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It is Nessesary Central Nervous Prophilaxis in Primary Testicular Lymphoma?

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1. Abstract

1.1. Background: Primary testicular lymphoma is a rare presentation of extranodal lymphomas,. Is considered of worse prognosis, because no specific treatment has been reported. Moreover 6 t 15% patients relapse at central nervous system (CNS), and more patients die before 2 years of relapse. Until now, the use of prophylaxis to prevent CNS did not proven to be benefit.

Thus we development control clinical trial, to assess if the use pf CNS prophylaxis is useful in the prevention of CNS relapse.

1.2. Patients and Methods: Patients with pathological diagnosis of diffuse large B-cell lymphoma, confined to testis and regional nodal involvement (stages I and II), age between 40 to 75 years, without previous treatment ,in complete response after 6 cycles of R-CHOP14 (rituximab, cyclophosphamide, vincristine ,doxorubicin and prednisone , were assigned 1:1, to received 6 g/m2 IV of methotrexate , every 28 das for 4 doses, or no received prophylaxis.

1.3. Results: From January 2014 to December 2019, 25 patients were recruit, 3 patients did not achieve response and were eliminate .Thus 22 patients were include, until now, 2 patients relapse as systemic disease, they receive stem cell transplant and are in complete response at 3.4 and 4.2 years. CNS relapse has not observed.

1.4. Conclusion: CNS prophylaxis in PTL appear to be not necessary in patients with PTL, treated with an intensive of immunochemotherapy.

2. Introduction

Primary testicular lymphoma (PTL) , is an rare entity of diffuse large B-cell lymphoma, account from approximately 1% of all malignant lymphomas and is the most common testicular lymphoma in older men .These lymphomas remain an subset of main interest , because have a different clinical and biological course. Taking in consideration the low incidence, controlled clinical trials has not been performed.

Although Complete Response (CR) is achieved in > 50% of cases, relapse is common , and is more frequent in extranodal sites, specially in central nervous system (CNS) , that is associate with a worse prognosis. At this time, multiple studies has been performed , but, the better therapy remain to be found; some bias has been observed that can influence the results : different stages; different chemotherapeutic regimens: radiotherapy, intrathecal methothexate (MTX) or cytosine arabinoside and MTX systemic at higher doses, an until now neithers of these therapeutic approaches has been demonstrated an clear benefit. Moreover, It has been with associated with clinical, biological and genetics factors [1-6].

CNS relapse is also and frequent (6 to 9%) in systemic diffuse large B-cell, and also, the same prophylaxis measures, has been dispute ,because the use of these measures, not real and evident benefit has not been observed [7-9].Thus, we began a controlled clinical trial in patients in pathological confirmed PTL that achieve CR after combined therapy.

3. Patients and Methods

The criteria entry were > 18 until 70 years age, pathological confirmation of DLBCL; stage I and II, normal complete blood counts, serum chemistry, hepatitis B and C , human immunodeficiency syndrome negatives, no neurological abnormalities (they were evaluated for a expert neurologist without knowledge of the case). Computed tomography of thorax, abdomen , pelvis and

head (from 2008 magnetic resonance were employed).

Determination of genotype for immunohistology tests, and lumbar puncture to examination of cerebral fluid.

Initially they were treated with rituximab an dose dense regimen anthracycline regimen (R-CHOP14) , at doses, schedules as has been previously reported 8. The study was approved by the Ethical and Scientific Committee; all patients signed an inform consent to participate in the study. Taking in consideration the probably risks in patients than can relapse, independently the patients will be received a second opinion, for another institution, they will be received legal, and it is necessary religious opinion.

4. Results

Initially 25 patients were included, but 3 patients did not achieved CR and were eliminated ,they were treated with autologous stem cell and achieved CR . Thus 22 patients were allocated in 1:1 proportion to received or not central nervous prophylaxis.

Table 1 show the clinical and laboratory characteristics of the 22 patients. No statistical differences were observed and were similar to the patients with PTL attended in the Oncology Hospital.

After 2 weeks CR was confirmed; the prophylaxis administered was : methotrexate 6 g/m, iv, every 3 weeks, for 4 cycles; folinic acid, rescue : 21 mg/m^2, was administered every 6 hours, until serum methotrexate was cleared in blood. Hydration and alkaline urine were conserved during treatment, serum creatinine was measured every 12 hours. No subsequently treatment was employed. Toxicities secondary to rophylaxis were minimal and well controlled The study was performed between January 2014 to December 2019, the median follow-up was 48.3 (range 36 to 62) months Until now, 2 relapses were observed: one in each group, as systemic relapsed ,and they were treated wit ASCT, both achieve CR and are alive in second CR at 24 and 34 months. No deaths were reported. Central nervous system relapse no has been observed.Toxicity was minimal mucositis grade 2 in 4 patients, and grade 1 in 5 patients. Hematological toxicities were not observed.

Table 1: Demoghrapic Charcateristics

			PROPHYLAXIS	
			YES	NO
NUMBER (%)		22 (100)	12(59.5)	10 (45.4)
Age (years)	Median		65.5	64.2
	Range		58-73	56-8
Stage	I	16(72.7)	8(66.6)	8(80)
	II	6(27.2)	4(33.3)	2(20)
Performance status				
	0,1	14(67.6)	7(58.3)	7(70)
	2	8(36.3)	5(41.5)	3(30)
Elevated LDH		3(13.6)	1(58.3)	2(20)
Elevated B2M		2(9.0)	1(8.3)	1(8.0)
IPI	Low	19(86.3)	11(91.6)	8(80)
	Low-intermediate	3(13.6)	1(8.3)	2(2)
Genotype	GCB	13(59.9)	8(66.6)	5(50)
	Non-GCB	9(40.9)	4(33.3)	5(50)
CNS IPI	Low	14(67.6)	7(50.0)	7(70)
	Intermediate	8(36.3)	5(41.5)	3(10)

5. Discussion

CNS relapse in patients with PTL, has been considered as the most frequent relapsing site and it is associated with a worse prognosis [7-9].

Multiple studies has been reported, with confusing results, probably because these studies included patients with advanced stage, that are associated with poor performance status, higher levels of LDH and B2M, higher IPI, and when performed CNS IPI, also higher, and the prophylaxis regimen are different : radiotherapy, intrathecal methotrexate, or cytosine arabinoside or both, intravenous high doses of methotrexate, in this case with multiple doses (< 4 g/m^2), two or four times [3-5]. However, neither of these studies observed any benefit.

In the other hand, in patients with nodal disease, has been observed that CNS would been have an higher number of patients with CNS relapse, and also prophylaxis has been employed, but, again a clear benefit has not been observe; some years ago, we performed an retrospective analysis in 3258 patients with nodal diffuse large lymphoma, that were treated with anthracycline based chemotherapy, and from 2002 adding rituximab, prophylaxis was administered as decision of the physician at charge; from 1005 patients who received prophylaxis ,CNS system relapse was observed in 10 cases (6.0%), that did not show statistical difference with the 2253

cases whose did not received CNS prophylaxis : 118 cases (5.9%), and overall survival was not affected: at 5-years actuarial curves were 53% in patients that received CNS prophylaxis compared with 49% in patients that received CNS prophylaxis; thus, from 2012 we eliminate the use in this setting of patients [12]. Recently, some studies has been addressed this problem and not definitive results has not been report [9-13] and two recent paper reported that CNS prophylaxis is not useful [14, 15]. Recently Yerram et al [16], reported that the use of higher doses of methotrexate and adding rituximab, is benefit in patients with primary lymphoma CNS, so how PTL have the same targetable genetic features [17] probably the use of aggressive chemotherapy and rituximab could be eliminated tumoral cells in PTL and delay the possibility of relapse, including CNS.

We present the preliminary findings of the first controlled clinical trial that assess if the prophylaxis to CNS in patients PTL is necessary. It is evident that some bias are observed, it was performed in a single center, the number of patients is low to achieve any definitive response. But, it was performed in an homogenous population, treated with an unique chemotherapy, and takin in consideration that CNS relapse in patients with PTL, is most frequent in the first years of follow-up, the time appear to be correct.

6. Conclusions

Based in this results , we suggested that patients with PTL and have : early stage , age < 60 years old, good performance status; IPI an CNS-IPI low , normal values of LDH and B2M , the use of prophilaxis could not be not useful. Is necessary increased the number of patients, and more longer follow-up.

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