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Clinical High Leves Of Beta 2 Microglobulin Worsened the Prognosis in Patients with Aggressive Diffuse Large B Cell Lymphoma

(***Short title: Beta 2 Microglobulin***)

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Abstract

Background: *Multiple studies have been performed a prognostic index, that can predict outcome and would be indicated the use of more aggressive treatment. We performed a retrospective analysis in patients with diffuse large B-cell lymphoma and higher clinical risk, according to the International Prognostic Index (IPI), to assess if another factor risk could be identified,*

Methods*: Between January 1999 to December 2015, 1388 patients with high-clinical risk, stage IIA or IV, presence of bulky disease (tumor > 10 cm), treated with R-CHOP: rituximab, cyclophosphamide, vincristine, doxorubicin, prednisone) were analyzed. Complete staging was performed and multiple prognostic factors were included.*

Results: *Complete response, progression-free survival(PFS) , and overall survival were worse in patients with high levels (> 3 mg/L) : 65% (95% Confidence Interval (CI : 59% to 71%) (p < 0.001) ; PFS 52% (95% CI: 43% t0 59%); 54% (95%CI: 45% to 61%) 68% (61% to 75%) (< 0.001); and 62% (95%CI: 55% to 79 to 68%) (p < 0.001) respectively when compared with patients with normal values (< 3.0 mg/L) : 74% (95% CI: 65% to,83%); 77%(95%CI: 69 % to 86%) and 78% (70% to 88%) respectively (p < 0.001).*

Conclusion: *B2M appear to be a no-expensive, simple and reproducible marker to help defined a worse prognosis in patients with high clinical risk, \. Thus, will be considered a necessary maker when clinical trials with different chemotherapy regimens.*

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma, and considerable progress has been resulted for the use of R-CHOP-R (cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab). Treatment based in the clinical risks defined by the in the International Index Project (IPI); however, the standard IPI have a suboptimal predictive power in high-risk patients, and new prognostic tools will be developed. In recent years it has become increasingly apparent that DLBCL it is not a single pathological entity the evaluation of such claims is however made difficult by the heterogeneity of the studied patients and lack a well-recognized set of prognostic factors: in some studies, has been proposed that molecular studies are necessary to identified those association with a lower probability of cure after standard treatment (1-3). However, in most cancer centers it is not feasible. In our Institution for multiple factors: economic, social, cultural, most patients presented with advance stages (III and IV, and high-clinical risk according to the IPI; thus, we need the need to developed other markers to help in the designed a better chemotherapeutic regimen.

In the search for prognostic factors it was suggested that beta 2 microglobuline (B2M) may be a useful indicator of disease extent and activity in lymphomas (4-8), some years ago we introduced the use of B2M in the staging procedures, in some patients, and in some of extranodal DLBCL, high levels of B2M can be significantly, high levels of B2M predict a poor outcome compared with patients with normal values (9-12).

Material and Methods

Between January 1999 to December 2015, patients that fulfilled the following criteria entry, were considered in these analyses: Age > 18 years without superior level, no gender differences, confirmed pathological diagnosis of DLBCL, with nodal presentation, advances stage: III or IV, high clinical risks based in the IPI model. Clinical staging included: physical examination, complete blood counts, serum chemistry including serum levels of B2M and lactate dehydrogenase, computed tomography of neck, thorax, abdomen and pelvis, aspirate and biopsy of bone marrow, virus tests: hepatitis B and C, immunodeficiency syndrome.

Patients were treated with CHOP-R (cyclophosphamide, vincristine, doxorubicin, prednisone and rituximab) at standard doses and schedules. Patients with nodal tumor masses > 10 cm, received adjuvant radiotherapy.

Ethical Aspects

The study was conducted according to the rules of Helsinki declaration, it was approved Ethical and Scientific Committees of our Institution and all patients signed an informed consent to participate in the study.

Statistical analysis

Levels of B2M in different groups were compared with the Mann-Whitney U test, and the proportion of patients with elevate levels compared by the X^2 tests. Univariate analysis of prognostic factors was carried out both the long-rank test with group separated by the normal range for continues variables and by the use of a univariate Cox model with logarithmic transformation for non-normal distributions. Multivariate analysis was performed using Cox multiple regression for both dichotomized and transformed variables for duration of remission and survival.

Results

A total of 1338 patients with DLBCL, who meet the inclusion criteria were included in the analysis. Clinical and laboratory characteristics of patients are show in Table 1.

Table 1: Baseline characteristics.

	Serum B2 Microglobulin (%)			
		< 3.mg/L	> 3.0 mg/L	p value
No %)	1338 (100)	752 (56%)	586 (43%)	0.211
Age (years:				
< 60	511(38%)	329 (43%)	182 (31%)	0.266
>60	827 (61%)	423 (52%)	404 (48%)	0.554
Sex:				
Male	628 (46%)	360(47%)	268 (42%)	0.581
Female	710 (53%)	392 (52%)	318(57)	0.444
PS *				
0-1	211 (15%)	66 (8.7%)	145 (24%)	0.106
≥ 2	1127 (84%)	686 (8%)	441 (75%)	0.08
Serum LDH				
Normal	101 (7%)	50 (7%)	50 (%)	0.912
Elevated	1237 (92%)	702(92%)	536 (91%)	0.878
IPI *				
High	1338 (100 %)	752 (56%)	586 (43%)	0.07
Stage IV	1338 (100%)	752 (56%)	586 (43%)	0.07
Bulky disease				
(> 10 cm)	511 (36%)	289 (56%)	222 (43%)	0.134
*Performance stage, IPI: International Project Index				

We divided the patients with normal levels (3 mg/L) and high levels (> 3.0 mg/L) . No statical differences were observed between patients with normal or high levels of B2M.Complete response: 65% (95%Confidence interval (CI): 59% -71%) compared with patients with normal levels (< 3 mg/L): 74% (65%-83%) (p. < 0.001) : progression-free survival : 54%(95%CI: 45%-61%) (p< 0.001) compared with 77%(95%CI) 69%-86%) and overall survival : 70% (95% CI: 69%-85%) , respectively. High levels of lactic dehydrogenase, age > 60 years, bulky disease and high levels of B2M, show significantly differences in univariate analysis (Table 2). However, only B2M and lactic dehydrogenase show statistical differences in PFS and OS in multivariate analysis (Table 3).

Table 2: Univariate analysis.

	Progression-free survival		Overall survival	
	HR (95%CI)	p	HR (95% CI)	p
B2M > 3 m/L	4.25 (3.23-5.51	< 0.001	5.76 (4.11-6.86)	< 0.001
Age > 60 years	3.67 (2.98-4.01)	0.066	3.81 (2.38 -4.06)	< 0.01
Male	0.67 (0.56-1.01	0.435	0.99 (0.76-1.28)	0.91
PS > 2	2.48(1.43-4.10)	0.01	2.78 (1.59-4.78)	0.031
High LDH	4.78(4.02-6.11)	<0.01	4.56-4.11-6.27)	< 0.01
Bulky disease	2.87-2.01-3.67	0.02	3.61 (1.98-3,02)	005
B2M: beta 2 microglobuline; PS: performed status; LDH: Lactic dehydrogenase				

Table 3: Multivariate analysis

	Progression free survival	p	Overall survival	p
	HR (95% CI)		HR *95 CI)	
B2M	2.23 (1.87-3.23)	< 001	2.0 (1.27m (2.87)	< 0.01
High LDH	2.34(1.99-3.33)	< 0.001	2.6(1.96-2.87)	< 0.01
>60 years	1.62 (1.23-2.11)	0.02	2.27(1.29)	0.02
Bulky disease	1.45(1.29-2.01)	0.03	1.60(1.25-2.43)	0.04

Discussion

We show the results of an open label clinical trial, to assess efficacy of B2M to increase the sensibility in patients with high clinical risk according to the IPI, and we observed that inside these group of patients, B2M can detect a sub-group that have a worse prognostic. In DLBCL, several prognostic indexes have been proposed during the last 30-years. Developed in 1993, the IPI was showed a great utility in identified four groups of different risks and was employed in most centers. However, in patients with high clinical risk several confound factors make some problems and some studies have been suggested that probably in these settings of patients it is not useful. Cassuto et al, were the first that show that B2M could be useful to detect and more aggressive form of lymphoma (4), these results were confirmed by Bathe and Forman (5), Scheneider et al (6); and Swan et al developed a prognostic system based in high levels of B2M and lactate dehydrogenase (7). In our experience, we observed that B2M is a powerful factor with extranodal lymphomas (9-11). Recently Seo et al (12) and Yoo et al)13), has been suggested that B2M could be aggregate to lactate dehydrogenase and performed a new prognostic system: inclusive B2M has been considered a useful marker in follicular lymphoma who were treated with rituximab (13), Recent advances in molecular biology has been proposed to will be incorporate to the stratification of aggressive DLBCL; however, expensive costs, long turnaround time and complex methods remain as an obstacle into real-clinical practice Our results show that that an one non-expensive ,simple and reproducible, as BM is accessible in most centers ,will be useful to increase the sensibility of the IPI. The study as conformed with a homogenous group: advanced stages, high clinical risk according to the IPI, treated with the same chemotherapy, thus we considered that B2M will be considered to agree to the actual IPI classification, and assess if the benefit of B2m, could be applied in patients with prognostic factors

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