

The Role of Radiotherapy in the Treatment of Early Stage Ocular Marginal Zone Lymphoma

Aviles A^{1*} and Cleto S²

¹Avenida Cuauhtemoc 330, Colonia Doctores, Ciudad de Mexico, 06760, Mexico

²Oncology Research Unit, Department of Hematology, Oncology Hospital, National Medical Center, IMSS, Mexico City, Mexico

*Corresponding author:

Agustin Aviles,
Avenida Cuauhtemoc 330, Colonia Doctores,
Ciudad de Mexico, 06760, Mexico,
E-mail: mirandaolder73@gmail.com

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1. Abstract

To evaluate the benefit of radiotherapy, compared with other treatment in ocular marginal zone lymphoma, retrospectively we analyzed our experience, with the end-points: efficacy, measured for complete response, Progression-Free Survival (PFS) and Overall Survival (OS).

Patients pathological confirmed as marginal zone, limited to ocular site, in early stage (I), without previous treatments, > 18 years, were included. From August 1988 to December 2015, 301 patients were treated with Radiotherapy (RT), RT + chemotherapy, and RT + rituximab. The median follow-up was 20.3 (range 6 to 34) years. Complete response, PFS and OS did not show any statistical difference. Acute and late toxicities were well tolerated, the most common were formation of cataracts, associated with more dose of RT, and did not employed, who did not protect with lens shielding. Late toxicities as acute leukemia and second neoplasms did not were observed.

The use of RT, especially with the introduction of low doses (2x 2 G), confirmed that this treatment will be considered the gold standard in these very special setting of patients. The addition of chemotherapy and rituximab did no showed any benefits.

2. Introduction

Extranodal Marginal Zone Lymphoma (EMZL) as defined as a unique lymphoid malignancy with marked differences from another lymphoma, with special pathological, immunohistochemical and clinical. In most cases, the initial presentation is in a unique organ, especially in stomach orbit and salivary glands. Primary ocular-(PO-MZL) have an indolent course and an excellent local

treatment, but, relapse is frequent, with an Overall Survival (OS) > 90% at 5-years. Until now, Radiotherapy (RT) is considered the treatment of choice, with excellent response and OS > 10 years. However, no controlled clinical trial has assessed to define the best treatment, probably because is a rare presentation. In the other hand, most of the studies mixed another subtypes of lymphomas, with a short follow-up, different stages and RT doses and techniques [1-3].

Recently the introduction of rituximab, an monoclonal antibody has been employed, but, follow-up is very short to define the benefit. Thus, we present a large and with longer follow-up in a single cancer center on PO-MZL, in we specifically the response rate, relapse, analysis of prognostic factors and presence of late adverse events.

3. Patients

Between August 1988 to December 2015, patients with confirmed pathological diagnosis of PO-MZL, stage I, untreated, and with a follow-up > 5 years, were retrospectively analyzed. The end-point is to analyze the duration of response, overall survival (OS), and early and late presence of adverse events.

Criteria entry: confirmed diagnosis, including immunohistochemical: CD20+, CD5-, CD10 -, cyclin 1 -, stage I, lactic dehydrogenase, beta 2 microglobulin, hepatitis A, and immunodeficiency virus tests. Pretreatment staging workup including clinical examination, complete blood counts, serum chemistry, computed tomography of bilateral orbits, neck, thorax, abdomen and pelvis, bone marrow biopsy, gastric endoscopy. The external ophthalmology assessed the best-correct visual activity, intraocular pressure, slit lamp

examination and dilated fundus exam.

Patients with advanced stages: III and IV, or central nervous system infiltration, were excluded

4. Treatments

4.1 Radiotherapy

Treatment of ocular lymphoma with RT is a challenging because lens, lacrimal gland and retina which are located near or within the target volume. Thus, we employed different techniques and doses, according with the time of treatment. Three-dimensional planning was done in 289 cases: electron beam therapy with a contact lens block were employed in 204 cases, doses were used, according with the development of the radiation doses and field: 64 patients received a median dose of 41 to 50 Gy (median 43 Gy), 146 (48.5 %) received a median dose of 34 Gy (range 21 to 40 Gy), and 55 (18.7%) were treated with ultra-low doses. Lens shielding were employed in 130 cases (43.1%). Target volume should include the entire orbit involvement. For superficial small lesions confined to the conjunctiva or eyelid, target volume should include the tumor plus an adequate margin.

4.2. Radiotherapy + Chemotherapy

Three or four weeks after radiotherapy, the patient received 6 cycles of CVP (cyclophosphamide, vincristine and prednisone), administered every 14 days.

4.3. Radiotherapy + Rituximab

Three weeks after RT, the patients received every 3 weeks, Rituximab ,375 mg/m², for six doses.

No maintenance or consolidation were employed. If relapse, local

or systemic, the patients were treated

according to the anatomic site, age, and comorbidities.

4.4. Statistical Analysis

We employed the Fisher's exact pr X² to compare groups for categorical variables and the Wilcoxon rand sum test to compare the number of responses. OS was calculating of the initial diagnosis until death from any causes or last follow-up (December 2015). Progression-free survival was calculated from the start of treatment until relapse or disease progression, death from any cause. Univariate and multivariate analysis were performed according to the Cox'x model.

5. Results

Complete response, PFS and OS, did not show any statistical significance (Table 1): Local relapse was observed in 12 cases treated with RT (12 (6.2) %, 2 treated with RT and CVP (: and 5 (91%) in patients treated with RT rituximab. Actuarial curves at 10-year, showed that PFS was 92% (95 % Confidence Interval (CI) 86.95 %-96 5% 0), 96 % (95%CI: 89 5 % -99.2%) and 90.8% (95%CI: 84-93 %), respectively.

All patients with local relapse were treated with RT, and a second response was observed in 20 (95.2%). Two cases had a second response at a median of 8.9 (range 6.9- 13.6) years. Actuarial curves at 10-year show that OS were 97 % (95%Confidence Interval (CI): 92%-100%); 89 % (95%CI: 83 % to 96%) and 96% (88% - 100%), respectively.

Actually, 98 (49.9%) of patients are alive at > 20 years, thus we believe that could have considered cured; and 154 (77.7%) remain in first response at > 10 years (Table 2).

Table 1: Clinical and laboratory characteristics

	RT	RT+CVP	RT+ Rituximab	p
	No (%)			
Number	195	48	55	
Age (years) median	58.8	63	59.4	0.234
Range	46-77	43-70	48.0-76	0.545
Sex: Male	93(47.6)	25(47.2)	26(42.2)	0.38
Female	102(52.1)	23(47.2)	29(57.7)	0.456
Performance status				
0	182 3(93.3)	46 (95.1)	50 (90.9)	0.487
1	13 (6.6)	2 (1.4)	5 (9.0)	0,884
Radiotherapy: Doses Gy)				
25 - 40	98 (50.2)	48 (100)		
41 - 50	38 (19.1)			
2 x 2G			55(100)	NA
Lens shielding	101 (56.7)	29 (60.4)		

Table 2: Response and outcome

	RT	RT = CVP	RT + rituximab	p
	No (%)			
Complete response	192 (98.4)	47(97.9)	51 (92.7)	0.91
Relapse				
Local	12 (6.25)	4 (8.5)	5(9.0)	0.13
Systemic	3 (4.5)	2 (4.2)	5 (9.0)	0.225
PFS	92 % (95%CI: 86%-95%)	96.9 % (89%-99 %)	90.8% (84%-93%)	0.61
OS	97 (92%-100%)	89%(83. % -96%)	96.8(88%- 100%)	0.763

PFS: actuarial curves at 10 years; OS; overall survival at 10 years.

6. Toxicities

Acute conjunctivitis was the most common side effect, was observed in 34 cases (17.3%), and were observed when not lens shielding were employed; topical treatment was used with complete response. The most common late toxicity was cataract formation, in 54 cases (27.2%), in all cases lens shielding were not employed. Until now, no second neoplasms or acute leukemia has been observed.

7. Discussion

We show the results of a retrospective analysis of patients with PO-EMZL, that were treated with RT, RT + CVP chemotherapy and RT + Rituximab, that compare response type and outcome, and define the best treatment in this setting of patients. The second-end point was to analyze the presence of late toxicities, with a longer follow-up, with a median 20.3 (range 6 to 34) years. Our results show that CR, PFS and OS, were similar in the arms of the study, taking in consideration that acute and late toxicities were similar in all cases, we considered that RT alone will be considered the treatment of choice in this very special setting of patients. The addition of chemotherapy or rituximab did not offer any benefit. In the other hand, we analyze the impact of different doses of RT, because during the time of the development of the study it was changed. CR was achieved in 146 out of 199 (73.3 %) in patients whose received between 20 to 40 Gy (median 3.2 Gy) 47 out of 48 (97.9%) in patients treated with 41 to 50 Gy (median 4.2 Gy), and 55 out of 55 (100 %) in patients treated with low dose Rt (2 x 2 Gy). However, OS did not show any statistical differences (Table 3).

Multiple studies have been employed different doses, techniques, and in most cases with a short follow-up, and taking in consideration that the biology of this special subtype of lymphomas, need years to define the impact of treatments in survival, and analyze the presence of late adverse events [4-13].

Recently, the use of RT in extranodal lymphomas has been defined and doses, fields and techniques, and the use of low doses is recommended in extranodal marginal zone in early stages [14]. employed chemotherapy in these setting of patients, but the number of patients were low and short follow-up [11]. Annibaldi, employed rituximab as initial treatment, although the response was well, the relapse was frequent, and the follow-up was short [13]. In the hand, use of RT has been associated with late toxicities, specially cataracts that need additional treatments and affect the quality of life [14, 15]. Some years ago, employed a very low doses of RT (2x 2 Gy), administered in a short time, the response, and outcome were excellent, and no acute or late toxicities were observed [16]. Subsequent studies confirmed the efficacy and low number of adverse events, with the 2 x 2 Gy technique [17-22]. Moreover, these treatments could be administered a repeated course, retain the efficacy and low number of complications.

Recently, reported that at large time, second neoplasms could be appeared in this setting of patient, our patient's studies did not report a second neoplasms in patients treated with low doses.

Table 3: Radiotherapy, Toxicities

Doses (Gy)	25-40	41-50	2x2
Acute			
Conjunctivitis	2	6	0
Keratitis	0	5	0
Late:			
Conjunctivitis	0	9	0
Cataracts	2	9	0

8. Conclusion

Based in our experience, we considered that RT will be considered the gold standard in patients with marginal zone lymphoma in early stage, taking in consideration that the 2 x 2 Gy will be considered as initial treatment, in case of relapse low doses may be repeat. Although, second neoplasms are at rare adverse events, taking in consideration the median age of this patients, surveillance will be the rule.

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