (100%)	Orbit 57 Conjunctiva 21 Lacrimal gland 3	IE Bilateral:9	66 (29-90)	74months (4-157 months)	RT(81)	RT: median 30 Gy (range30–36Gy) in 15–18 fractions
10	Shirota et al[21] 2016 III January 2008-December 2013	40 18/22	MALT40 (100%)	Conjunctiva 19 Retrobulbar 19 Lacrimal gland 2	IAE33 IIAE7	66.7 (26.2-89)	32months	RT(40)	RT: 30 Gy in 15 fractions

MALT: Mucosa-associated lymphoid tissue; DLBCL: Diffuse large B-cell ymphoma; RT: Radiotherapy; CT: Chemotherapy; CVP: Cyclophosphamide, Vincristine, Prednisolone; R-CVP: Rituximab+CVP; CHOP: Cyclosphosphamide, Doxorubicine, Vincristine, Prednisone; R-CHOP: Rituximab+CHOP; NA: Not available

Table 2. Outcome of Reviewed Studies

No	Authors, Year	Treatment (n)	Local Control			Disease-free survival	Overall survival	Complications
			CR	PR	NR			
Chemotherapy (CT)								
1	Jeon et al,2018[15]	CT(86)	81,4%	18,6%	NA	69,7%* (13 years)	92%* (13 years)	Hematologic: 111; Non hematologic: 86
2	Kim et al,2017[13]	CT(33)	93.9%	6.1%	0%	90.3±5.3% (4years)	100% (4years)	Anemia:6; Neutropenia:15 Paresthesia:11; Hepatotoxicity:9; Hyperglycemia:4
3	Maetal,2016[8]	CT(26)	87.5%	0%	NA	100% (3years)	100% (3years)	Neutropenia:7; Anemia:2; Increased liver enzymes:6
4	Paik et al,2012[7]	CT(16)	56.25%	0%	43.75 %	NA	NA	Grade 3 neutropenia: 2; Peripheral neuropathy: 3; ElevatedALT:1
5	Simon etal,2006[9]	CT(33)	79%	21%	0%	NA	NA	NA
6	Song et al,2007[11]	CT(21)	76%	24%	0%	90% (2years) 66.7% (5years)	NA	Mild to moderateneutropenia:13 Grade1anemia:1; ElevatedALT:1 ; Paresthesia:1
Radiotherapy (RT)								
1	Goda et al, 2011[10]	RT(89)	99%	1%	0%	76% (5 years) 64% (7years)	95% (5 years) 91% (7 years)	Cataract:22; Keratitis:3; Macular degeneration/ cystoidedema:2; Vitreous detachment:1
2	Jeon et al, 2018[15]	RT(117)	92%	NA	NA	69.7%* (13years)	92%* (13years)	Dryeyes:68; Cataract:38; Radiation retinopathy: 10; Corneal ulceration:17; Adnexal inflammation: 29; Nasolacrimal duct obstruction:3
3	Lim et al, 2011[14]	RT(95)	95%	5%	0%	97% (3years)	100% (3years)	Acute radiation conjunctivitis: 17; Periorbital erythema:13; Phimotic punctum:1; Filamentary keratitis + dry eye syndrome: 1
4	Ma et al, 2016[8]	RT(34)	92%	NA	NA	89.7% (5years)	90.4% (5years)	Cataract:5; Keratitis: 2; Retinopathy:1
5	Niwa et al, 2020[12]	RT(81)	70%	30%	0%	94.4% (3years)	98.8% (5years)	Dryeyes:3; Keratitis:4; Cataract:20
6	Paik et al, 2012[7]	RT(8)	100%	0%	0%	NA	NA	Cataract:8; Retinopathy:2
7	Shirota et al, 2016[21]	RT(40)	100%	0%	0%	100% (3years) 100% (5years)	100% (3years) 100% (5years)	NA?

CR: complete remission; PR, partial remission; NR: No Response; RT, radiotherapy; CT: chemotherapy; NA: not available. *disease-free and overall survival rate from Jeon et al,5 are for both groups.

Table 3 showed recurrence and relapses event. The most relapses event were reported by Goda et al (22 patients). Fifteen subjects experienced distant relapse to breast, retroperitoneal nodes, and prostates in median 3.3 years.[10] From chemotherapy group, Song et al and Simon et al, there was local recurrence that achieved complete response after secondary

radiotherapy.[9,11] Niwa et al reported relapses on the distant sites (parotid gland, cervix, lung, intraperitoneal cavity, and femur) in 42 months, treated with additional chemotherapy.[12]

Table 3. Recurrences and Relapses

No	Author, Years	Recurrences	Relapses
	Chemotherapy (CT)		
1	Jeon et al,2018[15]	NA	4
2	Ma et al,2016[8]	NA	2
3	Simon et al,2006[9]	1	3
4	Song et al,2007[11]	7 (2in CR, 5 in PR)	NA
	Radiotherapy (RT)		
1	Goda et al,2011[10]	NA	22
2	Jeon et al,2018[15]	NA	10
3	Lim et al,2011[14]	2	NA
4	Niwa et al,2020[12]	NA	5
5	Shirota et al,2016[21]	2	NA

NA: not available; CR: complete remission; PR: partial remission.

DISCUSSION

Extranodal marginal zone lymphoma generally develops after the fourth decade of life (median age 65 years) with female predominance, especially in western population.[3]However, studies from Asian population revealed that the median age was younger (45 years), with male predominance. This is aligned with our reviewed studies from Asian population, such as Kim et al[13], Lim et al[14], and Song et al[11], that had younger median age and male predominance.Meanwhile, study from Canada (Goda et al[10]) and Australia (Simon et al[9]) had older median age. The younger patients in the studies were given primarily chemotherapy as the first-line therapy.

The outcome of EMZL is generally favorable due to its slow progressive nature. However, there remains no consensus regarding the initial management of EMZL.[15] The International Lymphoma Radiation Oncology group recommends doses of 24-25 Gy in 1.5 to 2 Gy fractions with high local control and minimal toxicity.[16] This is in line with study from Goda et al that reported the local control rates equivalent to higher dose series with no statistical differences in ophthalmic complications.[10] Nevertheless, study by Jeon et al showed that the dose less than 26 Gy had less local control. There were three local ipsilateral failures and fivecontralateral relapses.[15]

Despite high local control rates in radiotherapy group, it induced both immediate and late ocular toxicity, especially cataract in this review. Another common ophthalmic complications were dry eyes, keratitis, and radiation retinopathy.[15,16] Goda et al reported that the ophthalmic complications might be reduced without compromising primary orbital and adnexal non-hodgkin lymphoma (POAL) treatment efficacyby decreasing the dose of

radiotherapy to 24–25 Gy and using a lens shield.[10] Conversely, study by Cho et al reported that even small doses of radiation exposuretended to increase the risk of cataracts.[17] Lens shielding methods reduced cataract formation by 10%, but not completely.[7] Study by Goda et al achieved high local control rates, but 22 of 89 subjects experienced distant relapses.[10] It indicates that low-dose radiotherapy can provide effective local control, with few late ophthalmological complications, but systemic relapse should be considered.

In chemotherapy group, different regimens were used including low-dose oral alkylating chemotherapy. Ma et al reported that the complete response rate of low dose oral alkylating chemotherapy was higher than the other regimens of chemotherapy (CHOP and R-CHOP regimens) for patients who cannot tolerate the effect of radiotherapy. That chemotherapy regimen resulted in manageable hematological and non-hematological complications without any radiotherapy related ophthalmic complications.[8] In adition, Simon et al that used oral chlorambucil also reported local control rate of 100% with 21% of the patients had partial response.[9] Although seven out of sixteen patients (43.75%) in Paik et al study retained lesions even after complete chemotherapy, it is important to note that they excluded the conjunctival lesions that are generally easier to treat.[7] This review indicates that chemotherapy is effective even in locally advanced-stage of EMZL, without localized ophthalmic complications.

The average disease-free survival rate were 87.5% for chemotherapy group and 87.8% for radiotherapy group, while the average overall survival rate between the two groups are 97.3% and 96.6%. Jeon at al said in their study that survival outcome of radiotherapy was slightly better than chemotherapy, but it was not superior statistically. The adverse events related to radiotherapy were mostly irreversible. Therefore, Jeon et al recommended that the younger patients could be treated with chemotherapy instead of radiotherapy because the ocular complications caused by radiotherapy could interfere quality of life. The older patients who might not be suitable for systemic chemotherapy could be given radiotherapy instead.[15]

When assessing quality of life after treatment in EMZL patients, it is important to consider the ophthalmologic outcomes, especially since EMZL itself does not show a high mortality rate. In Paik et al, the symptoms that persisted and affected ophthalmic quality of life was measured with ophthalmologic outcome criteria. Patients who received chemotherapy alone had a better score for ophthalmologic outcomes than those who received radiotherapy.[7]

Nearly one-third incidence of non-stage IE EMZL found to have systemic involvement on careful staging.[18] Desai et al reported 4% of EMZL transformed into

disseminated lymphoma in median follow-up of 63.5 months.[19]This is in line with this review that showed significant decreased of disease-free survival start from 5 years.

Recurrences were mostly occured locally in chemotherapy group. Addition of rituximab should reduce the recurrence rate, but longer follow-up would be needed.[20] Meanwhile, there were distant relapse to breast, retroperitoneal nodes, prostates, and so on in radiotherapy group.[10,12]Chemotherapy was given to salvage the tumor when distant relapse (systemic involvement) were happened. It is also noted that the location of primary tumors in lacrimal gland and soft tissues had higher rate of distant relapse rate than in conjunctiva.[10]

CONCLUSION

Radiotherapy and chemotherapy showed high local control rates and survival outcomes especially in the early stages of extranodal marginal zone lymphoma (EMZL). Since EMZL doesn't have high mortality rate, it is important to consider the treatment's complications and the possibilities of systemic involvement. Radiotherapy had a relatively high incidence of ophthalmic complications that could interfere with patient's quality of life, while chemotherapy did not. Therefore, chemotherapy could be considered especially in younger patients. However, as this review included only retrospective studies, further studies with better level of evidence and larger number of subjects are still needed.

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