EBV-positive diffuse large B-cell lymphoma of the elderly: A case series from Peru

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EBV-positive diffuse large B-cell lymphoma (DLBCL) of the elderly is an entity recently included in the WHO classification of lymphoid tumors. We have reviewed our experience and clinical outcomes of this distinct subtype of DLBCL. Between 2002 and 2009, cases of DLBCL were identified from medical records of the Hospital Nacional Edgardo Rebagliati Martins in Lima, Peru, and underwent pathological evaluation including immunohistochemistry for CD20, CD10, bcl-6, MUM1/IRF4, and EBV-encoded RNA in situ hybridization. Clinical data were gathered, tabulated, and reported descriptively. Survival analyses were performed using Kaplan-Meier estimates. Out of 199 cases of DLBCL, 28 cases of EBV-positive DLBCL of the elderly were identified. The median age was 75 years with male predominance (1.5:1). B-symptoms were present in 43%, advanced stage in 50% and International Prognostic Index (IPI) score > 2 in 57% of patients; 68% of patients had a nongerminal center (NGC) phenotype. The complete response rates to R-CHOP and CHOP were 63% and 33%, respectively. The median overall survival (OS) for the group was 5 months. In the univariate analysis, age $\geq$70 years, lymphocyte count <1.0 $\times$ 10^9/L, and advanced clinical stage were associated with worse OS in patients treated with chemotherapy with and without rituximab. EBV-positive DLBCL of the elderly is a clinically aggressive entity with a short OS and typically presents with advanced stage, high IPI score, and a NGC phenotype. Further studies are needed to investigate if rituximab-containing regimens are associated with better response and OS rates in EBV-positive DLBCL of the elderly. Am. J. Hematol. 86:663–667, 2011. © 2011 Wiley-Liss, Inc.

Introduction

The current World Health Organization (WHO) classification of lymphoid tumors describes more than 30 subtypes and establishes morphological, immunophenotypical, genetic, and clinical diagnostic criteria for lymphomas of B- and T-cell lineage [1]. The most common lymphoma worldwide is diffuse large B-cell lymphoma (DLBCL) and it accounts for ~31% of all non-Hodgkin lymphoma histological types [2].

Epstein Barr virus (EBV) infection has been associated to several lymphomas, such as Burkitt [3], plasmablastic [4], NK/T-cell [5], angioimmunoblastic [6], Hodgkin [7], hydroa-like T-cell lymphoma [8] and lymphomas associated with HIV infection, as well as post-transplant lymphoproliferations, and after exposure to certain cytotoxic or immunomodulator agents. However, the association between EBV and DLBCL in otherwise immunocompetent patients is matter of intense investigation.

In the latest update of the WHO classification of lymphoid tumors, a new provisional entity, EBV-positive DLBCL of the elderly, was incorporated [9]. The proposed diagnostic criteria include a pathological diagnosis of a CD20-positive DLBCL with expression of EBV by the malignant cells in a patient older than 50 years without underlying immunodeficiency. To the authors' knowledge, this is the first report on the pathological and clinical characteristics of EBV-positive DLBCL of the elderly from South America.

Patients and Methods

Between January 2002 and December 2009, all newly diagnosed patients with DLBCL were identified from the medical records of the Hospital Nacional Edgardo Rebagliati Martins in Lima, Peru. Pathological samples were retrieved and re-evaluated by two hematopathologists (DM and PQ). Each case underwent immunohistochemical evaluation using antibodies against CD20 (Dako, Carpinteria, CA: dilution 1:100), CD10 (Novocastra, Newcastle upon Tyne; UK; dilution 1:100), bcl-6 (Dako; dilution 1:10), and MUM1/IRF4 (Santa Cruz Biotechnology, Santa Cruz, CA; dilution 1:200). A cutoff of 30% expression was used to consider a sample positive for CD10, BCL6, and MUM/IRF4, according to the Hans algorithm [10]. The presence of EBV was evaluated by detecting EBER using a fluorescein-labeled peptide nucleic acid (PNA) probe (Dako) in conjunction with the Dako PNA in situ hybridization (ISH) detection kit for formalin-fixed paraffin-embedded tissue sections. The presence of EBER in $\geq$20% of malignant cells was considered positive. Cases of EBV-positive DLBCL of the elderly were defined by (1) age older than 50 years, (2) no clinical and/or laboratory evidence of immunodeficiency, (3) diffuse large cell morphology with positive expression of CD20, and (4) EBV-encoded RNA [11] positivity in the tumor cells. Transformed and primary cutaneous variants of DLBCL were excluded. Patients with clinical or laboratory evidence of coinfection by human immunodeficiency virus (HIV), hepatitis B, hepatitis C, or human T-lymphotrophic virus-1 were also excluded. Patients with clinical suspicion of immunodeficiency such as chronic infections, chronic diarrhea, and chronic eczema were excluded. Similarly, patients with history of chronic disease associated with leucopenia or lymphopenia, or low immunoglobulin levels were excluded. Clinical data including age, sex, complete blood counts, Eastern Cooperative Oncology Group (ECOG) performance status, presence of B symptoms, lactate dehydrogenase (LDH) levels, Ann Arbor stage, extranodal involvement, International Prognostic Index (IPI) score [12], therapy received, response to

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Conflict of interest: Nothing to report

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Received for publication 31 March 2011; Revised 30 April 2011; Accepted 3 May 2011

Am. J. Hematol. 86:663–667, 2011.

Published online 9 May 2011 in Wiley Online Library (wileyonlinelibrary.com).
DOI: 10.1002/ajh.22078

TABLE I. Clinical Characteristics of 28 Cases of EBV-Positive DLBCL of the Elderly

Case	Age	Sex	ECOG	LDH	Extranodal sites	Stage	B symptoms	IPI score	Oyama score[a]	Therapy	Response	Survival (months)	Outcome	Cause of death
1	69	F	2	Elevated		3	Present	4	1	RCHOP	CR	37	AWOD	
2	73	M	0	Normal	Tonsil	2	Absent	1	1	RCHOP	CR	19	AWOD	
3	74	M	1	Normal	Lung, ileum	4	Absent	3	1	RCHOP	CR	20	Dead	Lymphoma
4	74	M	0	Elevated	Stomach[b]	1	Present	2	2	RCHOP	PR	4	AWD	
5	75	F	2	Normal		2	Present	3	2	RCHOP	NR	4	AWD	
6	80	F	2	Normal		2	Present	2	2	RCHOP	CR	7	AWOD	
7	80	M	1	Normal	Cecum	2	Absent	2	2	RCHOP	NR	1	Dead	Lymphoma
8	81	M	1	Normal	Tonsil	2	Absent	1	1	RCHOP	CR	11	AWOD	
9	51	M	0	Normal		1	Absent	0	0	CHOP	CR	40	AWOD	
10	54	F	1	Normal		2	Absent	1	0	CHOP	CR	44	AWOD	
11	59	M	1	Normal		1	Absent	1	0	CHOP	CR	58	AWOD	
12	66	M	1	Normal	Stomach[b]	1	Absent	2	1	CHOP	CR	64	AWOD	
13	67	F	0	Elevated		3	Absent	3	0	CHOP	NR	18	AWOD	
14	71	M	4	Normal	Bone marrow	3	Present	3	2	CHOP	NR	12	Dead	Lymphoma
15	73	M	4	Normal		3	Absent	3	1	CHOP	NR	5	Dead	Lymphoma
16	73	F	3	Elevated		3	Present	4	2	CHOP	NR	1	Dead	Lymphoma
17	78	M	2	Elevated		3	Present	3	2	CHOP	NR	1	Dead	Lymphoma
18	79	M	3	Elevated	Peritoneum	4	Absent	4	3	CHOP	NR	1	Dead	Lymphoma
19	84	M	2	Elevated	Bone marrow	4	Present	4	2	CHOP	NR	2	Dead	Lymphoma
20	85	M	1	Normal		2	Absent	1	1	CHOP	CR	8	Dead	PJP
21	72	F	3	Normal		3	Absent	3	2	BSC		0	Dead	Lymphoma
22	73	F	4	Normal		3	Present	3	2	BSC		0	Dead	Lymphoma
23	78	F	4	Elevated	Pleura	4	Present	4	2	BSC		0	Dead	Lymphoma
24	81	F	4	Elevated	Bone	4	Present	5	2	BSC		4	Dead	Lymphoma
25	84	M	3	Elevated	Palate	4	Present	4	2	BSC		1	Dead	Lymphoma
26	86	F	1	Normal	Cecum	2	Absent	2	1	BSC		2	Dead	Lymphoma
27	88	M	2	Elevated	Stomach[b]	1	Absent	3	1	BSC		4	Dead	Lymphoma
28	95	M	3	Normal		2	Absent	2	1	BSC		5	Dead	Lymphoma

AWD, Alive with disease; AWOD, Alive without disease; BSC, best supportive care; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CR, complete response; ECOG, Eastern Cooperative Oncology Group; F, female; IPI, International Prognostic Index; LDH, lactate dehydrogenase; M, male; NR, no response; PJP, *Pneumocystis jiroveci* pneumonia; PR, partial response; R, rituximab.

[a] The Oyama score includes age $\geq$70 years and presence of B symptoms as adverse risk factors, dividing cases in three risk groups, low (0 factors), intermediate (1 factor), and high risk (2 factors).

[b] Primary extranodal disease.

therapy, and overall survival (OS) in months were gathered. The Oyama score, which uses age $\geq$70 years and presence of B symptoms to subdivide cases in three risk categories, was also calculated [13].

Clinical and pathological data are presented using descriptive statistics. Overall survival (OS) was defined as the time elapsed since initial lymphoma diagnosis and time of death or last follow up. Univariate survival analyses were performed using the Kaplan-Meier method for incomplete observations. The calculated survival curves were compared using the log-rank test. Multivariate survival analyses were not attempted due to the small number of cases. All graphics and calculations were obtained using the statistical software MedCalc version 11.5.1.0 (Mariakerke, Belgium).

Results

A total of 199 new cases of DLBCL were identified, from which 39 cases were positive for EBER expression. Five cases were excluded because of underlying immunodeficiency (two patients were HIV-positive, one patient was on methotrexate for rheumatoid arthritis, and two pediatric patients had congenital immunodeficiency), four cases because they were younger than 50 years, and two cases because of incomplete data. Based on the above definition, 28 patients met the criteria for EBV-positive DLBCL of the elderly, for an incidence rate of 14%.

Median age at diagnosis was 75 years, ranging from 51 to 95 years. With regard to sex, 17 patients were men and 11 were women (61% and 39%, respectively) with a male-to-female ratio of 1.5:1. Hemoglobin levels of $<$10 g/dL, platelets $<150 \times 10^9$/L, and lymphocytes $<1.0 \times 10^9$/L were seen in 61%, 21%, and 37% of the patients, respectively. ECOG performance status $>$1 was seen in 18 patients (64%), LDH levels were elevated in 11 (41%), and advanced clinical stages (i.e., Stage III or IV) were seen in 14 (50%). Fourteen patients (50%) presented exclusively with nodal disease, 11 patients (39%) had nodal and extranodal involvement, and three patients (11%) had primary extranodal disease, involving the stomach in all cases. The extranodal sites of involvement were gastrointestinal tract (n = 6), lung (n = 3), oropharynx (n = 3), bone marrow (n = 2), adrenals (n = 1), skin (n = 1), and bone (n = 1). B symptoms were reported in 12 cases (43%) and IPI scores $>$2 were seen in 16 cases (57%). Low, intermediate, and high Oyama scores were seen in 5 (18%), 12 (43%), and 11 (39%) patients, respectively. Complete clinical data are shown in Table I.

Histologically, all cases showed a diffuse pattern, composed of large cells; the majority appearing as monomorphic with a centroblastic or immunoblastic morphology, frequent mitoses, and usually associated with necrosis (68%). The remaining cases (32%) appeared polymorphic and showed large neoplastic cells with immunoblastic morphology admixed with variable amounts of small lymphocytes and histiocytes. All cases showed scattered Reed-Sternberg-like cells. By immunohistochemical studies, all cases uniformly expressed CD20 and showed expression of EBER by ISH. According to the Hans' classification, 19 patients (68%) had a non-germinal center (NGC) and nine (32%) had a germinal center (GC)-like phenotype. Images from a case of EBV-positive DLBCL of the elderly with an NGC profile are shown in Fig. 1. Ki-67 was evaluated in 14 patients, and the median rate of expression was 80% (range 50–90%). CD30 expression was positive in the Reed-Sternberg-like cells in 9 out of 10 patients tested (90%). Complete pathological data are shown in Table II.

With regard to therapy, 20 patients (71%) received chemotherapy; from which 12 patients (60%) received cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) and eight patients (40%) received rituximab in combination with CHOP (R-CHOP). Eight patients (29%) did not receive chemotherapy due to rapid progression of disease or poor performance status. In patients treated with CHOP or R-CHOP, a complete response (CR) was

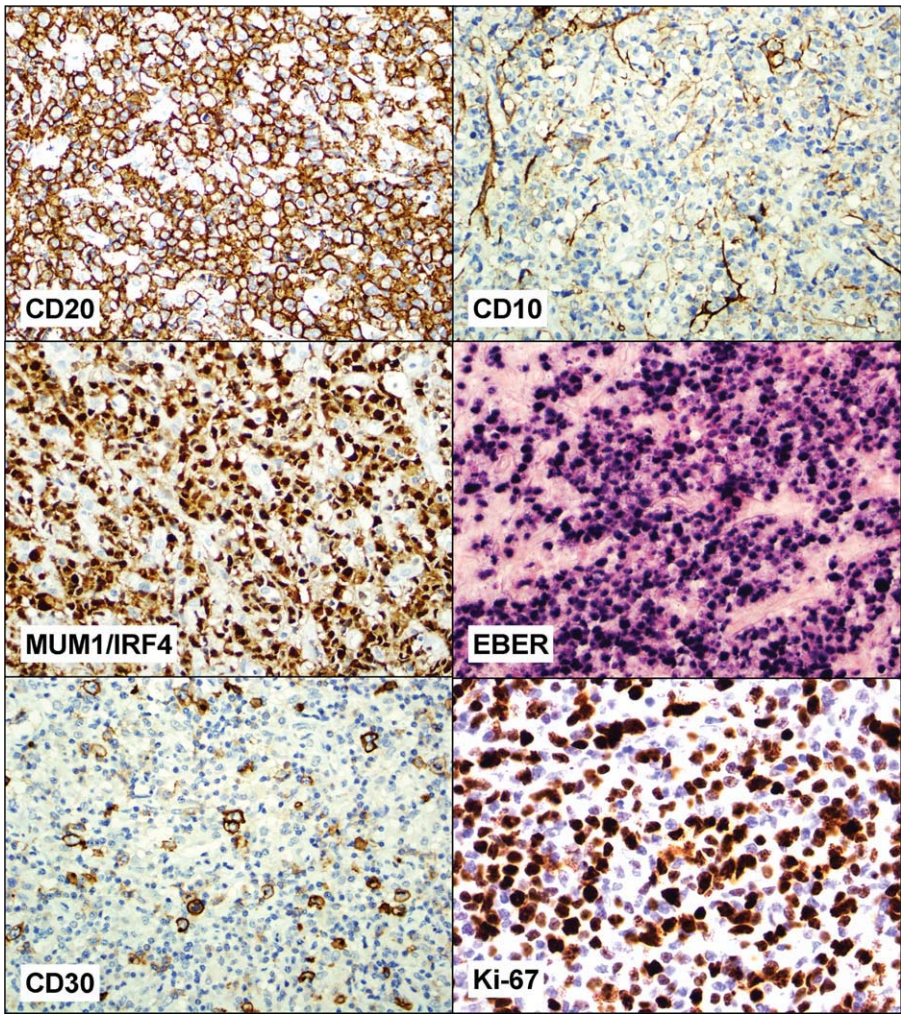

Figure 1. Immunohistochemical profile of a case of EBV-positive DLBCL of the elderly. CD20 positive, CD10 negative, and MUM1/IRF4 positive, suggesting a non-germinal center origin. EBER in situ hybridization showing presence of EBV genome within the malignant large B-cells. CD30 expression by Reed-Sternberg-like cells and a high proliferation index. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

achieved in 10 patients (50%), one patient (5%) had a partial response and nine patients (45%) did not respond to therapy. The CR rates to RCHOP and CHOP were 63% and 33%, respectively ($P = 0.3$). Regarding outcome, 75% and 33% of the RCHOP and CHOP groups, respectively, were alive at the time of this report ($P = 0.17$).

After a median follow up of 32 months, 18 patients (64%) have died; the large majority (83%) from lymphoma progression. The median overall survival (OS) for the entire group was 5 months and the 3-year OS was 33% (Fig. 2A). Six patients (21%) have survived for longer than 24 months. Patients who received R-CHOP ($n = 8$) or CHOP ($n = 12$) had median OS of 20 and 8 months, respectively, in contrast to a median OS of 1.5 months in patients who did not receive therapy ($n = 8$) ($P = 0.002$). However, the difference between the R-CHOP and CHOP groups was not statistically significant ($P = 0.3$). In patients who received R-CHOP or CHOP ($n = 20$), clinical variables associated with a worse median OS were age $\geq$70 years ($n = 14$; $P = 0.002$), advanced clinical stage ($n = 9$; $P = 0.02$), and an ALC of $<1.0 \times 10^9$/L ($n = 4$; $P = 0.004$). ECOG performance status > 1 ($n = 10$; $P = 0.06$), hemoglobin $<$10 g/dL ($n = 3$; $P = 0.06$), platelets $<200 \times 10^9$/L ($n = 5$; $P = 0.05$), and elevated LDH levels ($n = 7$; $P = 0.1$) showed a trend toward worse OS rates. Male gender and NGC phenotype were not statistically associated with a worst median OS. Patients with low/low-intermediate IPI scores (IPI score 0–2; $n = 10$) had a median OS of 64 months versus 5 months in patients with high/high-intermediate IPI scores (IPI score 3–5; $n = 10$) ($P = 0.03$; Fig. 2B). Following the Oyama score, the median OS was 64 months in patients with no risk factors ($n = 5$) and 8 months in and patients with one or two risk factors ($n = 15$) ($P = 0.01$; Fig. 2C).

Discussion

This report represents the first South American research of a detailed series of cases diagnosed with EBV-positive DLBCL of the elderly, an entity provisionally included in the latest WHO classification of lymphoid tumors [9]. We found that age >70, advanced stage and ALC $<1.0 \times 10^9$/L are associated with a worse OS rate, and it is suggested that R-CHOP may derive on better CR and OS rates than CHOP in patients with EBV-positive DLBCL of the elderly. It is important to note that the Peruvian health system is highly centralized and affected patients proceeding from distant geographic regions must plan to travel from several hours to few days to reach tertiary hospitals. Thus, delays of diagnosis and therapy are not uncommon and may explain the high number of patients who were not suitable candidates for therapy.

The incidence of EBV-positive DLBCL of the elderly seems to be variable depending on the geographical

location. Asian studies have shown an incidence ranging between 5 and 11% [13–15], whereas in Western populations, the incidence is lower than 5% [16,17]. In a previous study from our group [18], we found that 15% of our de novo DLBCL patients were EBV-positive. In the present report, we have an incidence of 14%, which is one of the highest reported to date. Although the pathophysiology of EBV-positive DLBCL of the elderly has not been fully elucidated, a close interaction is likely between chronic EBV infection, immunosenescence, and other potential factors such as HLA phenotype [19]. For instance, patients with EBV-positive DLBCL of the elderly can present with Type 2 and 3 EBV latency patterns, which are seen in patients with severe immunodeficiency, such as AIDS and post-transplant states [19]. Immunosenescence refers to an age-related process characterized by decreased number and function of T-cells in peripheral blood and lymph nodes, apoptosis dysregulation, and elevation of levels of proinflammatory molecules [20–23].

TABLE II. Immunophenotypical Characteristics of 28 Cases of EBV-Positive DLBCL of the Elderly

Case	CD10	BCL6	MUM1/IRF4	Profile	BCL2	CD30[a]	Ki-67	EBER
1	−	−	+	NGC				+ (50%)
2	−	+	+	NGC	+		80%	+ (30%)
3	−	−	+	NGC		+		+ (20%)
4	−	−	+	NGC		+	75%	+ (100%)
5	−	−	+	NGC			80%	+ (60%)
6	−	−	+	NGC	+			+ (30%)
7	+	−	−	GC	−	−	70%	+ (30%)
8	−	−	+	NGC	−		70%	+ (40%)
9	−	−	+	NGC				+ (50%)
10	−	+	−	GC			60%	+ (50%)
11	−	−	+	NGC	+	+	80%	+ (70%)
12	−	−	+	NGC	+		90%	+ (80%)
13	−	+	+	NGC				+ (100%)
14	−	−	+	NGC			90%	+ (60%)
15	+	+	−	GC			70%	+ (80%)
16	+	+	−	GC		+	90%	+ (40%)
17	−	+	+	NGC			50%	+ (30%)
18	−	−	+	NGC				+ (50%)
19	+	−	−	GC			90%	+ (60%)
20	+	+	−	GC				+ (70%)
21	−	−	+	NGC		+		+ (70%)
22	+	+	−	GC				+ (100%)
23	−	−	+	NGC				+ (50%)
24	+	+	−	GC			80%	+ (30%)
25	−	+	+	NGC		+		+ (40%)
26	+	+	−	GC				+ (80%)
27	−	−	+	NGC		+		+ (40%)
28	−	−	+	NGC		+		+ (30%)

EBER, EBV-encoded RNA in situ hybridization; GC, germinal center; NGC, non-germinal center.

[a] Expression in Reed-Sternberg-like cells.

Pathologically, diffuse large cell morphology, frequent necrosis, and scattered Reed-Sternberg-like cells are commonly seen. The malignant cells are CD20-positive and frequently have a NGC phenotype as defined by Hans and coworkers [19]. More recent studies have suggested the use of additional antibodies to obtain a better correlation with gene expression profiles [24,25]. However, due to economical restrictions, we were not able to perform onerous additional testing required. Furthermore, we believe that our overall distribution of cases with GC versus NGC phenotypes would be maintained whether we used the newly proposed testing.

On the basis of a multivariate analysis, Oyama et al. developed a prognostic index for EBV-positive DLBCL of the elderly, determined by two factors: age >70 years and the presence of B symptoms [13]. Patients with zero, one, or two factors showed median OS of 56, 25, and 9 months, respectively. Our experience demonstrates similar results,

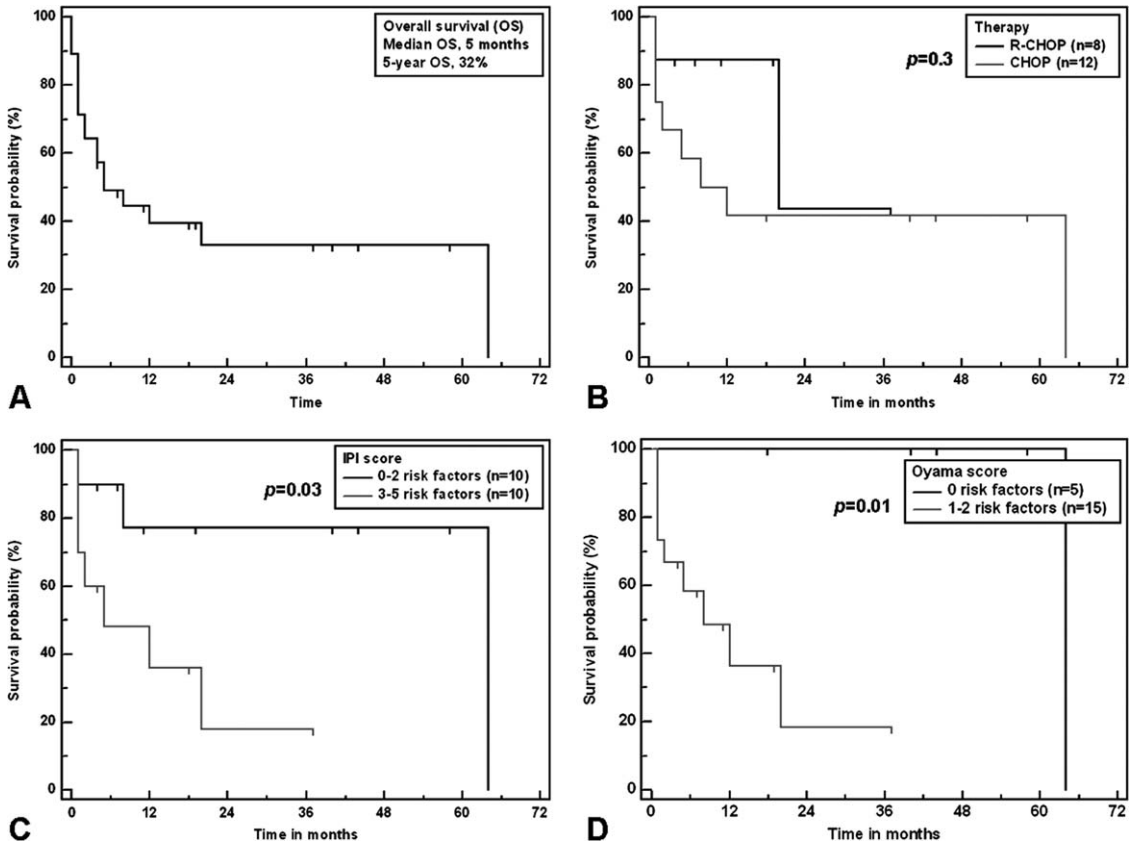

Figure 2. Kaplan-Meier survival estimates in 28 cases of EBV-positive DLBCL of the elderly according to therapy (A), and in 20 patients treated with chemotherapy or chemoimmunotherapy (B), and according to IPI score (C) and Oyama score (D).

with median OS of 64, 14, and 12 months, respectively. In our cohort of patients, both the IPI and the Oyama score performed well as risk-stratifying tools. Lymphopenia arose as a novel prognostic marker in patients with EBV-positive DLBCL of the elderly treated with chemotherapy or chemoimmunotherapy, which is consistent with previous studies in patients with DLBCL [26,27].

Few studies have investigated the potential predictive and/or prognostic role of EBV in patients with DLBCL. Park et al. showed that EBER-positive DLBCL patients showed poorer clinical response and worse OS rates than EBER-negative patients [15]. In a prior study from our group [18], the presence of EBER in DLBCL patients was also independently associated with a worse prognosis. It is important to note that these studies did not include patients treated with rituximab-containing regimens. Hence, the role of EBV in DLBCL in the rituximab era is unclear. In this case series, eight patients received rituximab in combination with CHOP. Rituximab is a very expensive medication for our health system; therefore, a subset of our patients could not afford it. Despite this limitation, our study suggests that treatment with R-CHOP might be associated with better CR rates and better outcomes. To the best of our knowledge, this is the largest series on patients with EBV-positive DLBCL of the elderly treated with R-CHOP ($n = 8$).

Novel strategies are been developed to treat EBV-positive lymphoma. Ganciclovir is a nucleoside analog that incorporates into DNA to promote growth arrest. EBV-infected B-cells, however, are inherently resistant to ganciclovir due to lack of thymidine kinase [22]. Arginine butyrate can induce the formation of TK in resting B-cells [28], and the combination of arginine butyrate and ganciclovir induced clinical responses in 10 of 15 patients (67%) diagnosed with EBV-positive lymphoma [29]. Preclinically, bortezomib [30] and simvastatin [31] have shown to be effective at inducing apoptosis in EBV-positive lymphoblastoid cell lines (LCLs) and at delaying onset of lymphoma and increasing survival in SCID mice injected with EBV-positive LCLs. Both medications seem to exert their effect by blocking NF-kB pathway signaling. Many trials for the treatment of lymphomas are currently ongoing using autologous and/or allogeneic EBV-specific cytotoxic T-cells [31]. However, none of these potentially effective strategies are currently been investigated in patients with EBV-positive DLBCL of the elderly.

Conclusions

We present clinical and pathological data from 28 Peruvian patients with a diagnosis of EBV-positive DLBCL of the elderly. On the basis of our findings, patients older than 70 years, with ALC $<1.0 \times 10^9$/L, and advanced stage show a worse OS rate. Also, our study suggests that R-CHOP may be associated with improved CR and OS rates in these patients. Further research is necessary to fully understand the pathogenetic mechanisms and prognostic factors in order to improve therapies in patients with EBV-positive DLBCL of the elderly. To date, there have not been prospective or randomized studies evaluating the incidence or therapy for EBV-positive DLBCL of the elderly.

Acknowledgments

Preliminary results from this study have been presented at the American Society of Clinical Oncology Annual Meeting in Chicago, Illinois, June 4–8, 2010 and the 52nd American Society of Hematology Annual Meeting in Orlando, Florida, December 4–7, 2010.

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