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Prognostic Factors in Diffuse Large-Cell B Lymphoma Treated With R-Chop - About 153 Cases

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Abstract: Introduction: *Diffuse large B-cell lymphomas account for almost a third of all non-Hodgkin's lymphomas. The advent of Rituximab has changed the prognosis of patients, demonstrating improved survival regardless of age and initial prognostic factors. The main objective of our study is to evaluate the different clinico-biological markers as prognostic factors of therapeutic response to RCHOP in diffuse large-cell B lymphoma.* ***Methodology:*** *This is a retrospective, descriptive, and analytical study carried out in the Internal Medicine and Onco-Hematology Department at the Hassan II University Hospital in Fez, covering a hospital series. This study is spread over 4 years, from January 2018 to December 2021.* ***Results:*** *The number of patients was 153, with a mean age of 56.16 years and a standard deviation of +/- 16.81 years. The F/H sex ratio was 1.12. Seventy-one patients presented with a tumor syndrome, mainly peripheral adenopathy. Fifty-three percent of patients had B symptoms. According to the Ann-Arbor classification, 61% of patients had extensive stages (III–IV) versus 39% who had localized stages (I–II). The IPI score was low in 25.5%, low intermediate in 36.6%, high intermediate in 36.8%, and high in 11.2%. Progression was marked by a 64% rate of good therapeutic response. Overall survival at 2 years was 77%. To explain this evolution, we studied the various parameters (clinical features, blood count abnormalities, lactate dehydrogenase levels, albuminemia, inflammatory syndrome) as factors influencing response, taking into account other factors such as age, disease stage, disease location, and diagnostic delay. At the end of this analysis, we found that the presence of a bulgy mass, monocytosis, and localized stage at the start of the disease were parameters significantly associated with a higher remission rate. In multivariate analysis, an association was found between the presence of monocytosis, time to diagnosis, and a good response to the RCHOP protocol.* ***Conclusion:*** *Extremely important advances have been made in the identification of prognostic features in diffuse large B-cell lymphoma. Our study has identified new factors that may improve the prognosis of this disease. These results warrant further research. In this context, we note the interest in larger multicenter studies.*

Keywords: diffuse large B-cell lymphoma, prognostic factor, monocytosis, rituximab.

Introduction:

Diffuse large B-cell lymphomas (DLBCL) account for around 40% of all non-Hodgkin's lymphomas, making them the most common aggressive lymphomas. These lymphomas are defined mainly by two histopathological criteria: the diffuse architecture of the tumor population and the large size of the tumor cells, which are mature lymphoid cells of the B phenotype. DLBCL is essentially a pathology of adults and the elderly, with a median age of around 65–70 years, according to studies. (1), (2), (3). The choice of treatment depends on the patient's age and the International Prognostic Index (IPI) prognostic score. It is based on the combination of rituximab and cyclophosphamide-doxorubicin-vincristine-prednisone (CHOP). The aim of treatment is to achieve a complete metabolic response, as assessed by FDG-PET. The addition of rituximab to CHOP chemotherapy (R-CHOP) has led to a marked improvement in survival and called into question the importance of previously recognized prognostic markers.

The primary objective of our study is to evaluate the different clinical-biological markers as prognostic factors of the therapeutic response to RCHOP in DLBCL.

The secondary objectives of this study are: to describe the epidemiological, clinical, and paraclinical characteristics of patients with DLBCL; To analyze other clinical and paraclinical determinants that may influence the course of the disease, to evaluate the R-ChOP protocol in terms of overall survival in the treatment of DLBCL in our patients, to relate our results to those of the literature and to formulate recommendations appropriate to our local context.

Methodology:

This is a retrospective, descriptive, and analytical study conducted in the Internal Medicine and Onco-Hematology Department at the Hassan II University Hospital in Fez, involving a hospital series of 153 patients. This study is spread

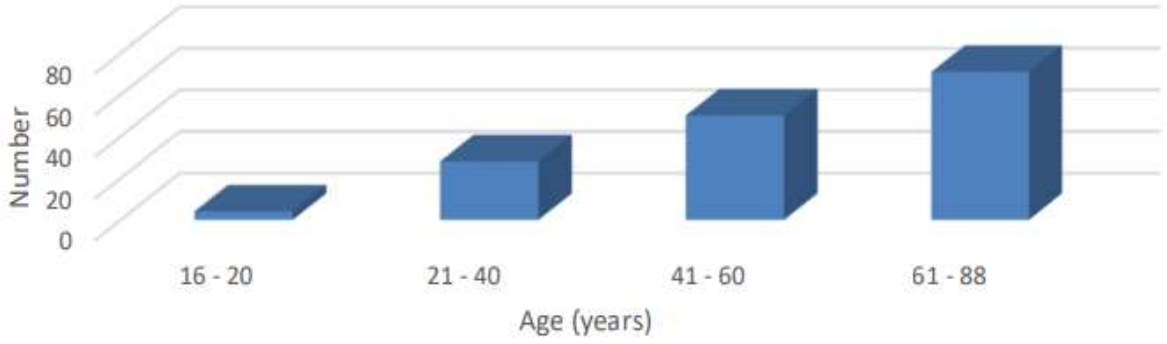
over 4 years, from January 2018 to December 2021. The inclusion criteria for our patients are: Age greater than 16 years, DLBC confirmed by histological examination, A follow-up of at least 12 months from the start of management

Data are collected from hospital records and entered into an Excel file. An operating sheet has been drawn up for each of our patients. Statistical analysis was carried out in collaboration with the Laboratory of Epidemiology, Clinical Research, and Community Health at the Faculty of Medicine and Pharmacy in Fez. The analysis was carried out using SPSS software (version 26). This involved univariate and multivariate analysis in search of determinants of disease progression, with simple logistic regression modeling assuming a $p \leq 0.05$. When comparing groups, we used classic parametric tests: the Chi2 test, the Student's t test, and the ANOVA, depending on the nature of the variables to be compared. The "good response" criterion corresponds to complete and partial remission, while the "poor response" criterion includes stabilization, progression. Survival curves were calculated using the non-parametric Kaplan-Meier method. The log rank test was used to compare survival curves. The confidence interval was set at 95%.

Results:

One hundred and fifty-three patients are enumerated in our study; the study period is spread from January 2018 to December 2021. The number of new cases per year is distributed as follows: The average number of new cases per year was 38.25 new cases per year during our study period. The mean age of our patients is 56.16 years, with a standard deviation of 16.81 years. The extremes were 16 and 88 years. The most common age group was over 60, with 71 patients.

Figure 1: Breakdown of study population according to age



The distribution of cases by gender showed a slight female predominance, with 81 cases representing 52.9% of women affected by DLBCL. On the other hand, 72 men were affected by the disease, representing 47.1%, with a sex ratio of 1.12. The average time between the onset of symptoms and confirmation of the disease is 5.55 months +/- 4.664 months. The maximum delay is 36 months, and the minimum is 1 month. Our study shows that 25% of our patients have a diagnostic delay of more than 6 months. Tumor syndrome: One hundred and nine patients, or 71.2% of cases, presented a tumor syndrome in the form of peripheral adenopathy. These adenopathies were associated with splenomegaly in 12 patients. General signs: "B symptoms" (fever, weight loss of more than 10% of body weight in the last 6 months, night sweats) were present in 82 patients (53.6% of cases). The diagnosis was confirmed by the histological examination of a biopsy specimen, which was performed on all our patients. All our patients underwent extensional CTAP. PET scans were not systematically performed as part of the initial extension work-up, as they are not available in our region. All our patients underwent a biological assessment of their progress and prechemotherapy. In our series, all cases benefited from an immunohistochemical study using Bcl6, MUM1, and CD10 antibodies in order to support the molecular subtype of these lymphomas. Based on Hans' immunohistochemical algorithm, activated type LBDG [ABC] was the most frequent molecular subtype in our series, with a percentage of 54.9% (n = 84). Centrogerminative DLBCL [CG] accounted for 40.5% (n = 62). Centrofollicular lymphoma was present in 2.6% of cases, and 2% were NOS. Ninety-four patients presented with advanced disease, with 83 patients at stage IV and 11 at stage III, compared with 59 who were at a localized stage, with 12 patients at stage II and 47 patients at stage I.

A bulky mass was present in 49 patients, representing 32% of cases. CBC showed anemia below 10 g/dl in 21 patients, or 13.7% of cases. The leukocyte count showed hyperleukocytosis greater than or equal to 11,000 elements/mm3 in 25 patients, or 16.3% of cases. Lymphopenia below 1000 elements/mm3 in 24 patients (15.7%) Monocytosis was observed in 21 patients (13.7% of cases). LDH was elevated (above 250 IU/l) in 92 patients (60.1%) of cases. Hypoalbuminemia below 40 g/l was present in 42 patients (27.5%) of cases. The IPI prognostic score was determined in all our patients: Score 0: 7.2%; Score 1: 18.3%; Score 2: 36.6%; Score 3: 36.8%; Score 4: 10.5%; and Score 5: 0.7%.

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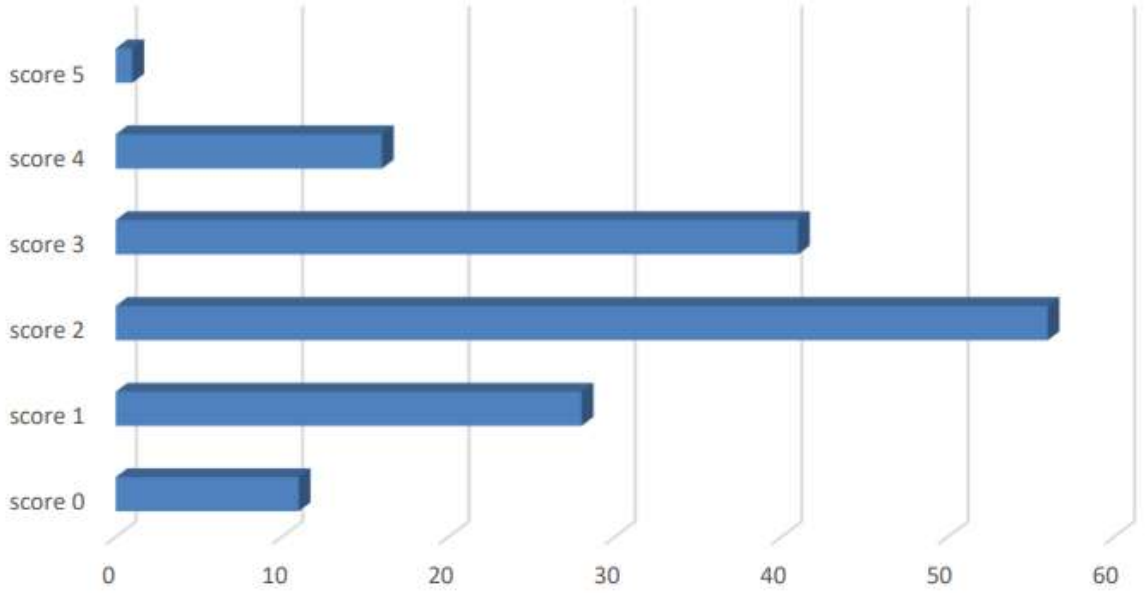
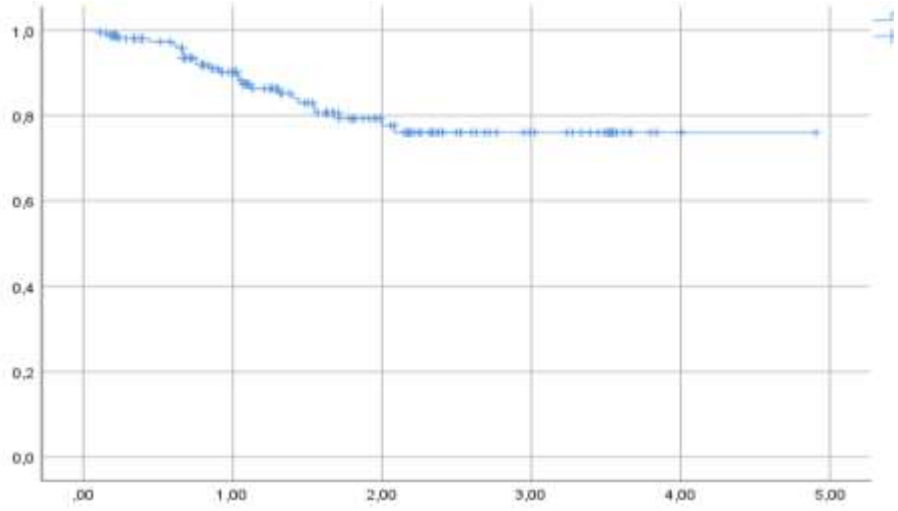
figure 3: Patient distribution by IPI score



All our patients received the RCHOP therapeutic protocol. The evaluation of therapeutic response at the end of the RCHOP protocol was in favor of good therapeutic response in 98 patients (64.1%). The mean overall survival was 4 years, with a standard deviation of +/- 0.16 years. [95% CI: 3.68–4.32%]. Overall survival at 2 years was 77%.

Figure 4: Overall survival curve



To define the markers with a prognostic impact on the evolution of the therapeutic response to the RCHOP protocol, we compared two subgroups of patients, positive and negative, for each aspect of the different disease variables. At the end of this analysis, we found that the presence of a bulky mass, as well as monocytosis and localized stage at disease onset, were parameters significantly associated with a higher remission rate. Diagnostic delay was a parameter significantly associated with a good response to the RCHOP protocol. An analysis of the IPI prognostic score showed no statistically significant correlation between the IPI score and the therapeutic response to the RCHOP protocol. In multivariate analysis, an

association was found between the presence of monocytosis, time to diagnosis, and a good response to the RCHOP protocol.

	Good response to RCHOP		
	Yes	No	*p*
Bulky mass	53,1%	46,9%	***0,05***
Bone location	82,4%	17,6%	0,09
Monocytosis	42,9%	57,1%	***0,02***
LDH >250 IU/l	57,6%	42,4%	0,041
Anemia	53,7%	46,3%	0,105
Thrombocytopenia	57,1%	42,9%	0,69
Accelerated VS	45,5%	54,5%	0,066
Increased CRP	55,9%	44,1%	0,060
Albumin < 35 g/l	54,8%	45,2%	0,141
Localized stage	58,1%	41,9%	***0,03***

	Good response to RCHOP		
	Yes	No	p
Diagnosis time	4,86 + / - 3,38	6,78 + /- 6,18	0,01

Table 1: Response to RCHOP according to two groups with or without unfavorable biological markers.

	P	OR	95% OR CI	
Monocytosis	0,02	3,01	1,162	7,841
Diagnosis time	0,01	0,906	0,83	0,98

Table 2: Factors predictive of a good response to RCHOP after Cox regression

Table 3: Comparison of overall survival between two groups with and without monocytosis.

Monocytosis	Estimate	Standard deviation	95% confidence interval		p
			Lower limit	Upper limit	
No	3,185	0,160	2,871	3,498	0,829
Yes	3,775	0,433	2,927	4,623	

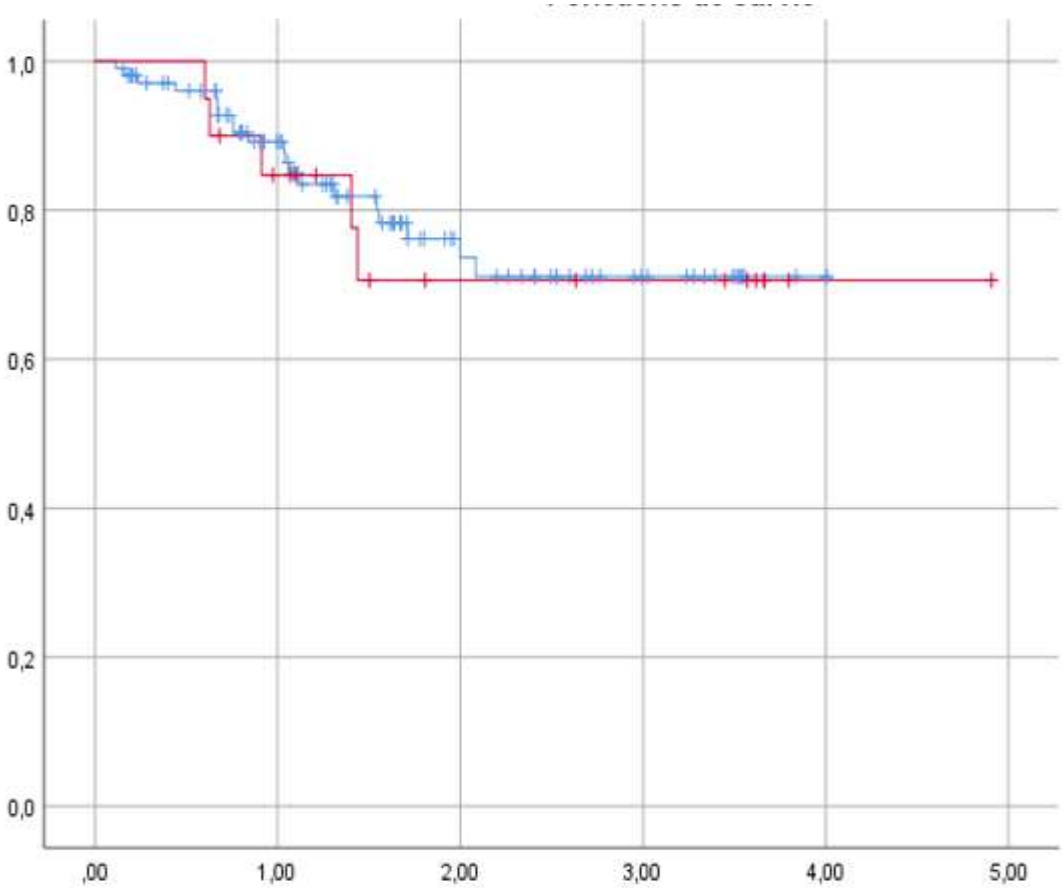


Figure 5: Overall survival in groups with and without monocytosis according to Kaplan-Meier curve

Discussion:

Diffuse large B-cell lymphoma is the most common aggressive lymphoma, accounting for around 25% of all non-Hodgkin's lymphomas (4). In 2012, the incidence of DLBCL was 4,096 new cases per year in France (5). It is now well recognized that there is no single DLBCL, but that the conditions so designated constitute a heterogeneous group of tumors. Classically diagnosed after the age of 60, it can occur in children and young adults. (6).

In our series, the median age of onset was 56 years, with a slight female predominance (sex ratio =1.12). Risk factors for developing DLBCL include advanced age (> 65 years), male gender, a family history of lymphoma, B-cell-activating autoimmune diseases, immunosuppressive treatments, viruses (hepatitis C, human immunodeficiency virus [HIV]), obesity (body mass index [BMI] ≥ 30), and smoking. An increased risk has been described in certain professions (farmer, painter, hairdresser using hair dyes, seamstress, delivery driver, etc.). Phytosanitary products used in agriculture and benzene have also been incriminated. (7-10) . Factors that appear to be associated with a reduced risk are high socio-economic status, atopy, recreational exposure to sunlight, low BMI, certain hormone treatments in women, alcohol consumption in men, and a history of transfusion. In over 75% of cases, DLBCL is revealed by lymph node involvement (persistent, painless, noninflammatory superficial adenopathies), with the possibility of extra-nodal clinical manifestations (ENT, digestive, bone, neurological, cutaneous, or testicular involvement). (11). In our study, lymph node localization accounted for 71.2% of cases. All large-cell B lymphomas do not have the same prognosis, and the search for prognostic factors quickly became essential.

-to propose individualized therapeutic strategies, some of which, because of their toxicity, should be reserved for the most serious cases.

-to enable comparison of the results of different therapeutic trials whose apparent discrepancies are linked to differences in patient prognosis.

The arrival of rituximab, an anti-CD20 antibody, has revolutionized the first-line management of DLBCL in combination with the CHOP regimen (R-CHOP regimen). The complete response rate rose from 63% to 76% (p = 0.005) (12). Although the current treatment of first-line DLBCL (the standard R-CHOP chemotherapy protocol) is associated with a high complete response rate of 70% to 80%, 10% to 15% of DLBCL patients are refractory, and nearly 40% of patients experience relapse within 2 to 3 years of the initial response (13), The study of a considerable number of homogeneously treated patients with diffuse large B-cell lymphoma has enabled us to identify a number of simple clinical and biological prognostic factors that condition both the complete response rate and overall survival. These factors are related to the tumor (LDH level, stage, tumor size, number of lymph node and extra-lymph node sites, marrow involvement), the host response to the tumor (performance status, B symptoms), and the patient's ability to tolerate treatment (performance status, age, marrow involvement). Various prognostic models have been proposed, but the one that has been retained is the IPI published by Shipp et al. in 1993 (15). In a multiparametric study, five factors were retained. Poor prognostic factors are age over 60, stage III or IV, number of extra-ganglionic sites ≥ 2, Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2, and high LDH. This gives so-called low-risk (zero or one factor), low-intermediate (two factors), intermediate-high (three factors), or high-risk (four or five factors) categories. The complete remission rate and 5-year survival clearly differ according to this score, and adaptations have been proposed, notably the age-stratified IPI score, aaIPI (age-adjusted IPI). Other variants, such as the rituximab-adapted score (R-IPI) and the elderly-adapted score (E-IPI), have not surpassed the performance and ease of use of the classic IPI. (16). However, it is becoming increasingly clear that patients with the same R-IPI score may have different prognoses. (17). Furthermore, none of these scores identifies a sub-group of very high-risk patients, such as primary refractory patients or those who relapse early. Finally, these scores cannot fully account for the great biological heterogeneity of DLBCL, which is of great importance in assessing the prognosis of patients at diagnosis. Indeed, many biological factors are of interest in estimating the patient's prognosis.

In addition to previously established prognostic scores, other socio-demographic, clinical, and paraclinical data were studied to assess their prognostic value.

Total metabolic tumor volume, determined by PET scans during initial staging, is a major prognostic factor independent of conventional prognostic factors (18). The higher it is, the shorter the progression-free survival and overall survival. Thus, a large total metabolic tumor volume isolates a group of patients at high risk of

relapse who may require more aggressive therapy (19). In our series, the absence of systematic disease assessment by PET scan (initially and after 2 courses of treatment) is the main limitation of our study. Given its unavailability in our region, PET scanning was not systematically performed as part of the initial extension workup, and we reserved it for therapeutic evaluation, especially when the scannographic results were inconclusive.

Monocytosis: It is well known that host adaptive immunity and the tumor microenvironment play an important role in lymphoma pathogenesis (20). A study conducted on patients at the M. D. Anderson Cancer Center (MDACC) evaluated a new score based on lymphocyte count and monocyte count, concluding that this score is a useful tool for further stratifying DLBCL patients with similar IPI scores and can help identify those who may benefit from more aggressive treatment or alternative therapies (21). In our analysis, we did not find a significant association between different IPI score classes and the achievement of CR. Whereas monocytosis greater than 1000 /mm3 and the presence of a bulky mass are prognostic factors in our series.

Ki67: The Ki67 proliferation index has no robust prognostic impact in univariate analysis. Some studies have shown more aggressive disease with an increased proliferation index (22) but other studies have invalidated these results (23).

Albumin level: Previous studies have shown that albumin at diagnosis can be used to predict outcome in patients with diffuse large B-cell lymphoma (24)

However, these prognostic indices do not take into account the molecular aberrations associated with lymphomas that cause particularly aggressive high-risk disease, such as cells of origin, activated B-cell DLBCL, MYC, and/or BCL2 and/or BCL6 gene rearrangements, or double or triple-hit lymphomas (25).

Depending on their cell of origin, GC or ABC, DLBCL differ in terms of chromosomal alteration, activated cellular pathways, and thus pathogenic mechanics, and more generally in terms of prognosis: forms with a germinal center phenotype ([CG], good prognosis) and forms with an activated phenotype ([ABC], poor prognosis) (26, 27). The use of DLBCL classification according to cell of origin (GCB, ABC) is common to guide the use of certain treatments, but its clinical benefits have yet to be confirmed (28). In our series, CD10 was expressed in 11.8% of cases, Bcl6 in 19.6%, and MUM1 in 26.8%.

Based on Hans' immunohistochemical algorithm, the activated phenotype was found in 54.9% of cases, and the centro-germinative phenotype represented only 40.5% of cases, which is discordant with the literature. This may be explained by our small sample size (153 cases).

Another interesting approach to refining prognosis is the determination of alterations in oncogenes and tumor suppressor genes. The presence of translocations of MYC, BCL2, and/or BCL6 (double-hit or triple-hit lymphomas) is associated with a high rate of non-response to initial treatment as well as a high risk of early relapse, with an unfavorable prognosis for these patients (median OS of 8 months for refractory or relapsed patients). (29).

In addition to these genetic and epigenetic mechanisms intrinsic to the B cell, the development and progression of a genuine B lymphoma are favored by the close interaction of B cells with their cellular and extra-cellular microenvironment (ME). It has been well demonstrated that ME plays an important role not only in lymphomagenesis but also in lymphoma cell survival, disease progression, and resistance to treatment (30), (31) and (32).

Conclusion:

Initial therapeutic advances have made it possible to develop a therapeutic strategy based on prognostic factors and to define an optimal standard treatment for each therapeutic prognostic group. However, forms resistant to initial treatment remain difficult to identify at the time of diagnosis. The IPI score is the most robust and reproducible clinico-biological prognostic factor currently known in DLBCL. Other prognostic factors appear to complement or surpass IPI in patients with DLBCL, including tumor-intrinsic variables such as cell of origin and certain genetic abnormalities (33) R-CHOP remains the reference first-line treatment in the majority of cases; however, certain alternatives exist, but their indications remain limited to certain situations. Our study demonstrates that, in addition to previously validated prognostic factors, the inclusion of new biological and

radiological factors may be useful in improving outcomes in DLBCL. In addition, studies of tumor biology and host genetics, an epidemiological approach, and the pursuit of therapeutic trials remain important challenges for a better understanding and optimization of therapeutic outcomes. All these data need to be confirmed for larger cohorts.

Recommendations:

Through this study, we can conclude that:

This is a pathology of the elderly.

More than two-thirds of patients consult a doctor more than 3 months after the onset of symptoms, and two-thirds of patients reach an advanced stage of the disease, which has a negative impact on the prognosis.

More than half of the patients were in the unfavorable prognostic groups on admission.

The main limitation of our study is the unavailability of PET scans for initial and post-treatment evaluations.

The OS in our series is similar to that in the international series.

In light of these data and in order to improve the management of our patients, we propose to:

Encourage early diagnosis of the disease, using every possible means to raise awareness among the general public (awareness campaigns, media, etc.), as well as among healthcare practitioners, through biopsies of any suspected adenopathy.

Carry out an optimal extension assessment, insisting on the need for a PET-scanner unit in our hospital structure.

Act to shorten the patient's circuit to compensate for delays in care within the department and the other services included in the circuit (radiology, medical analysis laboratory).

Unified patient management based on prognostic groups and therapeutic outcomes.

- Informing patients and their families about their pathology, the benefits of treatment, and the importance of keeping to the dates and times of consultation appointments, which will reduce the number of people lost to follow-up.

Implement an optimal therapeutic strategy based on clinical trials and adapted to local conditions.

Multiply prospective studies to better characterize our population and determine its needs.

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