REVISTA DE INVESTIGACIÓN CLÍNICA

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PERMANYER

Rev Inves Clin. 2018;70:46-52 ORIGINAL ARTICLE

A PROGNOSTIC SCORE FOR SURVIVAL IN PATIENTS OLDER THAN 65 YEARS WITH DIFFUSE LARGE B-CELL LYMPHOMA

MYRNA CANDELARIA[1]*, NANCY REYNOSO-NOVERÓN[1], MAYRA PONCE[1], RODRIGO CASTILLO-LLANOS[1], DIANA NOLASCO-MEDINA[2] AND DAVID CANTÚ-DE-LEON[1]

[1]Clinical Research Division and [2]Department of Hematology, Instituto Nacional de Cancerología, Mexico City, Mexico

ABSTRACT

Background: Available prognosis scores for patients with diffuse large B-cell lymphoma (DLBCL) included a limited number of patients ≥ 65 years of age, and most of them did not include comorbidities. Here, we propose a prognostic score for overall survival (OS) for this group of patients. **Materials and Methods:** Patients ≥ 65 years with DLBCL treated at a single national reference center were included. Clinical features including comorbidities and biochemical parameters were analyzed. **Results:** We included 141 patients. Response rate in the whole group was 77%. Based on multivariate analysis, the presence of the European Cooperative Oncology Group (ECOG) > 2, elevated levels of beta-2 microglobulin, bulky disease, and anemia (hemoglobin < 10 g/dL) had a significant effect on OS. These parameters were considered when computing the prognostic score, which identified three groups with differential survival: Low, intermediate, and high risk of death, with a probability of survival at 60 months of 80.05%, 55.5%, and 29.84%, respectively. **Discussion:** This score may select patients to optimize treatment. The presence of high levels of beta-2 microglobulin, bulky disease, and hemoglobin < 10 g/dL, and ECOG > 2 was associated with poor OS in elderly patients with DLBCL.

Key words: Diffuse large B-cell lymphoma. Prognostic score. Survival and lymphoma. Elderly and survival. Rituximab and prognosis.

INTRODUCTION

The life expectancy of the population has increased during recent decades, being approximately of 71.4 years worldwide; it is greater for women (73.7 years)[1]. The quality of life in people aged over 65 in Europe has been a focus of research since age is associated with sociodemographic characterist cs and clinical conditions[2].

According to the International Agency for Research on Cancer, in 2015, approximately 414,772 new cases of non-Hodgkin's lymphoma (NHL) were diagnosed worldwide. Of these, 43.6% were in individuals > 65 years old[3].

***Corresponding author:**
Myrna Candelaria
Clinical Research Division
Instituto Nacional de Cancerología
Av. San Fernando, 22
Col. Seccion XVI
C.P. 14080, Mexico City, Mexico
E-mail: candelariahmgloria@gmail.com

Received for publication: 22-11-2017
Approved for publication: 04-01-2018
doi: 10.24875/RIC.18002450

Diffuse large B-cell lymphoma (DLBCL) is the most frequent type of NHL. Although this disease is potentially curable, the outcome of patients ≥ 65 years old with DLBCL has been reported by different authors as suboptimal[4-6]. The presence in this group of patients of comorbidities, impaired bone marrow function, and altered drug metabolism may increase the number of treatment-related complications, as well as hospitalization and mortality rates. Frailty is a well-defined syndrome, which is a clinically recognizable state with increased vulnerability resulting from an aging-associated decline in reserve and function across multiple physiologic systems[7]. To date, prognostic scores designed to predict response and overall survival (OS) in NHL, as are the International Prognostic Index (IPI) or revised-IPI (R-IPI), included a limited number of patients older than 65 years; however, none of these scores assessed the presence of comorbidities[8,9]. In addition, all analyses were conducted before rituximab was integrated as part of the standard of care in patients with B-cell lymphomas. Therefore, the determination of a prognostic score for DLBCL patients ≥ 65 years of age treated during the rituximab era is necessary.

MATERIALS AND METHODS

Study design and subjects

With the aim of creating a prognostic score to predict the survival in patients older than 65 years with a diagnosis of DLBCL, a retrospective analysis was conducted at the National Cancer Institute in Mexico (Instituto Nacional de Cancerología) from January 2011 to June 2015. Inclusion criteria were patients ≥ 65 years of age with a histological diagnosis of DLBCL, who were treated with CHOP-rituximab or similar schemes containing rituximab. Since this study was retrospective and without risk, no informed consent forms were signed. This project was reviewed and approved by the Institutional Review Board (Rev/013).

Clinical characteristics included age, gender, and comorbidities (diabetes mellitus [DM], blood arterial hypertension, cardiopathy, history of hepatitis [hepatitis B and hepatitis C], and HIV status), and the presence of B symptoms (fever, diaphoresis, or weight loss > 10%) as well as the performance status defined by the European Cooperative Oncology Group (ECOG) scale[10], the presence of bulky disease (length > 7 cm), extranodal sites, and clinical stage. The following laboratory parameters at diagnosis were also included albumin (normal: 3.5–5 g/dL), hemoglobin (normal: 13–15 g/dL), leukocyte (normal: 4.8–10.8), lymphocyte-to-monocyte ratio (> 2.6 vs. < 2.6), platelet count (normal: 130–400), lactic dehydrogenase (LDH) (normal 114–198 IU vs. elevated), and beta-2 microglobulin levels (normal: 1.4–2.5 vs. elevated). The lymphocyte-to-monocyte ratio was categorized with a cutoff value of 2.6, based on the data reported by Katoh et al.[11].

DLBCL classification

Histological classification was performed according to the Hans nomogram and was based on the expression of CD10, BCL6, and MUM1, as previously described[12]. Briefly, samples expressing CD10 (+) or CD10 (−), BCL6 (+), and MUM1 (−) were defined as the germinal center (GC); samples expressing CD10 (−), BCL6 (−) or CD10 (−), BCL6 (+), and MUM1 (+) were considered non-germinal centers.

Treatment regimens

All patients were treated with a rituximab-based chemotherapy that was either R-CHOP: (375 mg/m^2 rituximab, 750 mg/m^2 cyclophosphamide, 50 mg/m^2 doxorubicin, 1.4 mg/m^2 vincristine [total maximal dose: 2 mg], and 100 mg/day/5 days prednisone), or an R-CHOP-like regimen, such as R-ChOP (375 mg/m^2 rituximab, 750 mg/m^2 cyclophosphamide, 25 mg/m^2 doxorubicin, 1.4 mg/m^2 vincristine [total maximal dose: 2 mg], and 100 mg/day/5 days prednisone) or R-COP (375 mg/m^2 rituximab, 750 mg/m^2 cyclophosphamide, 1.4 mg/m^2 vincristine [total maximal dose: 2 mg], and 100 mg/day/5 days prednisone). These three regimens are considered standard for patients with DLBCL.

The response to treatment was evaluated using standard international criteria. For patients in whom PET/CT were performed before and after treatment, Deauville criteria were used[13]. In cases with increased blood glucose levels (> 170 mg/dL), which contraindicated the performance of PET/CT, only a CT was performed, and the response was evaluated by standard CHESON criteria[14].

Statistical analysis

Descriptive analysis was performed for demographic and clinical characteristics. Significant differences between groups were obtained by Chi-square and Mann–Whitney U-tests. Survival was calculated by the Kaplan–Meier method, and differences between subgroups were determined by the Log-Rank test.

Cox regression analysis was used to identify the variables predicting OS, including the treatment schemes. After identification, each variable was awarded a score in accordance with the achieved hazard ratio (HR). The sum of these values resulted in three risk groups. OS was determined using life tables applied to distinctive prognostic groups on different days of follow-up. A value of $p < 0.05$ was considered statistically significant. All analyses were performed using STATA V.12.

The sample size required to identify an HR of 2.4, with 5% of censored observations, the confidence level of 95% and statistical power of 80%, was 43 patients per group. The HR to death obtained by the Cox Proportional Hazards model for the proposed risk group was > 2.4 in all comparisons between groups. Even though the high-risk group contained 30 patients, the differences with the intermediate and low-risk groups were statistically significant, allowing to identify the characteristics of the patients at greater risk of death.

RESULTS

We included in the analysis 141 patients seen between January 2011 and June 2015. The mean age of the patients was 74 years (range: 66–81 years, SD ± 6.6) and most (60%) were female (Table 1). The comorbidities documented were blood arterial hypertension in 29%, DM in 22%, and cardiopathy in 8% of patients.

Response to treatment

All patients had basal PET-CT. To evaluate response, PET-CT was done at the end of treatment in 138 cases, and 3 were evaluated by CHESON criteria with CT. Overall response rate (ORR = complete remission or

Table 1. Descriptive analysis of clinical characteristics and biochemical parameters at diagnosis of the whole group

Parameter	n (%)
AGE	74 ± 6.6
Body mass index	25.4 ± 4.5
Gender	
Female	85 (60.3)
Male	56 (39.7)
DM	
No	110 (78)
Yes	31 (22)
Blood arterial hypertension	
No	100 (70.9)
Yes	41 (29.1)
Cardiopathy	
No	130 (92.2)
Yes	11 (7.8)
B symptoms	
No	53 (37.6)
Yes	88 (62.4)
Bulky disease	
No	73 (51.7)
Yes	68 (48.3)
ECOG	
1	90 (63.8)
2	37 (26.2)
3	14 (9.9)
LDH	
Elevated	70 (49.7)
Normal	71 (51.3)
B-2 microglobulin	
Elevated	46 (33.8)
Normal	84 (61.7)
Not done	6 (4.4)
Albumin	
Normal >3.5 g/dL	75 (53.2)
2.6–3.4 g/dL	58 (41.1)
< 2.5 g/dL	8 (5.7)
Extranodal sites	
None	47 (33.3)
1	54 (38.3)
2	24 (17.0)
> 3	16 (11.4)
Ann Arbor clinical stage	
I	14 (9.9)
II	28 (19.8)
III	36 (25.5)
IV	63 (44.7)
International prognostic index	
Low	24 (17.0)
Intermediate low	31 (21.9)
Intermediate high	42 (29.8)
High	44 (31.2)
Bone marrow infiltration	
None	131 (92.9)
Positive	10 (7.1)
Hemoglobin	
> 13 g/dL	91 (64.5)
10.1–12.9 g/dL	37 (26.2)
8–10 g/dL	4 (2.8)
< 8 g/dL	9 (6.4)

(Continue)

Table 1. Descriptive analysis of clinical characteristics and biochemical parameters at diagnosis of the whole group (*Continued*)

Parameter	n (%)
Leukocytes	
>15.0×10³/L	1 (0.7)
10–15×10³/L	17 (12.1)
4–10×10³/L	119 (84.4)
2.5–3.9×10³/L	4 (2.8)
Platelets	
> 150×10³/L	137 (97.2)
100–149.9×10³/L	1 (0.7)
50–99.9×10³/L	2 (1.4)
< 50×10³/L	1 (0.7)
Lymphocytes	
> 1.0×10³/L	114 (80.8)
0.5–0.9×10³/L	24 (17.0)
< 0.5×10³/L	3 (2.2)
Lymphocyte/monocyte ratio	
< 2.6	44 (31.2)
> 2.6	97 (68.8)
HIV	
Negative	137 (97.2)
Positive	4 (2.8)

response [CR] + partial remission or response [PR]) was achieved in 77% (n = 108). The response rate achieved according to the chemotherapy regimen was 78%, 76%, and 75% in patients treated with R-CHOP, R-ChOP, and R-COP, respectively.

During the follow-up, 15 patients died; the most frequent cause was febrile neutropenia (n = 9, 12.6%), followed by hemorrhage (n = 5, 3.5%), and multiple organ failure in one case (0.7%).

Cox regression analysis was performed to determine the factors influencing OS. After univariate analysis, the following factors were statistically significant: ECOG > 2, presence of B symptoms, > 2 extranodal sites, the presence of bulky disease, hemoglobin < 10 g/dL, levels of LDH higher than the upper normal value, increased levels of beta-2 microglobulin, and albumin levels < 2.5 g/dL. However, after multivariate analysis, only the following factors remained significant for OS: ECOG >2, increased levels of beta-2 microglobulin, the presence of bulky disease and anemia (hemoglobin < 10 g/dL). Neither clinical stage, comorbidities, nor IPI status, or the lymphocyte-to-monocyte ratio were significant in this analysis (Table 2). Thereafter, factors identified in the multivariate analysis (ECOG, beta-2 microglobulin levels, the presence of bulky disease, and anemia) were used to compute the prognostic score, which

Table 2. Uni- and multi-variate analysis for overall survival.

Univariate analysis			
Parameter	**HR**	**95% CI**	**p value**
ECOG			
1	-	-	-
2	3.74	2.12–6.59	<0.001
3	5.02	2.33–10.83	<0.001
B symptoms			
No	-	-	
Yes	2.02	1.12–3.64	0.019
Extranodal sites:	-		
None		-	-
1	1.72	0.88–3.39	0.112
2	2.37	1.11–5.06	0.025
3 or more	1.84	0.73–4.61	0.193
Bulky disease			
No	-	-	-
Yes	1.89	1.11–3.20	0.018
ANN ARBOR			
Stage I	-	-	-
Stage II	1.00	0.31–3.27	0.987
Stage III	1.16	0.37–3.61	0.790
Stage IV	1.97	0.69–5.56	0.200
International prognostic index			
Low	-	-	-
Intermediate low	1.35	0.45–4.03	0.587
Intermediate high	2.88	1.08–7.65	0.033
High	3.13	1.19–8.25	0.021
Hemoglobin g/dL			
> 10	-	-	-
< 10	2.46	1.20–5.03	0.013
LDH			
Normal	-	-	-
Elevated	2.08	1.22–3.56	0.007
B2 microglobulin			
Normal			
Elevated	2.74	1.37–5.48	0.004
Albumin			
> 3.5 g/dL	-		
2.6–3.4 g/dL	1.48	0.83–2.63	0.184
< or 2.5 g/dL	4.23	2.09–8.55	0.000
DM			
No			
Yes	1.21	0.66–2.21	0.526
Blood arterial hypertension			
No			
Yes	0.98	0.56–1.74	0.970
Cardiopathy			
No			
Yes	1.37	0.54–3.43	0.500
Lymphocyte/monocyte ratio			
< 2.6	-	-	-
> 2.6	0.618	0.36–1.04	0.074
Treatment scheme			
R-CHOP	-		
R-ChOP	1.717	0.884–3.35	0.110
R-COP	1.844	0.924–3664	0.081
Multivariate analysis			
ECOG			
1	-		
2	3.38	1.84–6.19	<0.001
3	6.11	2.38–15.65	<0.001

(*Continue*)

Table 2. Uni- and multi-variate analysis for overall survival (*Continued*).

Multivariate analysis			
B2 mm			
Normal	-		
High	3.43	1.57–7.50	0.002
Ann Arbor stage			
Stage I-II	-		
Stage III-IV	1.22	0.64–2.30	0.539
Bulky disease			
No	-	1.03–3.32	0.037
Yes	1.85		
Hemoglobin			
> 10 g/dL			
< 10 g/dL	2.19	1.05–4.58	0.036

After multivariate analysis, the following parameters were significant for overall survival: ECOG >2, high levels of beta-2 microglobulin, the presence of bulky disease, and anemia (hemoglobin<10 g/dL)

Table 3. Score to predict survival in+65-year patients with diffuse large B-cell lymphoma.

Factor	Score	
ECOG:	-	
1	1	
2	2	
3	3	
Beta-2 microglobulin	-	
Normal	1	
Elevated	2	
Bulky disease	-	
No	1	
Yes	2	
Hemoglobin	-	
>10 g/dL	1	
<10g/dL	2	
Groups	Survival to 1 year (%)	Survival to 3 years (%)
Low risk: < 5 points	87.9	80.05
Intermediate risk: 6 points	62.7	55.5
High risk: > 6 points	38.64	19.84

Proposed score to predict survival in patients ≥65-years old with diffuse large B-cell lymphoma. Three groups were defined, with overall survival to 3 years of 80.05%, 55.5%, and 19.84% in low-, intermediate-, and high-risk groups, respectively.

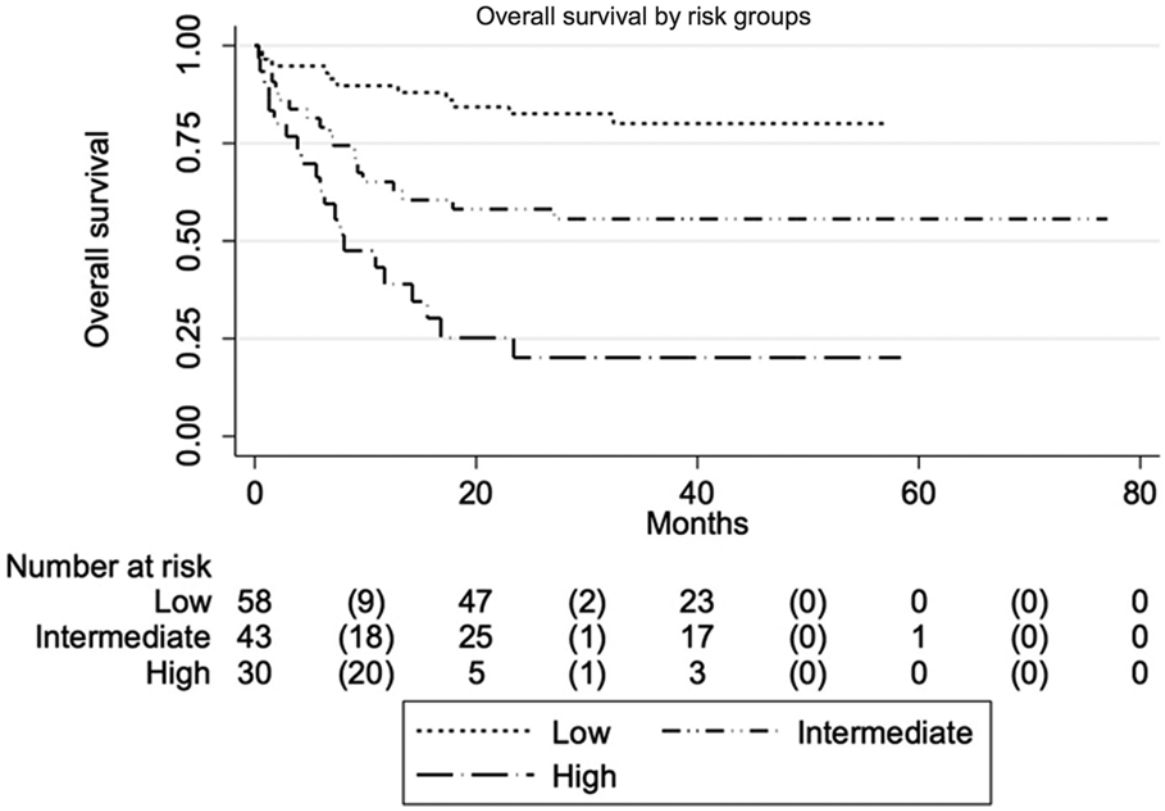
could identify groups with differential survival; the scores are shown in Table 3. A score of < 5 points comprised a group with low risk of death with an 87.9% probability of OS survival at 12 months, and thereafter an 80.5% plateau was documented up to 60 months. A score of 6 points comprised a group with an intermediate risk of death, with a 62.7% and 55.5% OS at 12 and 60 months, respectively. Finally, the high-risk group had a score of > 6 points, with an OS of 38.64% and 19.84% at 12 and 60 months, respectively (Fig. 1).

These results need to be validated in a prospective sample.

DISCUSSION

The concept of geriatric hematology-oncology has been developed in the past decade since the treatment of elderly patients has become an important concern. Prognostic scores in patients with DLBCL have included a limited proportion of elderly patients, and do not evaluate the presence of comorbidities, frequently occurring in this age group. Therefore, more defined criteria are needed to separate individuals capable of receiving standard chemotherapy from those who may require an alternative treatment strategy. This study evaluated biochemical parameters, comorbidities, and known standard international prognostic factors related to lymphoma. Few studies have examined the prognostic impact of markers other than the five factors considered in the International Prognostic Factors in this population[15-20]. Most studies are focused on blood markers. For instance, a study by Ochi et al., identified that a platelet count of < 100 × 10^3/L and an albumin level < 3.5 g/dL were associated with lower OS, independently of the IPI status, and patients with both factors at diagnosis had only a 20.2% OS to 5 years, compared to 81.5% in those without these parameters[15]. In that series, a greater degree of hypoalbuminemia (2.5 g/dL) had also a negative impact, but only by univariate analysis; this factor was not statistically significant after multivariate analysis[15]. In addition, Melchardt et al. observed that the presence of anemia, high C-reactive protein, and high bilirubin levels had an independent prognostic value for survival in multivariate analysis[20]. These results were not consistent with those reported by Ochi et al. in terms of the impact of platelets and the platelet-to-lymphocyte ratio on survival[15]. In our study, we evaluated all these blood parameters, and although by univariate analysis, the presence of anemia and increased levels of LDH and beta-2 microglobulin were statistically significant, after multivariate analysis, only the increased levels of beta-2 microglobulin and anemia had an impact on OS. In addition, Troppan et al. reported that high plasma fibrinogen levels were associated with a decreased 5-year OS, and 5-year DFS[21]. Since our results are retrospective, and fibrinogen was not routinely determined, we were not able to analyze this parameter. Recently, a personalized risk prediction for event-free

Figure 1. Overall survival, according to the risk of death groups: Low risk (< 5 points), intermediate risk (6 points), and high risk (> 6 points).



survival (EFS) at 24 months in patients with DLBCL was proposed by Maurer et al., and in a multivariate model, age (> 70 years), Ann Arbor stage, serum LDH, ECOG status, bulky disease and sex were identified as prognostic factors influencing OS[22]. This author also documented that EFS status at 24 months is a robust endpoint for assessing disease-related outcome in patients with DLBCL treated in the rituximab era. Our results supported the conclusion of this author, since in our three groups of patients, a plateau was observed from this time until 60 months of follow-up, and this time seems to be a useful endpoint to evaluate OS.

Since toxicity, particularly, febrile neutropenia and hemorrhage are leading causes of mortality secondary to chemotherapy and these complications are higher in patients with bone marrow infiltration, other authors have evaluated the impact of bone marrow infiltration on OS, documenting that the infiltration to this organ was not associated with CR rate or 2-year OS rates[23]. Our results are in agreement with this publication. Interestingly, the presence of cardiopathy, diabetes or hypertension did not have a negative impact on OS. Recently, Byun et al. and Hung et al. reported that the presence of age older than 75 and 70 years, respectively, was a factor that increased the risk of mortality related to treatment[16,24]. Interestingly, the series of Byun et al. reported 155 patients treated at a single reference center during 10 years in Asia[16]. Our sample size is similar to theirs, and it is important to note that Latin-American and Asian populations have been underrepresented in multicenter clinical trials.

Regarding the effect of histological or tumor factors on survival, the coexpression of T-cell markers, such as CD 5, has also been associated with a poor prognosis for elderly patients with DLBCL[25]. This immunohistochemical analysis was not performed in our patients. Although recently molecular analysis, particularly MYC dysregulation, including MYC rearrangement and Myc protein overexpression, has been of clinical importance in DLBCL, these alterations were not the focus of this study and were not evaluated[26].

In summary, the proposed score included clinical factors, and blood and lymphoma parameters that, after

multivariate analysis, clearly defined three risk groups. The presence of high levels of beta-2 microglobulin, bulky disease, anemia (hemoglobin < 10 g/dL), and ECOG > 2 were associated with poor OS in elderly patients with DLBCL. No prognostic score for DLBCL has been published before in geriatric Latin-American population. These results require validation in a prospective trial.

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