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Exist a Treatment for Relapsing/Refractory Primary Testicular Lymphoma?

Research Article

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Highlights

At relapse primary testicular lymphoma is considered was worse prognosis, and short survival, but , appear that studies about the treatment in this special setting of patients, has not been performed. We performed an retrospective analysis, and observed that relapse/refractory PTL, can be treated with excellent results. We conclude that PTL at relapse/refractory status will be treated as other diffuse large B-cell lymphoma.

Abstract

Background: Prognosis at relapse/refractory (R/R) status of Primary Refractory Lymphoma (PTL) is considered worse with survival <3 months, but, we did not found specific studies in this setting of patients. We performed an retrospective analysis of patients with R/R PTL to assess if these patients will be received an adequate treatment.

Patients and Methods: From August 1988 to December 2018, we diagnoses and treated 160 patients with diagnosis of PTL, in early stage, treated with conventional CHOP, dose-dense CHOP-14 and R-CHOP14: and analyzed the treatment at relapse or refractory status, and the results and outcome of these treatments.

Results: With a median follow-up of 14.9 (range 3,9 to 21,3) years, the best treatment in R/R patients were the use of autologous stem cell transplant and the use of dose -dense CHOP and rituximab (R-CHOP14).

Conclusion: Patients with PTL an R/R status will be treated according the guidelines for diffuse large B-cell lymphoma.

Introduction

Primary testicular lymphoma is a rare presentation of Diffuse Large B-Cell Lymphoma (DLBCL), accounts for less of 2% of hematological malignancies; although most patients presented with localized disease (stages I and II), nevertheless the outcome is poor and continuous risk of relapse and death related; even 10 years after diagnosis. Multiple studies has been performed to search the best therapeutic schedule .Initially , anthracycline based chemotherapy was employed, but, early relapse was observed in regional areas: scrotum, inguinal lymph nodes, and involved field radiotherapy was adding , that improve Progression-Free Survival (PFS) but not overall survival, because Central Nervous System CNS) relapse was frequent (20-22%) , and the use of preventive measures: intrathecal methotrexate, radiotherapy, higher-doses (>3 g/m2) did not show specific benefit [1-6]. In the other hand, multiple factors has been mentioned that increase the risks of relapse: advanced stage, age, poor performed status; all related to the advanced stages. Moreover, we did not found any report of the treat-

ment at relapse of PTL, thus, it is appear that PTL at relapse did no have any chance of treatment [7-9]. The end-point was to evaluate the role of treatment in patients in relapse/refractory status.

Patients and Methods

From August 1988 to December 2018,criteria entry were patients with confirmed pathology Diagnosis of Diffuse Large B-Cell Lymphoma (DLBCL) , stage I and II, previously treated, >18 years old without upper limit, physical examination, included evaluation of a neurologist, complete blood counts, serum chemistry, serum determinations of lactic dehydrogenase and beta 2 microglobulin, tests for acquired hepatitis B and C, acquired human immunodeficiency virus, bone marrow biopsy and aspirate, genotype (from 2005), computed tomography of neck, thorax, abdomen and pelvis; initially ,also of head (magnetic resonance was employed for 2009).

The studies were approved the Ethical and Scientific Committee of our Institute and all patients signed an informed consent to participate in the studies that were treated in our Institution and have a minimum of 3 years of follow-up (to avoid the risk of early relapse). All were treated with anthracycline based- chemotherapy, according to the different dates of diagnosis: CHOP (cyclophosphamide, doxorubicin , vincristine and prednisone, every 21 days for 6 cycles) , taking in consideration the poor response , PFS and OS, we change to a dose dense regimen (CHOP, with increased doses of doxorubicin and cyclophosphamide , administered every 14 days, for 6 cycles), adding involved radiotherapy to regional lymph nodes, and higher doses of IV methotrexate: 4 monthly doses): when rituximab was available in our institution, we adding rituximab to the CHOP14), radiotherapy and prophylaxis to CNS were the same [10,11].

Results

(Table 1) show the clinical and laboratory characteristics of the 160 patients and initial treatment. They were allocated to the type of treatment and did not were observed statical differences. With a median follow-up of 14.5 (range: 3.9 to 21.3) years It is evident that the use of CHOP at standard doses had poor complete response, PFS and OS, were worse (Table 2). The use of dose-dense regimen appear to improve outcome, but PFS and OS did not show statistical differences. The addition of Rituximab, show improvement in CR, PFS and OS. It is to noted that CNS relapse were not observed. At relapse, we followed the guidelines to the treatment of relapse DLBCL, and autologous stem cell transplantation was performed, if the patient is quimiosensitive, <75 years old, without severe comorbidities, and if the patient accept the treatment. In these cases, we offer combined chemotherapy based in the available drugs.

Table 1: Clinical and laboratory characteristics.

	CHOP/21	CHOP-14	R-CHOP14	Total	P
No (%)					
Number	39(24.30)	52(32.9)	69(43.1)	160	
Age (Years) median	51.8	65.6	63.4	60.7	0.344
Range	49-76	53-74	55-77	49-77	
Stage I	21(53.0)	34(61.3)	46(66.6)	101(63.1)	0.876
II	18(46.1)	18(34.1)	23(33.33)	59(36.8)	0.112
Tumor size (cm), range	4-9	5-9	3-9	3-9	
Median	6.8	6.3	6.6	6.4	
PS	28(71.7)	40 (76.9)	58(84.0)	126(78.1)	0.345
LDH>2N	6(15.3)	10 (19.2)	13(18.8)	29(28.1)	0.239
B2M	5(12.8)	11 (21.5)	14(20.2)	30(18.7)	0.875
IPI					
0,1	15(38,4)	19 (36.5)	21 (30.4)	55(34.3)	0.888
2	24(61.5)	33 (63.4)	48 (69.5)	105(65.6)	0.754
Genotype					
GCB	NP	10 (19.2)	8 (11.5)	18(14.8)	0.444
Non -GCB	NP	42 (80.7)	61 (88.4)	103(85.1)	

Abbreviations: PS: Performance Status; LDH: Lactic Dehydrogenase; B2M: Beta 2 Microglobulin; IPI: International Prognostic Index; GCB: Germinal Central B.

Table 2: Outcome.

	CR	Relapse	PFS	OS	Treatment
CHOP 21	20(51.2)	14(70)	22.3(15.8-26.6)	41.3(36.4-48.0)	2a line
					ASCT: 2 CR 1: 50%
					ESHAP 8 CR 5: 62.5
					GDP 4 CR 2: 50.0%
CHOP-14	44(84.6)	20(45.4)	49.0(44.2-54.7)	58.4(52.3-67.5)	

2a line					
					ASCT 10 CR 4: 40.0%
					R-ESHAP 10 CR 4: 40%
3a line					
					ASCT 6; CR: 4, 66.6
					R-GDP: 10, CR 6: 60 %
R-CHOP14	58(72.5)	18(31.0)	63.8(61.1-72.5)	88.4(81.4-92.0)	
2a line					
					ASCT 9, CR 6: 66.6%
					RGDP: 9, CR7: 77,7%
3a line					
					ASCT: 2, CR 1: 50%
					RGDP: 4, CR 3: (75%)

Abbreviations: CHOP 21: Cyclophosphamide Doxorubicine Vincristine Prednisone every 21 days; CHOP14: Dose dense CHOP every 14 days; RCHOP14: Dose dense CHOP and Rituximab every 14 days; ASCT: Autologous Stem Cell Transplant; ESAHP: Etoposide Methylprednisolone and Platinum; GDP: Gemcitabine Dexamethasone and Platinum; RGDP: GDP + Rituximab.

ASCT was performed in 21 cases with CR in 11(52.38%52%); ESHAP in 8 cases with CR in 5(62.5%), R-ESHAP was used in 29 cases with CR in 16(51.%), gemcitabine based regimen in 4 ,with CR in 2(50%), when adding rituximab in 23 cases CR was achieved in 16(56.7%). The most frequent toxicities were hematological, specially severe neutropenia and thrombocytopenia. However, no lethal toxicity were observed. At >10 years, 2 patients in CHOP-21(5.12%), 14 in the CHOP-14(26.9), and 30(43) in the RCHOP-14(43.4%). CNS relapse were not observed.

Discussion

We show the first analysis of PTL patients with longer follow-up, and specifically the use of this patients when relapse. We did not found any analysis in these specially setting of patients, and appear that when PTL relapse, they were not candidates an any treatment. We show that treatment these patients would be considered to be candidates at relapse, according with the guidelines for DLBCL. Thus, ASCT was employed as second line in most cases, with excellent outcome, 52.8 % of CR, and 2 of these patients are alive at >10 years. ESHAP was the most employed salvage regimen, with an CR of 62.5%, but the number of patients was small to definitive conclusions, no patients treated with ESHAP is alive at >10 years. The addition of Rituximab an dose dense CHOP, CR was observed in 16 of 29 cases (51%), and 14(43.4%) are alive at more >10 years. The use of gemcitabine based chemotherapy was employed in scares number of cases, the addition of Rituximab to GDP, increase CR rate, but these regimen was employed in 2012, thus we did not have any patient with longer follow-up, but at December 2021, 11 cases (78.5%) are alive free-disease.

As comment, we did not found any specific treatment guidelines for relapsing PTL. In this study we observed that PTL at relapse have a minor number of CR, but the use of R-GDP appear to be promissory in this setting of patients. The use of ASCT, remain the treatment of choice in relapse patients, even in PTL.

Conclusion

We considered that PTL at relapse would be treated, because the disease appear to be sensitive to another type of treatments. We suggested that in PTL at relapse will be treated wit ASCT, R-GCD will considered as the following treatment. We did not have any explanation to the fact that CNS were not observed in our patients. Some recent paper has been addressed that CNS prophylaxis in not benefit in DLBCL, and that the improvement in patients at risk, will be the results of intensive chemotherapy, that produce an quickly reduction of circulating number of tumoral cells and diminished the risk of CNS, but, this problem remain open [12-14].

Both authors contributed to design, data analysis, and wrote the final version.

Conflict of Interest

Both authors disclose any conflict of interest.

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