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ORIGINAL ARTICLE

Clinical characteristics and treatment response in adult patients with non-Hodgkin's chronic lymphocytic leukemia (CLL)

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Abstract

Objective: *To determine comorbidities, clinical characteristics, and treatment response in adult patients with chronic lymphocytic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL), and follicular lymphoma (FL).* **Methods:** *The design was observational from reviewing the medical records of patients seen in outpatient and inpatient settings. It included ≥ 50 subjects who demanded attention during the period 2008-2012 and that met specific inclusion/exclusion criteria. The main measures were: comorbidity (population group), clinical stage, patient treatment, response to treatment, overall survival, progression-free survival, and mortality. Statistical analysis: p < 0.05.* **Results:** *270 patients (CLL = 90, DLBCL = 81, FL = 99) were recruited, with a mean age of 72.5, 65.5, and 62.4 years, respectively. These groups of neoplasms, compared with the general population, showed a higher percentage of men (60.0, 56.8 and 52.6 vs. 46.2%) and morbidity (Charlson Comorbidity Index: 1.6, 1.5, 1.4 vs. 0.4, respectively; p < 0.05). The administration of chemotherapy treatment was 28.9 vs. 86.4 and 90.9%, respectively (p < 0.001). Overall survival at five years was 84.4, 45.0 and 68.5%, respectively (p = 0.027), while mortality rates were 17.0 vs. 35.3 and 20.6%, respectively (p = 0.041). Compared with other treatments, with administered rituximab the median progression-free survival was 6.8 vs. 4.2 years (p < 0.001). These differences were maintained for the three neoplasms.* **Conclusions:** *Comorbidity associated with hematological malignancies is high. The chronic lymphocytic leukemia group showed increased survival with lower mortality rate. Rituximab showed a higher progression-free survival in these neoplasms.*
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Introduction

Hematological neoplasms are characterized by high clinical heterogeneity, mainly owing to genetic alterations their cells can display[1]. These variations lead to proto-oncogenes activation or tumor-suppressant genes inactivation, which promote genomic unstability[2]. Among these tumors, chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphoma (NHL) are to be especially noted.

CLL (B-cell) is the most common form of leukemia in adults (25%): its incidence is 3-4 cases/100,000 inhabitants/year, and it increases with age (only 10-15% of

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patients are younger than 55 years[3]). In the past few years, large advances have been produced in the diagnosis and treatment of CLL[4]. Clinical evolution of patients with CLL is characterized by a continuous sequence of treatment responses and relapses, with a shortening of progression-free survival (PFS) over the cycles[5-8]. Clinical staging systems (Binet, Rai) are the most widely used indices in practice to establish the disease prognosis. CLLs in pro-lymphocitic transformation and CD38 and ZAP70-expressing patients exhibit lower survival[9].

NHLs account for 3-5% of cancer deaths, and their yearly incidence rate in our part of the world is 9 cases/100,000 inhabitants. They comprise a heterogeneous group of lymphoid neoplasms with different clinical and evolutionary behaviors. From all of them, diffuse large cell lymphoma (DLCL) and follicular lymphoma (FL) are highly frequent. The diffuse large B-cell lymphoma (DLBCL) is the most common type of lymphoma (30-50% of all new cases). More than half of the patients are older than 60 years, although it can appear at any age. The incidence rate in Europe is 3-4/100,000 inhabitants/year. It is a disease with aggressive clinical behavior, but curable[10]. FL is the second most frequent type of NHL, and its incidence has increased in recent years; in Spain, it accounts for 22-40% of all NHLs[11]. Most patients with FL present with advanced stage at diagnosis and, in spite of its relatively good prognosis, are still incurable with conventional treatments[12].

Rituximab, a monoclonal antibody that specifically binds to the CD20 antigen, has demonstrated efficacy and safety in patients with CLL and NHL. The therapeutic goal is to obtain the highest response with the least toxicity and best possible quality of life for the patient. For this, treatment has to be adjusted according to the patients' characteristics[13-16].

Studies available in Spain on the prevalence and impact of these hematological neoplasms are limited. Additionally, the administered treatments generate an elevated consumption of resources associated not only with pharmacological cost, but also with its preparation and administration and, hence, the conduction of this study could be relevant. The purpose was to determine associated comorbidities, clinical characteristics, administered hospital treatments and treatment response in adult patients with CLL, DLCL and FL; the cost associated with the preparation and administration of rituximab (as monotherapy or in combination with other chemotherapies) was assessed as well.

Patients and methods

Design and study population

A multi-center, longitudinal observational study was conducted, based on the review of medical records (electronic databases) of patients followed-up in the out- and inpatient settings. The study population was comprised by subjects pertaining to 6 primary care centers (*Apenins-Montigalà*, *Morera-Pomar*, *Montgat-Tiana*, *Nova Lloreda*, *Martí-Julià* and *El Progrés*) and 2 hospital centers (*Hospital Municipal* and *Hospital Universitari Germans Trias I Pujol*) from Badalona. The majority of the population assigned to the centers (105,200 inhabitants) was urban, of middle-low socioeconomic status and predominantly industrial.

Inclusion and exclusion criteria

The study included all patients who had sought outpatient and/or inpatient care between January 1, 2008, and December 31, 2012, and who had the following characteristics: ≥ 50 years of age; either gender; diagnosed with CLL, DLCL or FL, and whose follow-up could be warranted for at least 15 months after diagnosis or, by default, until death. Subjects who moved or were referred to other municipalities, and those with more than one concomitant hematological neoplasm were excluded.

CLL, DLCL and FL diagnosis

The diagnosis was obtained based on the International Classification of Primary Care (ICPC-2; codes B73, B74)[17] and on the International Classification of Diseases, 9th revision, clinical modification; ICD-9-CM (CLL: 204.1; DLBCL: 200.7; FL: 200, 202 and 208 [specific epigraphs]). The CLL diagnosis was established according to the International Workshop on Chronic Lymphocytic Leukemia criteria[18], which consider that peripheral blood must display absolute, persistent lymphocytosis with values higher than 5,000 or 10,000 lymphocytes; these lymphocytes have to be monoclonal and with the previously-described phenotype. Bone marrow must show lymphocyte infiltration higher than or equal to 30%. The NHL diagnosis was performed according to criteria established by scientific societies[19,20], according to which, accurate diagnosis is established by means of a biopsy (according to the situation). The inclusion criteria were based on baseline data at diagnosis.

Sociodemographic and comorbidity variables

The main variables of the study were the following: age (continuous and by ranges: 50-64, 65-74 and ≥ 75 years), gender and personal history (ICPC-2)[17]: hypertension (K86 and K87), diabetes mellitus (T90), lipid disorder (T93), obesity (T82), tobacco abuse (P17), chronic alcohol abuse (P15), all types of organ failure (heart, liver and kidney), ischemic heart disease (codes K74, K76 and K75), stroke (K90, K91 and K93), chronic obstructive pulmonary disease (COPD) (R95, chronic obstruction of the airflow), bronchial asthma (R96), dementia or memory disturbances (P70 and P20), neurological conditions (Parkinsonism [N87], epilepsy [N88], multiple sclerosis [N86] and other neurological diseases [99]), depressive disorder (P76), HIV (B90) and viral hepatitis (D72). The number of chronic diagnoses, in addition to the Charlson's comorbidity index[21], as an approach to the seriousness of the patient's condition, as well as the individual index of recorded cases, obtained using the Adjusted Clinical Groups (ACG), which is a system of patient classification by isoconsumption of resources, were used as a general comorbidity summary variable[22]. The ACG application provides the bands of resources use (BUR – *Bandas de Utilización de Recursos*), whereby each patient, according to his/her general comorbidity, is grouped in one of five mutually excluding categories (1: healthy or very low morbidity users; 2: low morbidity; 3: moderate morbidity; 4: high morbidity, and 5: very high morbidity). The following biochemical and anthropometric parameters were also determined: body mass index (BMI, kg/m^2), serum creatinine (mg/dl) and body surface area (in CLL and NHL, m^2).

Clinical process variables

The following variables were obtained at diagnosis: date of diagnosis, Eastern Cooperative Oncology Group (ECOG) performance status, which measures the quality of life of a cancer patient, and clinical stage (which details the disease prognosis); these were the following: Rai and Binet classifications[18] for CLL, International Prognostic Index[19] for DLCL and International prognostic Index 2[20] for FL.

Administered treatment, treatment response and survival

This was a non-interventional study where both information and clinical data of patients treated in the past were collected (retrospective). Assignation of a patient to a specific strategy was determined by standard practice. Records of the administered drugs were obtained:

- In CLL: R: rituximab (monotherapy), R-FC: rituximab + fludarabine + cyclophosphamide, F: fludarabine, FC: fludarabine + cyclophosphamide, and other combinations.
- In NHL: R: rituximab (monotherapy), R-CHOP: rituximab + cyclophosphamide + adriamycin + vincristine + prednisone, and other combinations.

In addition, treatment was assessed as being administered in first or second line/relapse and whether bone marrow transplantation, blood transfusion and/or radiotherapy were carried out concomitantly with the pharmacological treatment. The number of cycles (period of treatment followed by a period of recovery) was quantified for each patient.

The following was considered as treatment response: stable disease, tumor reduction (partial or complete) and disease progression according to clinical criteria. With regard to survival: progression-free survival (PFS, time elapsed from treatment initiation to disease progression or death), overall survival (OS) (period elapsed from treatment administration to the last recorded follow-up or death of the patient) and 5-year OS rate (percentage of patients alive after 5 years). Death (direct cause or tumor-related) and discontinuation due to side effects related to drug administration were also taken into account.

Treatment preparation and administration-associated costs

The cost system of was quantified taking into account the organizations' characteristics and the degree of development of available information systems. Drug preparation (hospital pharmacy) and administration (day hospital) times were analyzed according to whether it was rituximab (monotherapy o combination) for each study group (CLL, DLCL, FL). Cost/patient average/unit was calculated by multiplying the time by the equivalent wages of the technical personnel, nurse or pharmacist (source: own analytical accounting). The preparation process time was measured from the extraction, dilution and mixture of the preparation until its storage, whereas administration time was measured from pre-medication until the completion of the intravenous infusion. The information was obtained from the centers' electronic records.

Information confidentiality

Confidentiality of the records was respected as stated by the Data Protection Organic Law (15/1999, of December 13), by dissociating the information. The study was classified by the Spanish Agency of Dugs and Healthcare Products (AEMPS – *Agencia Española de Medicamentos y Productos Sanitarios*) as a post-marketing-other designs trial and subsequently approved by the Clinical Research Ethics Committee of *the Hospital Universitari Germans Trias I Pujol* of Badalona, in Barcelona.

Statistical analysis

A descriptive univariate statistical analysis was conducted, with mean and standard deviation values and 95% confidence intervals (CI), and normality of distribution was verified with the Kolmogorov-Smirnov test. The chi-square test and the variance analysis were used in the bivariate analysis; in case the conditions for their use were not met, the Kruskal-Wallis or Mann-Whitney's U non-parametrical tests were used. To quantify survival, the Kaplan-Meier curves were used, with median time estimates (in years). A logistic regression analysis was carried out to obtain variables associated with the profile of the patient with CLL and NHL (dependent variable), in comparison with a population group, with the enter procedure (statistic: Wald). By means of this procedure, mortality-associated factors were also quantified (procedure: consecutive steps). The SPSSWIN, version 17, software was used, and statistical significance was established for p-values < 0.05.

Results

Of an initial selection of 47,576 subjects ≥ 50 years of age assigned to the centers, 42,815 were regularly treated during the study period. In total, 6.5% (n = 292) had the selected diagnoses (CLL: n = 95, 2.2%; 95% CI: 1.8-2.6%; DLCL: n = 86; 2.0%; 95% CI: 1.6-2.4%; FL: n = 101; 2.3%; 95% CI: 1.8-2.7%). Twenty-two patients were excluded: 10 because of having CLL + NHL, 10 were lost to follow-up and 2 because the diagnosis was not clearly confirmed. Finally, 270 patients were recruited (age range: 50-89 years): 90 with CLL, 81 with DLCL and 99 with FL. A reference population-based group within the same age range was selected (n = 35,035).

Baseline characteristics of the study population in comparison with a population-based group are detailed in table 1. The CLL group had a mean age higher than the population-based group: 72.5 versus 64.1 years (p < 0.01). The CLL, DLCL and FL groups showed a higher percentage of males than the general population (60.0, 56.8 and 52.6 vs. 46.2%; p < 0.05), as well as higher burden of general morbidity (Charlson average: 1.6, 1.5 and 1.4 vs. 0.4; p < 0.001) and lower rates of dyslipidemia (33.3, 35.8 and 31.6 vs. 50.7%; p < 0.05) and obesity (16.7, 14.8 and 15.5 vs. 20.9%; p < 0.05). In the logistic model, when compared with the population-based group, CLL was associated with age (odds ratio [OR]: 1.1; 95% CI: 1.0-1.2) and the Charlson index (OR: 2.8; 95% CI: 2.3-3.3), whereas NHLs (DLCL and FL) were associated with Charlson's index (OR: 2.4; 95% CI: 1.9-2.8; p < 0.01) and viral hepatitis (OR: 1.2; 95% CI: 1.1-1.4; p < 0.01).

Patient distribution, clinical stages and administered treatments by study group are described in table 2. Chemotherapy administration was 28.9, 86.4 and 90.9% for CLL, DLCL and FL, respectively.Administered chemotherapy by study group is detailed in table 3. Treatment administration as first line was slightly higher for CLL: 84.6 versus 67.1 and 72.6%, respectively (p < 0.05). Treatment cycles average was similar in all 3 groups: 7.0 versus 6.7 and 6.8, respectively (p = 0.778). Discontinuation due to side effects associated with drug administration was low. During the rituximab infusion, 15 patients experienced mild effects (tremors, hypotension, swelling, allergic reaction and nausea/vomiting) and 3 had to discontinue the treatment due to the presence of thrombocytopenia. With other treatments, 8 patients experienced mild effects (tremors, hypotension, swelling, allergic reaction and nausea/vomiting) and 2 had to abandon the medication due to tumor lysis syndrome and sepsis. There were no significant differences between the different study groups.

Treatment response with partial or complete reduction was similar in patients with CLL, DLCL and FL: 67.7, 66.4 and 70.0% (Table 4). Mortality rates were 17.0, 35.3 and 20.6%, respectively. In the logistic model, the mortality-associated factors were age (OR: 1.1; 95% CI: 1.0-1.3), male gender (OR: 1.8: 95% CI: 1.2-3.3) and advanced clinical stages (OR: 3.4; 95% CI: 1.8-5.1).

The general comparison between patients on treatment with or without rituximab (as monotherapy or combination) according to the different study groups is shown in table 5. In CLL, treated patients were younger (71.4 vs. 77.5 years; p < 0.05) and there was a larger percentage of men (78.6 vs. 58.3%; p < 0.05),

Table 1. Baseline characteristics of the series in comparison with a population-based group*

Study groups Number of patients	Population† (n = 35,035)	CLL (n = 90)	L (n = 180)	DLCL (n = 81)	FL (n = 99)
Sociodemographic characteristics					
Age average (years)	64.1 (9.7)	72.5 (9.0)‡	64.8 (9.3)	65.5 (9.3)	62.4 (9.6)
Ranges: 50-64 years	56.3%	23.3%	50.2%	42.0%	58.4%‡
65-74 years	25.4%	31.1%	35.4%	45.7%‡	25.8%
≥ 75 years	18.4%	45.6%‡	13.5%	12.3%	15.8%
Gender (males)	46.2%	60.0%¶	54.7%	56.8%¶	52.6%§
Pensioner status (social security)	56.1%	81.1%¶	79.2%	80.2%¶	78.9%¶
General comorbidity					
Average of diagnoses	5.8 (2.6)	4.6 (2.4)	4.6 (3.1)	4.4 (2.9)	4.9 (3.5)
Charlson index average	0.4 (1.6)	1.6 (1.6)‡	1.4 (0.9)	1.5 (1.0)‡	1.4 (0.7) ‡
BUR average	2.7 (0.9)	2.8 (0.8)§	2.8 (0.7)	2.9 (0.7)§	2.8 (0.7)§
BUR-1	7.0%	0.0%	0.0%	0.0%	0.0%
BUR-2	19.3%	44.4%¶	38.1%	35.8%¶	42.1%¶
BUR-3	67.3%	33.3%§	42.7%	44.4%¶	41.1%¶
BUR-4	5.9%	16.7%	16.9%	18.5%¶	15.8%§
BUR-5	0.6%	5.6%§	1.1%	1.2%	1.0%
Associated comorbidities					
Arterial hypertension	40.2%	45.6%	44.2%	44.4%	44.1%
Diabetes mellitus	16.6%	21.1%	20.6%	21.0%	19.8%
Dyslipidemia	50.7%	33.3%¶	33.7%	35.8%¶	31.6%¶
Obesity	20.9%	16.7%§	15.0%	14.8%§	15.5%§
Smoking	21.3%	27.3%	27.2%	28.0%	26.3%
Alcoholism	3.4%	6.7%§	6.5%	7.3%§	5.8%
Ischemic heart disease	6.1%	21.1%¶	16.3%	17.3%§	15.8%
Stroke	7.7%	18.9%¶	16.3%	17.3%¶	15.8%¶
Asthma	4.6%	6.7%	6.4%	7.4%	5.3%
Organ failure (all)	10.4%	30.0%¶	33.7%	35.8%¶	31.6%¶
Renal failure	3.3%	9.4%§	10.2%	11.2%§	9.9%§
COPD	4.5%	12.2%¶	11.3%	12.3%¶	10.5%¶
Neuropathies	0.9%	4.9%§	2.5%	2.9%	2.3%
Dementia	1.5%	4.4%§	5.8%	6.2%§	5.3%
Depressive syndrome	18.7%	23.3%	25.1%	23.5%	26.3%
Viral hepatitis	2.5%	3.8%	3.8%	3.2%	4.3%
HIV	0.3%	2.1%	4.6%	4.5%§	3.4%
Parameters					
BMI (kg/m^2)	28.6 (1.2)	28.0 (3.7)	26.8 (4.1)	26.0 (3.5)‡	27.1 (4.9)§
Serum creatinine (mg/dl)	1.1 (0.9)	1.7 (0.8)‡	1.8 (0.6)	1.7 (0.8)‡	1.8 (0.5)‡
Body surface area (m^2)	–	1.92 (0.2)	1.88 (0.2)	1.89 (0.2)	1.88 (0.2)

L: all lymphomas.
*Values expressed as percentages or means (SD).
†Statistical significance; paired comparison taking the general population as reference.
‡p < 0.001.
§p < 0.05.
¶p < 0.01.

as well as higher morbidity burden (Charlson: 3.3 vs. 2.5; p < 0.05). In DLCL and FL, there were no important differences from the statistical point of view.

In general, when rituximab was compared with other administered treatments, median PFS was higher (6.8 vs. 4.2 years; p < 0.001). These differences were maintained for CLL (7.8 vs. 5.5 years; p = 0.037), DLCL (5.1 vs. 3.2 years; p = 0.048) and FL (5.9 vs. 4.1 years, p = 0.044) (Fig. 1). Unit costs for rituximab preparation and administration are described in table 6. Total average/unit per session ranged from 237.7 to 307.3 Euros.

Table 2. Patient distribution, clinical stages and administered treatments by study group*

Study groups Number of patients	CLL (n = 90)	L (n = 180)	DLCL (n = 81)	FL (n = 99)
ECOG performance status†				
0	42.2%	26.1%	25.9%	26.3%
1	33.3%	39.5%	42.0%	36.6%
2	17.8%	17.3%	12.3%	21.4%
3	6.7%	17.7%	19.8%	15.7%
Clinical stages				
Low risk	63.3%	15.1%	13.6%	16.8%
Intermediate risk	27.8%	46.5%	42.0%	51.2%
High risk	8.9%	43.2%	44.4%	42.0%
Treatments				
Bone marrow transplantation	2.2%	19.1%	6.2%	22.2%
Blood transfusion	5.6%	12.4%	13.6%	12.3%
Radiotherapy	1.2%	22.3%	17.3%	25.8%
Chemotherapy, n (%)	n = 26 (28.9%)	n = 160 (88.4)	n = 70 (86.4%)	n = 90 (90.9%)

L: all lymphomas.
*Values expressed as percentages; p: statistical significance.
†No patients were classified in groups 4 or 5.

Discussion

Clinical characteristics, administered treatments, response and survival are shown in adult patients with CLL, DLCL and FL, three of the most common hematological neoplasms in clinical practice. Although these conditions have an important heterogeneity and clinical variability and have low incidence, its combined inclusion should be interpreted as one of the study's strengths.

The comparison of CLL and NHL epidemiological data is not without difficulties, since there is certain tendency towards grouping histological types (especially in the case of lymphomas), with large variability by geographical zones. Most of the published records come from the International Association of Cancer Registries (IACR), which uses the WHO's previous classifications. With regard to CLL, Panovska et al.[23], in a series of 540 cases, obtained an incidence rate of 5.8 in 2006; Marcos-Gragera et al.[24], in the Population Cancer Registry of Gerona (1994-2001), obtained an incidence of 4.7, and for González Rodríguez et al.[3], the adjusted rate was 3.5. In the case of NHL, the rates range from 4 to 8, although there is greater variability. The studies by Bosetti et al.[25] and Shankland[11] are within these ranges and our results are consistent with these data[26].

In comparison with the general population, the groups with CLL, DLCL and FL showed a larger percentage of men and higher morbidity burden. In the reviewed literature, we have not found any publication quantifying general morbidity of these patients on a single index. Conversely, there are evidences of some associated conditions; this way, in CLL, age, male gender, white race and family history of lymphatic system cancer are described, whereas in NHL type 1 diabetes, rheumatoid arthritis, HIV (DLCL) and the hepatitis B virus (marginal lymphoma) can be associated[27-29]. The study results could only find an association with some of these factors: a history of diabetes mellitus was found, but not specifically of type 1 and, for rheumatoid arthritis, obtaining information was not planned *a priori*. The limited number of selected cases makes it difficult to establish comparisons.

Compared to DLCL and FL, CLL showed lower risk, with a 5-year OS of 84.4 versus 45.0 and 68.5%, respectively. It should be pointed out that, although in the reviewed literature there is large variability in survival outcomes, in the analyzed series, survival is consistent with the majority of reviewed studies. In CLL, the European Society of Medical Oncology (ESMO) guidelines[27], depending on risk level (low, intermediate, high), state that OS is > 10, > 8 and > 6.5 years. In our case, in the high-risk stages, the results were

Table 3. Administered chemotherapy by study group*

Study groups Number of patients	CLL (n = 26)	L (n = 160)	DLCL (n = 70)	FL (n = 90)
Type of treatment (chemotherapy)				
First line treatment	84.6%†	69.8%	67.1%	72.6%
Second line/relapse	15.4%†	30.1%	32.9%	27.4%
Administered drugs				
R	3.8%			
R-FC	50.0%			
F	3.8%			
FC	19.2%			
Other combinations	23.1%			
R		6.6%	8.6%	4.4%
R-CHOP		79.2%	78.6%	80.3%
CHOP		6.5%	8.6%	4.4%
Other combinations		3.1%	4.2%	2.2%
Administered/specific drugs First line: n = 129				
R	4.5%			
R-FC	40.9%			
F	4.5%			
FC	22.7%			
Other combinations	27.3%			
R		3.1%	4.2%	2.2%
R-CHOP		88.0%	86.2%	89.1%
CHOP		6.4%	4.3%	8.7%
Other combinations		2.8%	5.3%	–
Treatment cycles				
Mean (SD)	7.0 (2.4)	6.6 (3.8)	6.7 (3.6)	6.8 (4.4)
Median (P25-P75)	6.0 (4.0-8.0)	6.0 (5.7-8.0)	6.0 (5.8-8.0)	6.0 (5.7-8.0)

L: all lymphomas; R: rituximab (monotherapy); R-FC: rituximab + fludarabine + cyclophosphamide; FC: fludarabine + cyclophosphamide; R-CHOP: rituximab + cyclophosphamide + adriamycin + vincristine + prednisone; CHOP: cyclophosphamide + adriamycin + vincristine + prednisone; P: percentile.
*Values expressed as means (SD) and percentages.
†$p < 0.05$.

Table 4. Treatment response the and OS and PFS between study groups*

Study groups Number of patients	CLL (n = 26)	L (n = 160)	DLCL (n = 70)	FL (n = 90)
Treatment response				
Stable disease	26.9%	20.6%	19.3%	21.8%
Partial/complete reduction	57.7%	68.4%	66.4%	70.0%
Disease progression	15.4%	11.8%	14.3%	8.2%
Survival				
OS (years)				
Mean (SD)	10.1 (5.1)	7.3 (2.2)	6.6 (2.1)	8.2 (2.2)
Median (P25-P75)	8.9 (6.5-14.5)	7.3 (4.6-9.7)	6.5 (4.6-8.8)	8.0 (6.5-10.5)
PFS (years)				
Mean (SD)	6.0 (3.3)	5.7 (2.3)	5.4 (2.6)	5.9 (2.3)
Median (P25-P75)	6.5 (2.9-8.4)	4.7 (3.1-6.8)	4.4 (2.6-6.5)	5.5 (3.5-7.3)

L: all lymphomas.
*Values expressed as means (SD) and percentages; p: statistical significance.

Table 5. Overall comparison between patients on treatment with or without rituximab (as monotherapy or combination) according to the different study groups*

Study groups	CLL		DLCL		FL	
On treatment Number of patients	Without rituximab (n = 12)	With rituximab (n = 14)	Without rituximab (n = 9)	With rituximab (n = 61)	Without rituximab (n = 14)	With rituximab (n = 76)
Sociodemographic characteristics						
Age average (years)	77.5 (6)	71.4 (10.1)†	65.4 (9)	65.7 (9.8)	62.1 (7.7)	62.7 (9.5)
Ranges: 50-64 years	8.0%	21.4%	47.4%	43.8%	71.8%	66.7%
65-74 years	33.3%	42.9%	36.8%	43.8%	18.2%	16.7%
≥ 75 years	58.7%	35.7%	15.8%	12.5%	10.0%	16.7%
Gender (males)	58.3%	78.6%†	60.5%	53.1%	54.5%	50.0%
General comorbidity						
Average of diagnoses	3.4 (1.6)	5.6 (3.9)†	4.5 (2.6)	4.4 (2.1)	3.7 (2.9)	3.5 (2.7)
Charlson index average	2.5 (0.7)	3.3 (1.2)†	2.9 (0.8)	2.8 (0.7)	2.8 (0.8)	2.7 (0.8)
BUR (mean)	1.3 (1.5)	1.7 (1.6)	1.6 (1.8)	1.5 (1.5)	1.4 (1.0)	1.3 (1.0)
Associated comorbidities						
Arterial hypertension	41.7%	42.9%	44.7%	43.8%	37.3%	40.0%
Diabetes mellitus	8.3%	18.6%	28.9%	15.6%	9.1%	16.7%
Ischemic heart disease	31.7%	28.6%	21.1%	15.6%	18.2%	10.0%
Stroke	8.3%	19.4%	15.8%	18.8%	18.2%	16.7%
Parameters						
BMI (kg/m^2)	25.8 (1.1)	27.2 (1.7)	26 (3.2)	25.6 (4.4)	27.5 (3.1)	27.1 (4.2)
Clinical stages						
Low risk	0.0%	0.0%	12.3%	13.1%	19.1%	16.7%
Intermediate risk	66.7%	71.4%	43.1%	41.1%	37.3%	43.3%
High risk	33.3%	28.6%	44.6%	45.8%	43.6%	40.0%
Type of treatment (chemotherapy)						
First line treatment	92.0%	71.4%	67.9%	67.1%	54.5%	71.4%†
Second line/relapse	8.0%	28.6%	32.1%	32.9%	45.5%	28.6%
Treatment response						
Stable disease	33.3%	21.4%	28.7%	18.0%	29.1%	16.7%
Partial/complete response	48.3%	57.2%	50.0%	67.4%	55.1%	79.0%
Progressive disease	18.4%	21.4%	21.3%	14.6%	15.8%	4.3%
Mortality (all causes)	16.7%	17.9%	38.6%	34.3%	20.5%	20.7%

*Values expressed as means (SD) and percentages.
†Statistical significance: $p < 0.05$.

Table 6. Rituximab preparation and administration cost/unit*

Phases	Preparation†		Administration‡		Total	
Modality	Time§	Cost¶	Time§	Cost¶	Time§	Cost¶
R-monotherapy						
First line	28.6 (10.2)	34.3	145.3 (20.1)	203.4	173.9 (16.9)	237.7
Second line	30.3 (12.3)	36.4	152.5 (19.5)	213.5	182.8 (15.2)	249.9
R-combination						
First line	45.8 (14.1)	55.0	170.9 (22.1)	239.3	216.7 (17.7)	294.2
Second line	48.3 (13.8)	58.0	178.1 (18.6)	249.3	226.4 (15.9)	307.3

*The cost was calculated by multiplying the time by the personnel equivalent salary of. There were no significant differences between the different study groups. At drug first infusion, administration time was slightly longer.
†Preparation time is measured from the extraction, dilution and mixing of the preparation until its storage.
‡Administration time includes from pre-medication until the completion of the intravenous infusion.
§Time expressed in minutes.
¶Cost expressed in Euros (average/unit per session).

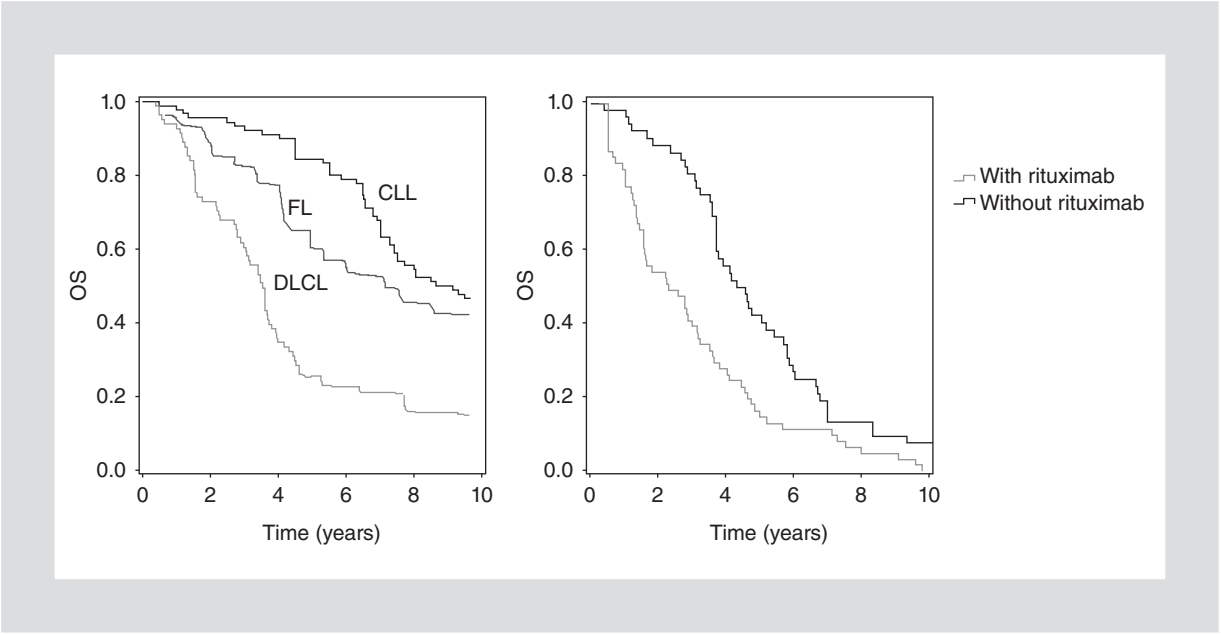

Figure 1. *OS curves of the studied series showing:* **A:** *survival according to the type of neoplasm.* **B:** *survival according to administered treatment. *The results for each tumor type (CLL or lymphoma) were similar, p < 0.05.*

slightly lower. This circumstance might be explained by the existence of factors that difficult a normal treatment response (treatment resistance), presence of genotypes that cause a worse prognosis of the disease (lymphocyte duplication time, β_2-microglobulin/thymidine kinase, new markers with karyotype aberrations, IgVH mutational status, serum free light chains) or other factors (diagnostic delay) that can cause for the natural course of the disease to change in high-risk patients[28-30], or even due to the low number of patients on treatment.

DLCL is a highly aggressive B-phenotype NHL. It is common in adult age and accounts for 80% of aggressive lymphomas. Due to its complexity, some authors recommend personalized treatment by means of genotyping (biomarkers)[31]. Our results would be consistent with the meta-analysis conducted by Feng et al.[32], where 1,206 patients were included and OS was 2.7 years in high-risk patients. However, there is large discordance of results in the reviewed literature.

FL is characterized by an indolent evolution; usually, it is diagnosed at advanced stages, with prolonged survival times; many are refractory to chemotherapy treatments and, thus, response rates are low. The reviewed publications indicate that treatment is quite variable and includes options such as radiotherapy and multiple chemotherapy. The outcome is rather variable, although our results are similar to those in other reviewed studies[33,34]. As in DLCL, there is certain need to identify useful biomarkers for the prediction of the disease course. FL prognosis is associated with the type, number and activation of follicle immune cells[34]. In general, rituximab (as monotherapy or in combination), in comparison with other administered treatments, improved patient PFS. In spite of the limitations of the study with regard to the modest number of patients to enable the analysis of specific subgroups (first, second line of treatment, maintenance, clinical risk, treatment response, etc.) or other series of unidentified factors, it appears to be an effective measure, and there are numerous reviews in these three types of neoplasms (CLL, DLCL, FL) demonstrating it[14-16, 27.29,35].

Possible limitations of the study involve disease typing and potential patient classification bias. Therefore, the article shows the retrospective studies' typical limitations, such as, for example, under-registration of the disease or likely variability of healthcare professionals and patients as a result of the observational design. However, the main limitation of the study is the reduced number of cases on each study group, which renders a more detailed sub-analysis impossible, in addition to the lack of some variables that were not measured and that might be related to the obtained results (genetic expressions, phenotype, clinical stage changes, etc.). Nevertheless, in spite of its limitations, the study constitutes an approach to the clinical reality presented by

these hematological neoplasms in real-life conditions. Future investigations will require having studies available on diagnostic delay, biomarkers that enable a better approach to therapeutic options and to treatments' cost/effectiveness, in addition to replicating the study on other healthcare organizations. In conclusion, comorbidity associated with these hematological neoplasms is elevated. CLL showed higher survival and lower mortality rate than NHLs. Rituximab showed greater PFS in these neoplasms.

Conflict of interests

The study has been sponsored by Roche Farma, without this having influenced on the results.

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