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RESEARCH ARTICLE

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A new prognostic model identifies patients aged 80 years and older with diffuse large B-cell lymphoma who may benefit from curative treatment: A multicenter, retrospective analysis by the Spanish GELTAMO group

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Abstract

The means of optimally managing very elderly patients with diffuse large B-cell lymphoma (DLBCL) has not been established. We retrospectively analyzed 252 patients aged 80-100 years, diagnosed with DLBCL or grade 3B follicular lymphoma, treated in 19 hospitals from the GELTAMO group. Primary objective was to analyze the influence of the type of treatment and comorbidity scales on progression-free survival (PFS) and overall survival (OS). One hundred sixty-three patients (63%) were treated with chemotherapy that included anthracyclines and/or rituximab, whereas 15% received no chemotherapeutic treatment. With a median follow-up of 44 months, median PFS and OS were 9.5 and 12.5 months, respectively. In an analysis restricted to the 205 patients treated with any kind of chemotherapy, comorbidity scales did not influence the choice of treatment type significantly. Independent factors associated with better PFS and OS were: age < 86 years, cumulative illness rating scale (CIRS) score < 6, intermediate risk (1-2) R-IPI, and treatment with R-CHOP at full or reduced doses. We developed a prognostic model based on the multivariate analysis of the 108 patients treated with R-CHOP-like: median OS was 45 vs. 12 months ($P = .001$), respectively, for patients with 0-1 *vs.* 2-3 risk factors (age > 85 years, R-IPI 3-5 or CIRS > 5). In conclusion, treatment with R-CHOP-like is associated with good survival in a significant proportion of patients. We have developed a simple prognostic model that may aid the selection patients who could benefit from a curative treatment, although it needs to be validated in larger series.

1 | INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most commonly diagnosed non-Hodgkin lymphoma in Western countries.[1] It is also a disease of the elderly, with a median age at diagnosis of 70 years,[2] and almost one-third of newly diagnosed patients are over the age of 75 years.[3] While DLBCL is a potentially curable malignancy, evidence suggests that elderly patients do worse than their younger counterparts.[4] These inferior outcomes may reflect undertreatment resulting from hematologists' perception that elderly patients are unable to tolerate aggressive therapy[1]. In addition, older individuals often have a variety of comorbidities that may preclude administration of effective therapies at the appropriate dose intensity.[5] Conversely, DLBCL in elderly patients may be biologically and molecularly different from DLBCL in younger patients.[6]

These observations have minimized the participation of elderly patients in clinical trials, especially those over 80 years, and treatment strategies are often based on results from studies conducted with younger, relatively fit patients, or on retrospective analysis that are often limited by the sample size.[1,7–9] Although there is some evidence suggesting that R-CHOP should be used in this age group,[8–12] other studies have shown that full-dose chemotherapy may be associated with poorer survival because of excess toxicities.[9,13,14]

In the present study, we have retrospectively analyzed the clinical characteristics and outcomes of a large series of patients with DLBCL who were older than 80 years and treated in 19 member hospitals of the GELTAMO group. Specifically, we investigated factors associated with treatment selection and examined the impact of the type of treatment and comorbidities on survival.

2 | METHODS

2.1 | Study design and patients

Nineteen GELTAMO centers participated in this retrospective study. Investigators from each center were required to report all patients who met the following inclusion criteria: (1) patients $\geq$ 80 years old; (2) initial diagnosis between January 2002 and December 2014; (3) histological diagnosis of DLBCL (de novo or transformed), or grade 3B follicular lymphoma. All centers completed a comprehensive case report form for every eligible patient. The study was approved by the Complejo Hospitalario de Salamanca Ethics Committee.

2.2 | Assessment of comorbidities

Comorbidities, defined as chronic medical conditions that can affect patient life span, were assessed retrospectively using the following methods:

1. Cumulative illness rating scale (CIRS),[15,16] which assesses the severity of coexisting diseases in 14 organ systems/scales, scored from 0 to 4.
2. CIRS-G (CIRS revised and validated to reflect common geriatric problems) including the presence of eight specific geriatric syndromes at diagnosis: dementia, delirium, depression, osteoporosis, incontinence, falls, failure to thrive, and neglect/abuse.[17–20] This reflected the loss of activities of daily living (ADLs): loss in the ability to undertake the activities of bathing, dressing, toileting, transferring, feeding, and/or maintaining continence. Patients were classified as "fit" if they had no loss of ADLs, less than three grade 3 CIRS-G comorbidities, no grade 4 CIRS-G, and did not have a geriatric syndrome at the time of initial diagnosis, or "unfit" if any of these were present.[21,22]
3. Charlson Comorbidity Index (CCI).[23] This scoring system classifies comorbidities such as heart, lung, and liver diseases, diabetes, cerebrovascular disease, and cancer using a weighted system. A high comorbidity was defined as CCI $\geq$ 2.

2.3 | Centralized histopathological review

Seventy-nine FFPE diagnostic samples with available material were retrieved from the centers and a centralized histopathological review of the diagnoses was performed. Seventy-six cases corresponded to DLBCL cases according to the 2008 WHO classification, two cases were diagnosed as follicular B cell lymphoma (grade 3A and grade 2), and one was diagnosed as gastric MALT lymphoma after review. A tissue microarray was constructed with 53 such cases for whom enough material in the FFPE block remained after the diagnostic work-up. A panel of immunohistochemical (IHC) markers including CD20, CD3, BCL2, CD10, BCL6, CD30, EBV- LMP1, EBER (CISH), Ki67, p53, c-MYC, CD5, MUM1, PD1, and PDL-1 was applied using conventional automated methods (DAKO). IHC results were scored using previously established cutoffs and algorithms.[24]

2.4 | Endpoint definitions and statistical analysis

The primary objective of this study was to analyze the influence of the type of treatment and comorbidity scales on progression-free survival (PFS) and overall survival (OS). PFS was measured from the time of diagnosis until relapse, progression or death from any cause. OS was calculated from the date of diagnosis until the date of death from any cause, the date of movement to the palliative care unit, or the date of last follow-up while alive. Survival rates were computed according to the Kaplan–Meier method and compared using the two-tailed log-rank test. Secondary objectives were to analyze response rates and treatment-related mortality, according to univariate Chi-square tests. Covariates with a value of $P < .05$ were entered stepwise into the multivariate Cox proportional hazards model. Hazard ratios (HRs) and their 95% confidence intervals (CIs) were reported. All statistical analysis were conducted with SPSS version 20.0 (IBM SPSS Inc., Armonk, New York).

3 | RESULTS

3.1 | Patient characteristics

Two-hundred fifty-two patients were included in this analysis. Their main characteristics and the treatment they received are summarized

in Table 1. The median age was 83 years (range, 80–100 years) and 59 patients (23%) were older than 85 years. Histology was consistent with DLBCL in 95% of patients. 160 patients (63%) were treated with chemotherapy including anthracyclines and/or rituximab, whereas 37 patients (15%) did not receive any chemotherapeutic treatment and 19 patients (7.5%) did not receive any treatment at all.

3.2 | Survival analysis in the overall series

With a median follow-up of 44 months (range, 12–142 months), median PFS and OS in the overall series were 9.5 and 12.5 months, respectively (27% and 34% at 3 years) (Supporting Information Figure S1). In the univariate analyzes (Supporting Information Table S1), age $\geq$ 86 years, CIRS $\geq$ 6, being "unfit," CCI $\geq$ 2, high-risk R-IPI, no rituximab treatment and no anthracycline treatment were significantly associated with worse PFS and OS. In the multivariate analysis, age $<$ 86, CIRS $<$ 6, intermediate-risk R-IPI and rituximab treatment remained independent risk factors predicting better OS and PFS, as shown in Supporting Information Table S2.

3.3 | Analysis restricted to patients treated with chemotherapy

We performed an analysis restricted to patients treated with chemotherapy ($N = 215$), excluding those receiving radiotherapy, surgery or rituximab alone, as well as untreated patients. Fifty-two (24%) patients received R-CHOP at full doses, whereas 56 (26%) received R-CHOP at reduced doses (R-CHOPr) (37 patients from the beginning and 19 patients during treatment due to complications or following their physician's decision). Thirty (14%) patients received R-CVP, 22 (10%) received CHOP and, 55 (26%) patients were administered palliative treatment (as definitive treatment and not as a prephase) consisting of cyclophosphamide +/- prednisone +/- vincristine. Patient characteristics by the type of treatment are shown in Table 2. Patients receiving anthracycline-containing treatments (CHOP or R-CHOP) were younger than those receiving R-CVP or palliative treatment. Significantly more patients in the CHOP group had a high-risk R-IPI ($P = .021$). Comorbidity indexes were not apparently of value in the choice of treatment type (Table 2).

The median number of cycles administered was 5 and 6 in the R-CHOP and R-CHOPr groups, respectively, significantly higher than the median of cycles administered in the R-CVP and CHOP groups (3 and 4, respectively) (Table 2). CR and OR rates were significantly better in patients receiving R-CHOP and R-CHOPr, as shown in Table 2. Treatment-related mortality was lower in the R-CHOPr and palliative groups, although the difference from the other groups was not statistically significant. However, lymphoma-related mortality was significantly lower in patients treated with rituximab-containing regimens (R-CHOP, R-CHOPr, or R-CVP) (Table 2).

PFS and OS Kaplan–Meier curves are shown in Figure 1. PFS and OS were significantly better in the R-CHOP (median of 28 and 40 months, respectively) and R-CHOPr groups (19 and 24 months) than in the R-CVP (7 and 12 months), CHOP (6 and 7 months), and palliative (4 and 6 months) groups ($P < .001$). Other factors significantly affecting PFS or OS in univariate analysis are shown in Supporting Information Table S3. In the multivariate analysis of PFS and OS, treatment with R-CHOP and R-CHOPr maintained the statistical significance, independently of age, CIRS and R-IPI, as shown in Table 3.

TABLE 1 Patient characteristics

Characteristic	N	%
Total number of evaluable patients	252	
Male sex	100	40
Age, years: median (range)	83 (80–100)	
Older than 85	59	23
Histological diagnosis (local Pathology assessment)		
DLBCL de novo	239	95
Transformed DLBCL	4	1
Grade 3B follicular lymphoma	9	4
ECOG 0–1	147	58
Extranodal disease	157	64
2 or more sites	50	23
Central nervous system disease	2	1
Testicular infiltration	5	2
Ann-Arbor Stage I-II	90	36
R-IPI		
Intermediate risk (1–2)	99	41
High risk (3–5)	145	59
CIRS $<$ 6	126	50
Fit patients (CIRS-G)	152	60
Charlson Comorbidity Index		
Low-intermediate (0–1)	177	70
High-very high (2–5)	75	30
First-line treatment		
R-CHOP or similar	108	43
R-CVP or similar	30	12
CHOP or similar	22	9
CVP or similar	9	4
Cyclophosphamide +/- prednisone	46	18
Radiotherapy +/- prednisone	15	6
Rituximab monotherapy	2	1
Splenectomy	1	0.5
No treatment	19	7.5
Number of treatment lines		
1	180	71
2	31	12
$>$2	13	5
Rituximab treatment in first or subsequent lines	147	58
Anthracycline treatment in first or subsequent lines	130	51

BL, Burkitt lymphoma; CIRS, Cumulative Illness Rating Scale; CIRS-G, CIRS revised and validated to reflect common geriatric problems; DLBCL, diffuse large B-cell lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CVP, rituximab, cyclophosphamide, vincristine, prednisone; R-IPI, Revised International Prognostic Index.

TABLE 2 Patient characteristics, response rates and toxicity by first-line regimen

	R-CHOP N = 52	R-CHOPr N = 56	R-CVP N = 30	CHOP N = 22	Palliative N = 55	P
Median age (range) (years)	82 (80–88)	83 (80–92)	84 (80–100)	82 (80–91)	84 (80–93)	.01
< 86 (%)	67	82	73	77	67	.08
CIRS < 6 (%)	48	55	47	77	40	> .1
Fit (%)	69	71	57	50	58	> .1
CCI < 2 (%)	75	79	60	77	60	> .1
R-IPI, high risk (3–5) (%)	44	63	57	86	67	.02
Number of cycles and response						
Median number cycles	5 (1–8)	6 (1–8)	3 (1–8)	4 (1–6)		.01
≥ 4 (%)	60	73	47	54		.09
≥ 6 (%)	42	57	33	32		.08
Complete response (%)	63.5	59.5	47	23	7	<.001
Overall response (%)	75	80	60	36	25.5	<.001
Deaths						
Toxicity (%)	21	9	20	14	11	> .1
Lymphoma (%)	35	29	40	64	67	<.001

CCI, Charlson comorbidity index; CIRS, cumulative illness rating scale; Palliative, includes cyclophosphamide +/- prednisone +/- vincristine; R-CHOP, rituximab, cyclophosphamide, adriamycin, vincristine, prednisone; R-CHOPr: R-CHOP with any type of dose reduction; R-CVP: rituximab, cyclophosphamide, vincristine, prednisone.

3.4 | Prognostic factors of OS in patients treated with R-CHOP

Finally, as the best results were observed in patients treated with R-CHOP and R-CHOPr, we performed a subanalysis of this group (108 patients). In the univariate analyzes of PFS and OS, age < 86 years, CIRS < 6, "fit" patients, CCI < 2 and R-IPI intermediate-risk were associated with better PFS and OS. In the multivariate analysis only age, CIRS and R-IPI were independent prognostic factors of OS. Based on this, a prognostic score was obtained, which revealed two groups with significantly different OS (Supporting Information Figure S2): 3-year OS and PFS were 58% and 50% (median, 45 and 35 months) *vs.* 25% and 22% (median, 12 and 10 months) ($P = .001$), respectively, in patients with 0–1 vs. 2–3 risk factors.

3.5 | Centralized histopathological review

CD20 was expressed in all samples from the 53 cases with sufficient material available for a complete IHC workup. The samples were divided into GCB (33 cases, 62%) and non-GCB (20 cases, 38%) based on the Hans algorithm. 13 cases (15%) were double-positive for MYC and BCL2 and no association with the GCB or non-GCB phenotypes was found ($P = .819$). In 9 cases (17%) CD30+ cells were identified in at least 5% of the neoplastic infiltrate. This prevalence is consistent with previously published results from a large retrospective series.[25] PDL-1 (using clone 22C3) was positive in 6 cases (11%) with no apparent association with EBV infection (none of these cases was EBV positive). It is likely that genetic alterations at the 9q24 locus are related with PDL1 overexpression, in the absence of EBV infection in the tumoral cells.[26] The low prevalence of EBV+ large B-cell lymphoma in this series of very elderly patients should also be noted. We found a single case (2%) of EBV + DLBCL, which is consistent with its prevalence in western populations.[27]

4 | DISCUSSION

In the present study, we have analyzed a large series of patients aged at least 80 years with aggressive B-cell lymphoma treated between 2002 and 2014 in 19 hospitals from the GELTAMO group. Strikingly, only 43% of patients received standard treatment with R-CHOP at full or reduced doses, while the remaining patients received a variety of less intense regimens (15% without any chemotherapeutic agent), and 7.5% received no treatment whatsever. These data reflect two facts already described in other studies[7,8,12]: (i) it is highly likely that very elderly patients with DLBCL will not receive treatment with curative intent; and (ii) there is no standard treatment for patients considered to be frail, i.e., those whose treating physician believes them incapable of tolerating a regimen with curative intent.

In our study, patients treated with R-CHOP at full or reduced doses had good results in terms of OS (median, 40 and 24 months, respectively), significantly better than those receiving R-CVP (12 months), CHOP (7 months) or palliative treatment (6 months). These results are in agreement with those of other groups,[8,9] and indicate that, as in younger patients in whom randomized studies have been conducted, R-CHOP or similar is also the treatment of choice for patients over 80 years old who can tolerate it.

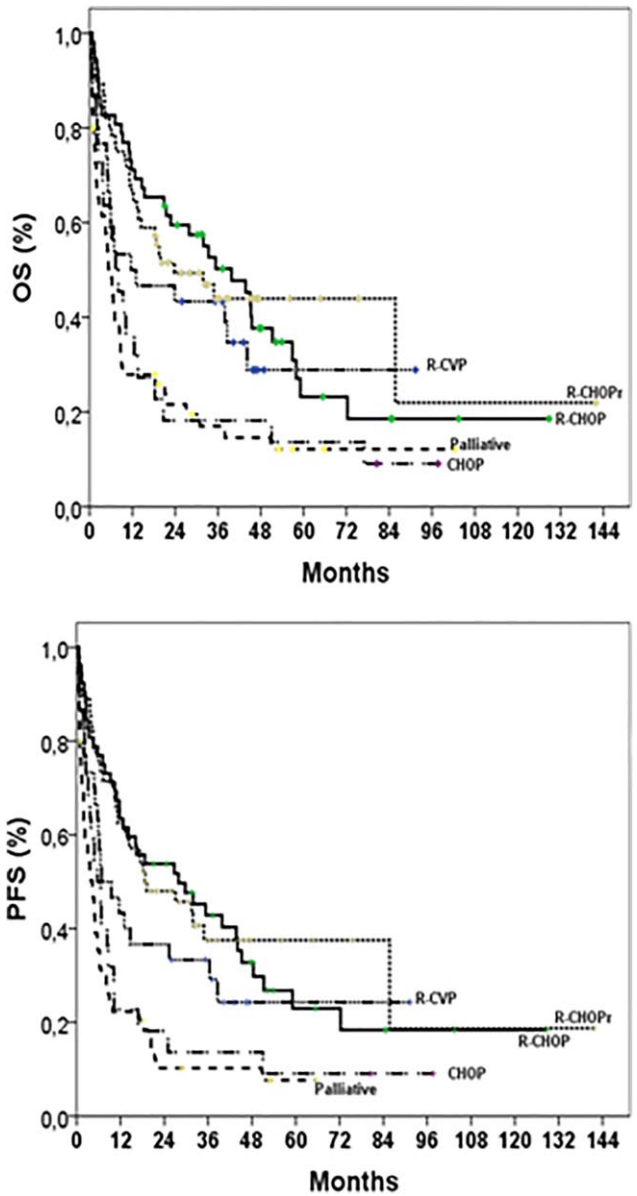

FIGURE 1 Overall survival (OS) and progression-free survival (PFS) by first-line regimen. Median of overall survival in months (95% CI): R-CHOP: 40 (25–55), R-CHOPr: 24 (5–43), R-CVP: 12 (0–35), CHOP: 7 (3–11), Palliative: 6 (4–8), Median of PFS in months (95% CI): R-CHOP: 28 (8–48), R-CHOPr: 19 (3–34), R-CVP: 7 (0–14), CHOP: 6 (2–9), Palliative: 4 (2–6) [Color figure can be viewed at wileyonlinelibrary.com]

In a prospective phase 2 trial, Peyrade et al.[11] investigated the R-mini-CHOP regimen in 149 patients with DLBCL who were more than 80 years of age. This trial confirmed the feasibility and efficacy (49% OS at 4 years) of this reduced R-CHOP in very old patients, and, since then, R-mini-CHOP has become the preferred regimen in many centers for patients over 80 years old. In our study, the best survival results were observed in patients treated with full-dose R-CHOP, but these had higher treatment-related mortality than patients treated with reduced doses. The small numbers of patients in our series who received reduced-dose R-CHOP prevented us reaching firm conclusions about the dose intensity of R-CHOP and its outcomes.

Another finding of our study is the survival benefit to patients receiving rituximab, which proved to be an independent prognostic factor in the multivariate analyzes of PFS and OS in the global series. This is an important finding because published prospective randomized studies comparing R-CHOP with CHOP are limited to patients in the age range of 60–80 years, and there are no published randomized studies demonstrating the benefit of administering rituximab to patients older than 80 years.[11]

Conversely, the presence of comorbidities was a key prognostic factor of survival in our study, although the comorbidity scales did not seem to influence the choice of treatment type (curative or palliative) significantly, as shown in Table 2. All the comorbidity scales analyzed had a prognostic influence on PFS and OS in the univariate analyzes, and the CIRS scale maintained its independent prognostic influence in the multivariate analysis. Other studies have shown the prognostic impact of functional status and comorbidities on survival,[5,9,28–31] indicating that it is very important to identify patients without irreversible comorbidities who have a significantly long life expectancy and who would benefit most from receiving the optimal treatment regimen. However, as pointed out by Bron et al.,[32] the strict application of a scale could lead to undertreatment of patients, thereby undermining their chances of being cured. Therefore, easy-to-use screening tools validated in prospective studies are essential for determining patient fitness, but close collaboration between geriatricians and

TABLE 3 Multivariate analysis of survival in patients treated with chemotherapy

Prognostic factor	PFS RR (IC 95%)	*P*	OS RR (IC 95%)	*P*
Age				
< 86 years	0.7 (0.5-0.9)	.031	0.7 (0.5-0.9)	.041
≥ 86 years				
CIRS				
< 6	0.6 (0.4-0.9)	.004	0.6 (0.4-0.9)	.009
≥ 6				
R-IPI				
Intermediate risk (1–2)	0.6 (0.4-0.8)	.001	0.5 (0.3-0.7)	<.001
High risk (3–5)				
First-line treatment				
R-CHOP	0.4 (0.3-0.7)	<.001	0.5 (0.3-0.8)	.002
R-CHOPr	0.4 (0.2-0.6)	<.001	0.4 (0.3-0.7)	.001
R-CVP	0.7 (0.4-1.2)	.2	0.7 (0.4-1.1)	.1
CHOP	0.9 (0.5-1.5)	.6	0.9 (0.5-1.5)	.6
Palliative				

CIRS, cumulative illness rating scale; OS, overall survival; Palliative, includes cyclophosphamide +/- prednisone +/- vincristine; PFS, progression-free survival; R-CHOP, rituximab, cyclophosphamide, adriamycin, vincristine, prednisone; R-CHOPr: R-CHOP with any type of dose reduction; R-CVP: rituximab, cyclophosphamide, vincristine, prednisone; R-IPI, Revised International Prognostic Index.

hemato-oncologists may also be necessary to better evaluate the fitness of these patients.

In our study, we created a prognostic model based on multivariate analysis of the 108 patients treated with the R-CHOP-like regimen. Patients with 0–1 adverse prognostic factors (aged > 85 years, R-IPI 3–5 or CIRS> 5) had very good results with R-CHOP-like treatment (median OS, 45 months), whereas patients with 2–3 adverse factors had a median OS of only 12 months. This prognostic model may help to select patients who could benefit from a curative treatment with R-CHOP-like immunochemotherapy, although it should be validated in a larger series of patients. Saygin et al.[30] created another prognostic model based on IPI and CCI, although their series ($N = 413$) included patients older than 60 years who were treated in a single center.

Our study, like most of those on very elderly patients with aggressive B-cell lymphomas, has the inherent limitations of retrospective studies. Comorbidity indexes were calculated based on the information collected from the medical records, which entails a potential bias from missing data.

Regarding the histopathological subset analysis, we can conclude that phenotypic heterogeneity in DLBCL of elderly patients mirrors the phenotype profiles found in unselected populations with DLBCL. Novel markers such as CD30 and PDL1, which are overexpressed in a significant fraction of cases, might be potential therapeutic targets with new drugs.

In summary, in very elderly patients with DLBCL, we face the dilemma that an optimal treatment with immunochemotherapy may be curative, but, at the same time, might cause considerable morbimortality in many of them. The results of our study indicate that treatment with R-CHOP at full or reduced doses is associated with very good survival results in a significant proportion of patients. The results of our multivariate analysis have enabled us to develop a simple prognostic model based on age, IPI and the CIRS scale that may help select patients who could benefit from a curative treatment. Further studies with a larger number of patients are needed to validate this prognostic model. Although the presence of comorbidities was a key prognostic factor of survival in our study, the comorbidity scales did not seem to influence the choice of treatment type significantly. So, prospective studies should incorporate comorbidity scales and comprehensive geriatric assessment with the objective of establishing the optimal model for evaluating the fitness of these patients.

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CONFLICT OF INTERESTS

Authors declare no competing financial interests related to the present paper.

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SUPPORTING INFORMATION

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