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Is Necessary the Use of Aggressive Chemotherapy in Relapsed Extranodal Marginal Zone Lymphoma Patient

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Abstract

Background: Treatment in patients with relapse Extranodal Marginal Zone Lymphoma (EMZL), remain unsolved, because this group of lymphoma, have a longer evolution, relapses are common, and the use of chemotherapy will be considered that can be associated with excessive toxicities, and even if complete response are obtained the risk of subsequent relapses will be considered.

Aims: We performed an clinical trial, phase II, employed low doses of thalidomide, dexamethasone and rituximab, in first relapse in patients with MZL, previously treated with radiotherapy alone, to search if the regimen is well tolerated and response and outcome will be benefit.

Methods: Patients with pathological confirmation of relapse EMZL, age >18 years old, with no upper limit, no gender differences, performed status, <2, and without use of chemotherapy, were included. They received 6 cycles of 28 days, thalidomide 200 mg, standard dose, days 1 to 21, dexamethasone 40 mg, oral, days 1 and 2, rituximab 375 mg/m^2, day 1. Response evaluation was performed at 3, 6 and 9 months.

Results: Forty-two patients were included, response was improved between 3 and 9 months, final overall response rate were observed in 41 (97.6%) patients, and complete response in 40 (92.2%). Four patients relapse, actuarial curves at 5-years show progression-free survival was 89.4%: Actuarial curves at 5-years show that progression-free survival were 89.47 (95% Acute toxicities were minimal and well controlled, no late adverse events has been observed).

Conclusion: We show that the use of an low-toxic regimen in relapse MZL, response is very well and outcome were excellent, thus, we believed that the use of aggressive chemotherapy will not been considered as an adequate treatment in this special stings of patients.

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Introduction

Alderucci et al. [1] analyzed 237 patients that received Rituximab and Bendamustine, and maintenance with rituximab, 179 (25.5%) were at advance stage, ORR was 93.2% and CR: 81%; PFS at 5 years were 80.5% (95% CI: 73.6-86.0), and OS: 80.5% (95% CI: 73.6-86.1) [2]. Moreover, late adverse events has been reported [3,4]. Thus, it is appear that, the best treatment has not been developed. Troch et al. [5], began a study with higher doses of thalidomide, when they observed in the first eight patients that no response the close the study. However, response in patients with EMZL appears to be slowly, as showed in our study and the study of Salar et al. [6].

In our study, will be some bias will been considered: the study was conducted in a single center, the number of patients is small, all patients were in early stage (I and II), and only five had elevated levels of lactic dehydrogenase and beta 2 microglobulin, that has been considered as adverse prognostic factors, but our center is tertiary cancer center, we have a coverage of about 23,000,000 populations, even in others studies the number of patients appear to be low.

We considered that the use of elevated doses of chemotherapy agents will be dangerous to these patients, and taking in consideration that we will expected to observe any relapse, will be Extranodal Marginal Zone Lymphoma (EMZL), as defined an unique lymphoid malignancy with marked differences from another lymphomas, and that show pathological, molecular findings and clinical features. The incidence is low, and ideal treatment has not well defined [7]. Taking in consideration that limited presentation is the most common excellent results has been obtained with radiotherapy. Addition of chemotherapy or immunomodulation agents did not show any benefit [1,2,8].

Overall survival is prolonged, but, as low-grade lymphomas, relapses are the rule. At this point no treatment has no well defined, because the patients are generally >70 years age, comorbidities

Table 1: Clinical and laboratory characteristics.

	No (%)
Number	42 (100)
Sex	
Male	20 (42.5)
Female	22 (53.5)
Age (years) median	61.8
Range	43-78
Stage	
I	28 (66.8)
II	14 (32.8)
Performance status	
0, 1	28 (66.8)
2	14 (32.8)
Lactic dehydrogenase elevated	2 (4.8)
Beta 2 microglobulin elevated	3 (7.0)
Time to last treatment (years)	
<1	0
1-3	4 (9.7)
4-6	11 (25.8)
6-10	17 (38.0)
>10	5 (12.9)
Anatomical site:	
Stomach	22 (53.3)
Lung	7 (16.6)
Tonsils	6 (14.2)
Breast	6 (14.2)

are common and the risk of severe adverse events will be considered.

Rituximab lenalidomide, bendamustine, ibrutinib alone or combined has been employed with contradictory results, and they were associated to frequent and severe adverse events.

Thalidomide was the first immunodulatory agent that show effective in some hematological malignancies; when lenalidomide was introduce; thalidomide was eliminated, although only a clinical trial was performed. On the other hand, lenalidomide is expensive, and in countries with middle-income as our country, it is difficult to acquire.

Methods

Patients with pathological confirmation of relapse of EMZL, age >18 years old, without upper limit, no gender differences, performance status <2, previously treated with localized radiotherapy, were included.

Treatment: Thalidomide 200 mg, oral standard dose, days 1 to 21 of each cycle that were administered every 28 days: Dexamethasone 40 mg, oral, days 1 and 2, rituximab 375 mg/m^2, iv, day 1. Taking in consideration that the response is low in this setting of patients, we performed a complete restaging study an 3, 6 and 9 months.

The study was approved for the Ethical and Scientific Committee: HO-2012/7, and all patients signed inform consent to participate in the study. From June 2009 to December 2019.

Results

Forty-two patients were included. Table 1 show the clinical and laboratory characteristics. The times of the response after radiotherapy were 3.8 to 8.7 years (median 7.3). Overall response rate were observed in 41 (97.6%) cases, and complete response was observed in 40 (92.2%) patients. Four patients relapse, thus, actuarial curves at 5-years Progression Free Survival (PFS) was 89.47% (95% Confidence Interval (CI): 82.7-96.01). Three achieved a third response are in complete response; two patients die, one refractory to three salvage schedules, and one patients that were failure, refuse more treatment; thus, actuarial curves at 5-years were 97.61 (95% CI: 92.4-102.7). Adverse events were mild, granulocytopenia grade I or II in 4 patients (1.56%) and thrombocytopenia grade I in two patients (1.39%) for the 240 cycles. Until now, no late infections, acute leukemia or second neoplasms have been observed.

Discussion

In the present study, we show an excellent overall response rate complete response and outcome, with minimal toxicity and without late adverse events. Reports of Treatment of patients with EMZL at relapse are scarce: Ahmadi et al. [9] lead an study in relapsed indolent lymphomas, lenalidomide in combination with dexamethasone and rituximab report with a good response, but severe hematological events were observed, and dose will be decreased, moreover the study included only one patients with EMZL, and median follow-up was very short: 33.1 (range 1.4 to 44.6) months, Overall Response Rate (ORR) were 58%, progression free-survival was 15.7% (95% Confidence Interval (CI): 12.2% to 30.4%); and lenalidomide has been associated in multiple myeloma patients with the development of second neoplasms (45). Noy et al. [10] performed an study to evaluate the usefulness of Ibrutinib in 63 patients, with MZL, the median follow-up was 33.1 (range: 1.4-44.6) months; median PFS was 15.7 (95% CI: 12.1 to 30.3), but toxicity were severe, 71% of patients had grade III; 8% developed atrial fibrillation, and bleeding was observed in 68% patients, with 3 patients grade III and infections: 8%, moreover 17.6% of patients discontinued the treatment. Salar et al. [6] performed an study with Rituximab and Bendamustine in 57 patients, including early and advanced stages, ORR and CR were 100%, estimated OFS was 92.8% (95% CI: 81.9-97.2), 36 (60%) of patients developed adverse events, and 3 cases developed a second neoplasm, considered the quality of life and presence of comorbidities. We conclude that the treatment of patients with EMZL at relapse will be considered moreover the response and overall survival, thus, moderate doses of cytotoxic agents will be considered, as the present study.

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