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Blood 142 (2023) 6155–6156

The 65th ASH Annual Meeting Abstracts

ONLINE PUBLICATION ONLY

623.MANTLE CELL, FOLLICULAR, AND OTHER INDOLENT B CELL LYMPHOMAS: CLINICAL AND EPIDEMIOLOGICAL

Outcomes, Prognostic Factors, Predictors for Transformation to High-Grade B-Cell Lymphoma, and Therapeutic Management in Follicular Lymphoma: Real-World Evidence from a Large and Long-Term Latin-American Cohort

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Introduction: Follicular lymphoma (FL) is the most common low-grade B-cell NHL, encompassing 20-25% of all NHLs. Although classically indolent, it has heterogeneous biological behavior and variable clinical outcomes. Histologic transformation (HT) to high-grade B-cell NHL compose its natural history, being associated with dismal survival. The therapeutic management of FL and its prognosis are highly dependent on its staging and tumor burden. Based on this premise, the present study aims to describe clinical-laboratory characteristics, assess outcomes, determine predictors of survival and HT, and compare responses between different therapeutic strategies applied in a large cohort of FL patients.
Methods: This retrospective and single-center study involved 223 patients with FL grades 1-3A, diagnosed at the University of São Paulo, Brazil, from 2006 to 2022. FL patients were categorized into early-stage disease (I/II) (ES), advanced-stage (AS) (III/IV) with low tumor burden (LTV), and AS with high tumor burden (HTV) according to the GELF criteria. Endpoints included OS, PFS, early-relapse (< 24 months from diagnosis) and HT rates. Survival curves were constructed using the Kaplan-Meier method and the Log-Rank test was used to assess the relationship between variables and outcomes. Univariate analysis was performed using the Cox test and multivariate analysis by Cox regression method or proportional ratios model. The results were presented in HR and 95% CI, and a p-value ≤ 0.05 was considered statistically significant.
Results: The median age at diagnosis was 60 years (30-98) and 54.8% (121/223) were female. Approximately 15% of cases (33/223) had ES, 18.4% (41/224) had AS-LTV, and 66.8% (149/223) had AS-HTV. BM involvement, leukemic presentation, splenomegaly, and serous effusions occurred in 48.9% (109/223), 11.7% (26/223), 12.6% (28/223), and 21.1% (47/223), respectively. Bulky $\geq$ 7 cm, B-symptoms, ECOG $\geq$ 2, and involvement of $\geq$ 4 nodal areas were observed in 44.4% (99/223), 51.6% (115/223), 15.2% (34/223), and 56% (125/223), respectively - **Table 1**. Forty-nine percent of patients (110/223) were categorized as high-risk according to the FLIPI score. **Table 2** summarizes the main outcomes and up-front therapeutic modalities applied in the whole cohort. With a median follow-up of 79.5 months (95% CI: 67.0-92.0) the OS medians were 18 years (95% CI: 14.9-21.1), 11 years (95% CI: 9.2-12.9), and 10.5 years (95% CI: 9.3-11.8) for ES, AS-LTV, and AS-HTV, respectively, p=0.138 **Figure 1A**. Similarly, the PFS medians were 6.7 years (95% CI: 3.6-9.8), 8.4 years (95% CI: 2.0-14.8), and 3.5 years (95 CI: 1.8-5.3) for ES, AS-LTV, and AS-HTV, respectively, p=0.171 **Figure 1B**. Early-relapses occurred in 36.3% (81/223) of cases, being 18.2% (6/33), 31.7% (13/41), and 41.0% (62/149) for ES, AS-LTV, and AS-HTV, respectively, p=0.032 **Table 2**. The overall mortality rate was 29.1% (65/223) for the whole cohort. HT was documented in 16.7% (37/223) of cases, being 3.0% (1/33), 14.6% (6/41) and 20.1% (30/149) for ES, AS-LTV, and AS-HTV, respectively, p=0.053 **Table 2**. Among patients with AS-HTV, the R-CHOP regimen did

not promote increased OS compared to the R-CVP regimen (p=0.415), however it was associated with a substantial increase in PFS (p=0.005) **Figure 2**. Age ≥ 60 years (HR: 1.06, p<0.001), ≥ 2 comorbidities (HR: 3.85, p=0.014), B-symptoms (HR: 2.35, p=0.015), HT (HR: 2.77, p=0.002) and thrombocytopenia (HR: 2.96, p=0.028) were predictors of poor OS. Similarly, age ≥ 60 years (HR> 1.08, p<0.001), involvelment of ≥ 4 nodal areas (HR: 1.27, p<0.001), and high LDH levels (HR: 1.65, p=0.002) predicted decreased PFS. Additionally, serous effusions (HR: 2.09, p=0.05), albumin < 3.5 g/dL (HR: 2.82, p=0.05), B-symptoms (HR: 2.00, p=0.006), involvement of ≥ 4 nodal areas (HR: 1.21, p=0.014), and BM infiltration (HR: 2.11, p=0 .05) were the main predictors for HT.

Conclusion: Although it is characteristically an indolent disease, our study demonstrated that a significant portion of FL patients have shortened survival. Here, we confirmed this prognostic heterogeneity, particularly considering the clinical staging and tumor burden. Therefore, FL patients with AS-HTV had higher HT rates and early-relapses, both classic adverse prognostic markers, as well as a tendency to higher mortality. We also identified clinical and laboratory predictors for HT, which may in a near future direct adapted-risk therapeutic strategies.

Disclosures No relevant conflicts of interest to declare.

Table 1 – Baseline demographic and clinical-laboratory characteristics of 223 FL patients

Baseline characteristic	N=223	%
Female	121	54.8
Median age (range)	60 years (30-98)	---
≥ 2 comorbidities	31	13.9
ECOG ≥ 2	34	15.2
CS III/IV	190	85.3
B-symptoms	115	51.6
Bulky disease ≥ 7 cm	99	44.4
Serous effusion	47	21.1
PB involvement	26	11.7
Splenomegaly	28	12.6
BM involvement	109	48.9
≥ 4 nodal areas involved by FL	125	56.0
FLIPI score		
- low	51	22.9
- intermediate	62	27.8
- high	110	49.3
FLIPI-2 score		
- low	35	15.7
- intermediate	87	39.0
- high	101	45.3
Laboratory feature	**Median**	**Range (min-max)**
Hemoglobin (g/L)	132	40-177
WBC (x 109 cells/L)	6.5	1.86-153.4
Neutrophils (x 109 cells/L)	4.0	0.65-13.3
Lymphocytes (x 109 cells/L)	1.5	0.3-150.4
Monocytes (x 109 cells/L)	0.6	0-6.1
Platelets (z 109 cells/L)	204	43-522
LDH (U/L)	302	97-3405
LDHp/LDHc ratio	0.89	0.33-8.58
B2-microglobulin (mg/dL)	2.6	0.30-32.2
Albumin (g/dL)	4.4	2.0-5.4
Globulin (g/dL)	2.5	1.3-3.6

ECOG: Eastern Cooperative Oncology Group; CS: clinical stage; PB: peripheral blood; BM: bone marrow; FL: follicular lymphoma; FLIPI: Follicular Lymphoma International Prognostic Index; WBC: white blood count; LDH: lactate dehydrogenase; LDHp/LDHc: LDH patient/control ratio.

Table 2 – Outcomes and up-front therapeutic modalities by staging and tumor burden

Outcome	ES (I/II) (N=33)	AS (III/IV) LTV (N=41)	AS (III/IV) HTV (N=149)	p-value
Mortality	5 (15.2%)	12 (29.3%)	48 (32.2%)	0.145
Early-relapses*	6 (18.2%)	13 (31.7%)	62 (41.0%)	0.032
HT	1 (3.0%)	6 (14.6%)	30 (18.2%)	0.053
Treatment	**ES (I/II)**	**AS (III/IV) LTV**	**AS (III/IV) HTV**	**----**
WW	28/33 – 85.0%	41/41 – 100%	2/149 – 1.3%	----
Rituximab	0/33 – 0%	0/41 – 0%	116/149 – 77.8%	----
(R)-CHOP-like	0/33 – 0%	0/41 – 0%	89/149 – 59.7%	----
(R)-CVP-like	0/33 - 0%	0/41 – 0%	42/149 – 28.2%	----
Isolated IF-RT	5/33 – 15.1%	0/41 – 0%	0/149 – 0%	----
Other ICT regimens	0/33 – 0%	0/41 – 0%	16/149 – 10.7%	----

ES: early-stage; AS: advanced-stage; LTV: low tumor volume; HTV: high tumor volume; HT: histologic transformation to high-grade B-cell lymphoma; WW: watchful & waiting approach; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CVP: rituximab, cyclophosphamide, vincristine, and prednisone; IF-RT: involved-field radiotherapy; ICT: immunochemotherapy. *Early-relapses: < 24 months from diagnosis.

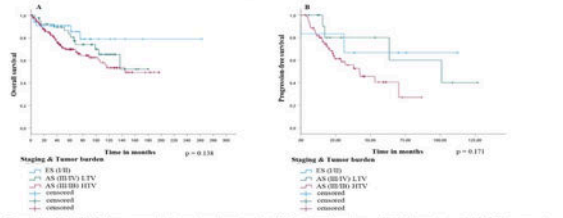

Figure 1: (A) – OS and (B) – PFS curves categorized by staging and tumor burden in 223 FL patients. ES: early-stage (I/II); AS: advanced-stage (III/IV); LTV: low tumor volume; HTV: high tumor volume.

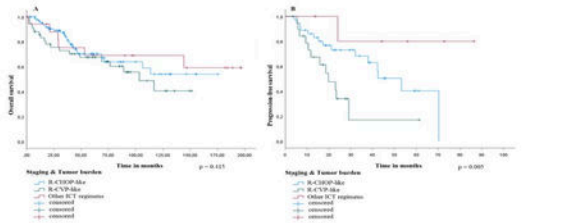

Figure 2: (A) – OS and (B) – PFS curves categorized by treatment modality in 149 FL patients with AS (III/IV) HTV. R-CHOP: rituximab, cyclophosphamide, vincristine and prednisone; R-CVP: rituximab, cyclophosphamide, vincristine and prednisone; Other ICT regimes: combinations based on fludarabine plus rituximab +/- cyclophosphamide.

Figure 1

https://doi.org/10.1182/blood-2023-186375