Follicular Lymphoma Grade 3: A Comprehensive Review

Alfadel Alshaibani, MD,[1] Riad El Fakih, MD,[1] Anna Sureda, MD, PhD,[2] Mohamed A. Kharfan-Dabaja, MD, MBA,[3] and Mahmoud Aljurf, MD[1]

[1]King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

[2]Institut Català d'Oncologia L'Hospitalet, Barcelona, Spain

[3]Division of Hematology-Oncology, Blood and Marrow Transplantation Program, Mayo Clinic, Jacksonville, Florida

Corresponding author:
Alfadel Alshaibani, MBBS
King Faisal Specialist Hospital and Research Center
Almathar Ash Shamali
Riyadh 11564
Saudi Arabia
Tel: +966114647272, ext 82143
Email: Aalshaibani@kfshrc.edu.sa

Abstract: Follicular lymphoma (FL) is a heterogeneous entity with disparate outcomes based on clinical and pathologic characteristics. An increasingly detailed understanding of high-grade FL (grade 3) has led to the identification of separate categories of FL3A and FL3B. Recently, genomic studies have made much progress in delineating the genetic differences between FL3A and FL3B. Although a general consensus exists that FL3B follows an aggressive course matching that of diffuse large B-cell lymphoma, there is less certainty regarding the course of FL3A. Uncertainty also exists regarding the management of high-grade FL. Given that a majority of the prospective landmark trials in FL have excluded patients with high-grade FL, most of the available evidence is retrospective. This review summarizes the recent advances in the management of high-grade FL.

Keywords
Follicular lymphoma, high-grade FL, indolent lymphoma, non-Hodgkin lymphoma

Introduction

Follicular lymphoma (FL) is an indolent lymphoma with an annual incidence of approximately 3.18 cases per 100,000 people.[1] The incidence, which has been stable over time but varies by ethnicity, is highest among White individuals.[1] FL accounts for 22% of non-Hodgkin lymphomas and affects mainly adults; the median age at diagnosis is 59 years.[2]

FL has been divided into 4 different grades; most cases are grade 1 or 2. The clinical course and optimal treatment regimen for FL grade 3 are less certain than those for grades 1 and 2. FL grade 3 has been subdivided into grade 3A (FL3A) and grade 3B (FL3B). Although a consensus exists that FL3B follows an aggressive course matching that of diffuse large B-cell lymphoma (DLBCL), there is less certainty about the course of FL3A. Some authors suggest that it is similar to the indolent clinical course of FL grades 1 and 2, which

is characterized by features such as slow progression, frequent relapse, and a limited possibility of cure.[3-5] Others, however, suggest that FL3A has a clinical course similar to that of FL3B, which is more aggressive but can be cured with chemotherapy.[6-8]

Pathology

FL comprises a group of malignant lymphomas consisting of follicle center cells—a mixture of cleaved cells (centrocytes) and non-cleaved large cells (centroblasts). FL is a germinal center–derived neoplasm that typically grows in a follicular pattern—hence the name FL. The histologic grade of FL depends on the number of centroblasts and centrocytes in a given sample.

The Mann and Berard grading system was first incorporated into the diagnostic criteria for FL in 1994, when FL with more than 15 centroblasts per high-power field was defined as FL grade 3. The World Health Organization further divides FL grade 3 into FL3A and FL3B depending on the presence or absence of centrocytes, respectively.[9-11] A predominance of centroblasts is, interestingly, a typical cytologic feature of another aggressive lymphoma—namely, diffuse large B-cell lymphoma (DLBCL).[12] Despite the presence of centroblasts, FL3B is typically differentiated from DLBCL by the existence of a focal follicular pattern to a certain degree.[12] Even among specialized hematopathologists and despite all harmonization efforts, significant interobserver variability and a lack of reproducibility still occur when the grade of FL is being determined.[6,13-15]

The Ki67 proliferation index is typically higher than 20 in FL grade 3, whereas it is generally less than 20 in most cases of FL grade 1 or 2.[16,17] A minority of cases of low-grade FL with a high Ki67 index behave more aggressively than cases with a low Ki67 index and exhibit clinical behavior similar to that of FL grade 3.[17]

Immunophenotype and Cytogenetic Abnormalities

Because the tumor cells in FL have a germinal center origin, they typically express B-cell–related antigens (eg, CD19, CD20, CD22, and CD79a) and surface immunoglobulins (IgM with or without IgD, IgG, or rarely IgA). Additionally, CD10, BCL2, and BCL6 expression is typically positive, whereas CD43 and CD5 expression is typically negative.[12,18-22]

The hallmark of FL is BCL2 upregulation caused by the chromosomal translocation t(14;18). This translocation is expressed in 90% of cases of FL grades 1 and 2.[12] It is also present less frequently in FL grade 3, occurring in 73% of cases of FL3A and 13% of cases of FL3B. The incidence of BCL6 rearrangement (3q27 breaks) is higher in FL3B than in FL3A.[21,23]

Table. Subtypes of Follicular Lymphoma Grade 3B

Subtypes	t(14;18)	3q27 Aberration	Remarks
Group 1	Present	Absent	–
Group 2	Absent	Absent	Other cytogenetic aberrations can be identified
Group 3	Absent	Present	More commonly associated with concomitant DLBCL

DLBCL, diffuse large B-cell lymphoma.

The genetic differences between FL3A and FL3B are mirrored in their immunohistochemical status. CD10 expression is predominantly positive in most cases of FL3A (90%), whereas nearly half of cases of FL3B are negative for CD10 expression. In addition, 44% of cases of FL3B expressed IRF4/MUM1+ and no cases of FL3A expressed IRF4/MUM1 in one report.[24] This finding supports a late germinal center B-cell phenotype for FL3B.[25]

Because of the unique cytologic profile of FL3B, 3 distinct entity subtypes have been described (Table): group 1, t(14;18) with no 3q27/BCL6 rearrangement; group 2, cytogenetic aberrations with no t(14;18) and no 3q27/BCL6 rearrangement; and group 3, 3q27/BCL6 rearrangement with no t(14;18).[26] Breaks in 3q27 have been identified in cases of FL3B with accompanying DLBCL. Cases of FL3B typically lack both abnormalities.[27] Furthermore, IRF4 (MUM1) and MYC breaks are more frequent than in grades 1 through 3A.[24] It is important to note that although DLBCL and FL3B share a rearrangement affecting 3q27, which conceptually suggests a similar pathogenesis, the consistent observation of different break point regions in 3q27 suggests an alternative pathogenesis for FL3B.[12,28]

Because of the interobserver variability in FL grades, the expression profile of 81 genes has been used to distinguish low-grade FL from high-grade FL, with a high accuracy rate of 100%.[29] However, cost reduction and further validation are required before this gene expression profile can be routinely adopted.[15]

Clinical Course

FL commonly presents in middle-aged patients.[30,31] Most patients present with widespread lymph node enlargement that typically waxes and wanes spontaneously.[2] Hilar and mediastinal lymph nodes are frequently involved, but

bulky disease is quite rare.[32,33] B symptoms (night sweats, weight loss, and fever) are encountered in approximately 20% of cases.[33] In contrast to lower-grade FL, FL3B tends to involve the bone marrow or peripheral blood less often, and patients typically have larger lymph nodes. Approximately 65% to 70% of patients with FL grade 3 present with advanced disease.[34] Despite the existence of widespread disease at presentation, most patients with FL are asymptomatic at diagnosis.

Management and Prognosis

The management of patients with low-grade FL (grades 1 and 2) depends on the stage of disease at presentation and whether symptoms are present. Management ranges from a watch-and-wait approach to chemoimmunotherapy.[36-38] The most commonly used chemoimmunotherapy regimens are bendamustine and rituximab (BR) and rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP).[37-39] The outcomes with BR are comparable to those of R-CHOP, with less toxicity; therefore, BR has been widely adopted as frontline chemotherapy in patients with low-grade FL.

The management of high-grade FL (grades 3A and 3B) is less certain. Patients with FL grade 3 were excluded from the landmark trials StiL[39] and BRIGHT.[40] Most of the trials in FL grade 3 were of a retrospective nature. Currently, it is uncertain whether patients with FL3A should be treated as if they have aggressive or indolent lymphoma. Pouyiourou and colleagues retrospectively looked at the outcomes of 95 patients with a diagnosis of FL3A who were treated with R-CHOP or BR. The response rate was higher (95% vs 76%) and the overall survival (OS) rate at 3 years was also higher (89% vs 73%; *P*=.008) in the patients who received R-CHOP. The difference in progression-free survival (PFS) was not statistically significant. The rate of transformation into aggressive lymphoma was the same in both arms. This trial suggested a benefit of R-CHOP over BR for FL3A.[35]

Mondello and colleagues retrospectively assessed the outcomes of 132 patients with FL3A treated with either BR or R-CHOP in the first-line setting. In contrast to the previous study, the complete remission rates were similar for R-CHOP and BR (97% and 96%, respectively; *P*=.3). The relapse rate was higher in the patients who received R-CHOP than in those who received BR (41% vs 16%, respectively), which translated into a longer PFS in the BR-treated patients (15 vs 11.7 years). The 3-year OS rates did not differ between the 2 regimens.[41] It is worth noting that the risk for relapse was also lower with BR than with R-CHOP in the StiL trial, which looked at patients with low-grade FL (39% vs 57%, respectively).[39] This finding is likely secondary to the higher rate of tumor eradication with the 2-drug regimen.[41] Prospective trials to validate these findings are lacking.

The contradictory results from these 2 retrospective trials likely reflect the heterogeneity of FL3A and the limitations of retrospective trials in general. In fact, the heterogeneity of FL3A is evident in the published literature, in which FL3A appears to be similar to FL grades 1 and 2 from an immunohistochemical standpoint and also at the molecular level (in the BCL2 and BCL6 translocations) while resembling FL3B in terms of gene expression profiling.[35]

In terms of side effects, rates of grades 3 and 4 neutropenia are lower with BR than with R-CHOP, translating into a significantly reduced occurrence of infections.[39] However, the risk for nausea, vomiting, and skin reaction is significantly higher with BR than with R-CHOP.[40]

Because of the aggressive nature of FL3B and its molecular similarity to DLBCL, international guidelines from organizations such as the European Society for Medical Oncology[42] and the National Comprehensive Cancer Network[43] have advocated use of the chemoimmunotherapy regimens prescribed for clinically aggressive lymphomas (eg, DLBCL). Most of the studies that formed the basis for this recommendation were conducted in the pre-rituximab era, which limits their clinical application in current practice.[15] No high-quality data are available to guide therapeutic options in patients with FL3B. Most of the available data are retrospective, and FL3B is often included with low-grade lymphoma or DLBCL.

Barraclough and colleagues reported the largest retrospective study, in which records from 161 patients with FL3B and 171 patients with DLBCL were reviewed. In 96% of the cases, the treatment given was rituximab or obinutuzumab (Gazyva, Genentech) plus CHOP, with or without radiation therapy. With a median follow-up of 4 years, the PFS rate was 72% and the OS rate was 84%. The survival outcomes of patients with FL3B were similar to those of patients with FL3A/FL3B and patients with FL3B/DLBCL (PFS, *P*=.23; OS, *P*=.27). Interestingly, and contradicting the findings in other studies, an ongoing pattern of relapse was noted in the patients with FL3B, with most biopsied cases demonstrating DLBCL.[44]

In another study, of 53 patients with FL3A and FL3B, R-CHOP was the initial treatment in 79% of the patients with FL3B and in 72% of those with FL3A. Both PFS and OS were similar in the 2 groups. As in other trials, a PFS plateau was observed in the patients with FL3B, confirming a higher cure rate in this patient population.

Despite the improved effectiveness with chemoimmunotherapy regimens in patients with FL, progression

of disease occurs in approximately 20% within 24 months of first-line therapy (POD24). The risk for death within 5 years after diagnosis is substantially greater in patients with POD24 than in patients who do not have disease progression within 24 months.[45] This finding has been validated by the German Low Grade Lymphoma Study Group (GLSG), which looked at the prognostic value of POD24 in patients treated with frontline R-CHOP, and by the British Columbia Cancer Agency in a population-based cohort treated with rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP). POD24 occurred in 17% of patients in the GLSG study and 23% of those in the BC Cancer Agency study; the 5-year OS rates were 41% in the GLSG patients and 26% in the British Columbia Cancer Agency patients with POD24, whereas they were 91% and 86%, respectively, for the patients without POD24 (P<.001).[46]

Autologous stem cell transplant (autoSCT) consolidation after salvage chemoimmunotherapy for eligible (ie, young and fit) patients with relapsed FL can result in sustained remission. A European phase 3 randomized trial called CUP compared chemotherapy vs autoSCT. At a median follow-up of 69 months, the patients who underwent transplant had a higher 4-year PFS rate (55%-58% vs 26%) and OS rate (71%-77% vs 46%) than those who received chemotherapy.[47] It is important to keep in mind that this trial was conducted before the rituximab era.

Some evidence suggests that aggressive salvage therapies and autoSCT may override the negative effect of early relapsed disease,[48] as demonstrated in the follow-up study of GLSG1996 and GLSG2000. In patients with POD24, autoSCT was associated with a survival advantage in comparison with no transplant (5-year OS rates, 77% vs 59%, respectively; P=.039).

The benefit of autoSCT also was examined in a retrospective analysis of data from the Center for International Blood and Marrow Transplant Research (CIBMTR) and the National LymphoCare Study. The analysis involved patients who received frontline treatment with rituximab-based combination therapy and either progressed within 2 years or did not respond to initial therapy. When the population was analyzed as a whole, OS was similar in the autoSCT and non-autoSCT groups. However, in a subset analysis of patients with early treatment failure, the 5-year OS rate was higher in the autoSCT group than in the non-transplant group (73% vs 60%; P=.5).[49]

Allogeneic stem cell transplant (alloSCT) is a valid option for the treatment of patients with relapsed FL. When compared with autoSCT, alloSCT is associated with a higher rate of transplant mortality but a lower risk for relapse and a greater potential for cure. This finding was demonstrated in an analysis of CIBMTR data from 440 patients with POD24 who were treated with autoSCT, matched sibling donor (MSD) alloSCT, or matched unrelated donor (MUD) alloSCT. With a median follow-up of 69 to 73 months, the adjusted probability of 5-year OS was significantly higher after autoSCT (70%) or MSD alloSCT (73%) than after MUD alloSCT (49%; P=.0008). The 5-year adjusted probability of non-relapse mortality was significantly lower for autoSCT (5%) than for MSD alloSCT (17%) or MUD alloSCT (33%; P≤.0001). The adjusted probability of 5-year disease relapse was lower with MSD alloSCT (31%) or MUD alloSCT (23%) than with autoSCT (58%; P<.0001).[50]

When alloSCT is used for patients with FL, nonmyeloablative preparative regimens are typically the preferred regimens. Khouri and colleagues published the results of 47 patients with relapsed FL after MSD nonmyeloablative alloSCT in which a fludarabine, cyclophosphamide, and rituximab conditioning regimen was used. The estimated 5-year OS rate was 85%, and the estimated 5-year PFS rate was 83%. The incidence of grade 2 to 4 acute graft-vs-host disease was 11%.[51]

Chimeric antigen receptor (CAR) T-cell therapy is a treatment option for patients with multiple relapses of FL. Axicabtagene ciloleucel (Yescarta, Kite Pharma), also known as axi-cel, received accelerated approval from the US Food and Drug Administration (FDA) for patients whose disease progressed through 2 or more lines of therapies. The approval was based on the phase 2 ZUMA-5 study, in which 124 patients with relapsed or refractory FL received axi-cel. Data are available only for a subgroup of patients with FL (n=84) who had follow-up after 12 months or longer. Treatment with axi-cel resulted in an 80% complete remission rate. The median PFS and OS were not reached. Details about FL grading were not presented in the abstract.[52] The TRANSCEND NHL 001 trial studied lisocabtagene maraleucel (Breyanzi, Juno Therapeutics), also known as liso-cel, in patients with relapsed or refractory large B-cell lymphoma. Of 44 patients, 3 had FL3B, and all remained in complete response after 1 year of therapy. It should be noted that although initial studies suggest activity of CAR T-cell therapy against relapsed FL, the quality of the available evidence is low because of the limited number of patients included in these trials and the relatively short follow-ups. Additionally, CAR T-cell therapy can be associated with significant toxicity and high cost.

Mosunetuzumab is a novel agent that shows promise in the treatment of FL. It is a CD20/CD3 bispecific antibody that redirects T cells to target and eliminate malignant B cells. In a phase 1/2 trial of a total of 90 patients with FL that had relapsed or was refractory to at least 2 prior lines of therapy, mosunetuzumab was

associated with a complete response rate of 60% and a median PFS of 17.9 months. Mosunetuzumab had a manageable safety profile, with a low discontinuation rate due to adverse events (4%). Most of the cases of cytokine release syndrome were mild and occurred in cycle 1, and they resolved in all patients after a median of 3 days.[53,54]

Prognosis

The prognosis in patients with FL is variable. Some patients have waxing and waning disease for many years without therapy.[55] Others have a more aggressive clinical course and poor outcomes.[45] Because of the variability in the clinical course of FL, many prognostic indices have been proposed, including the International Prognostic Index (IPI),[56] the Follicular Lymphoma International Prognostic Index (FLIPI),[32] FLIPI2,[57] and the Primary Rituximab and Maintenance Prognostic Index (PRIMA-PI).[58] Although the histologic grade of FL is relevant to patient survival, grade was not included in the original FLIPI scoring system. Among these scoring systems, FLIPI2 and PRIMA-PI included patients with FL3A but not FL3B, and they can be used for prognostication of FL3A. Because of the rarity of FL3B, patients with FL3B were not included in the primary analysis of these trials. Retrospective series suggest that the proportion of patients with high-risk IPI scores is higher in FL3B subgroups than in FL3A subgroups (36% vs 17%; P=.03),[4] but lower than in patients with DLBCL (25% vs 54%; P≤.001).[15] This finding may suggest the utility of the IPI in FL3B. Notably, the relapse rate after 5 years is fairly low in FL3B disease, with a majority of these patients considered cured.[7]

It is worth mentioning that although earlier reports suggested similar survival curves for grades 3A and 3B,[4,5,59] most of these studies had few patients with FL3B and short follow-ups. Wahlin and colleagues demonstrated that after longer follow-up, outcomes in patients with FL3B are inferior to those in patients with FL3A. In a retrospective analysis of 505 patients with FL (94 with FL3A) who had a median follow-up of 10 years, the clinical course for grade 3A disease was similar to that for grades 1 and 2 disease. Mortality rates were higher for FL3B than for FL grades 1 through 3A (P=.008), but outcomes were improved after an upfront anthracycline-containing regimen (P=.015). Patients with FL3B had no relapses or deaths beyond 5 years of follow-up.[7]

The prognostic significance of BCL2 has been evaluated in clinical trials. Earlier trials failed to show any effect of BCL2 protein expression on survival[60,61]; however, subsequent reports suggested a worse prognosis in patients with BCL2 protein expression.[42,64-67] Trial results, however, are conflicting regarding the prognostic value of BCL6 expression; some suggest a negative effect on survival,[68-70] whereas others failed to demonstrate such an effect.[71-74] Transformation into aggressive lymphoma and failure to reach a complete or partial response were independent risk factors for shorter OS in a multivariable analysis.[35] Uptake on positron emission tomography does not seem to correlate with either the grade of lymphoma or the outcome following R-CHOP treatment in patients with FL.[73]

Conclusion

In summary, the prognosis for patients with FL is quite favorable. However, the disease course can be more aggressive for a subgroup of patients. Only a limited number of trials have looked at the optimal management of patients with FL grade 3. Large, prospective trials evaluating the optimal evidence-based management approach to patients with FL grade 3 are lacking and strongly needed.

Disclosures

None of the authors have any conflicts of interest to disclose related to the topic of follicular lymphoma grade 3.

References

1. Morton LM, Wang SS, Devesa SS, Hartge P, Weisenburger DD, Linet MS. Lymphoma incidence patterns by WHO subtype in the United States, 1992-2001. *Blood*. 2006;107(1):265-276.
2. Armitage JO. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. *Blood*. 1997;89(11):3909-3918.
3. Maeshima AM, Taniguchi H, Nomoto J, et al. Prognostic implications of histologic grade and intensity of Bcl-2 expression in follicular lymphomas undergoing rituximab-containing therapy. *Hum Pathol*. 2013;44(11):2529-2535.
4. Shustik J, Quinn M, Connors JM, Gascoyne RD, Skinnider B, Sehn LH. Follicular non-Hodgkin lymphoma grades 3A and 3B have a similar outcome and appear incurable with anthracycline-based therapy. *Ann Oncol*. 2011;22(5):1164-1169.
5. Hsi ED, Mirza I, Lozanski G, et al. A clinicopathologic evaluation of follicular lymphoma grade 3A versus grade 3B reveals no survival differences. *Arch Pathol Lab Med*. 2004;128(8):863-868.
6. Koch K, Hoster E, Ziepert M, et al. Clinical, pathological and genetic features of follicular lymphoma grade 3A: a joint analysis of the German low-grade and high-grade lymphoma study groups GLSG and DSHNHL. *Ann Oncol*. 2016;27(7):1323-1329.
7. Wahlin BE, Yri OE, Kimby E, et al. Clinical significance of the WHO grades of follicular lymphoma in a population-based cohort of 505 patients with long follow-up times. *Br J Haematol*. 2012;156(2):225-233.
8. Ganti AK, Weisenburger DD, Smith LM, et al. Patients with grade 3 follicular lymphoma have prolonged relapse-free survival following anthracycline-based chemotherapy: the Nebraska Lymphoma Study Group Experience. *Ann Oncol*. 2006;17(6):920-927.
9. Sabattini E, Bacci F, Sagramoso C, Pileri SA. WHO classification of tumours of haematopoietic and lymphoid tissues in 2008: an overview. *Pathologica*. 2010;102(3):83-87.
10. Mann RB, Berard CW. Criteria for the cytologic subclassification of follicular lymphomas: a proposed alternative method. *Hematol Oncol*. 1983;1(2):187-192.
11. Harris NL, Jaffe ES, Stein H, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. *Blood*. 1994;84(5):1361-1392.
12. Bosga-Bouwer AG, van den Berg A, Haralambieva E, et al. Molecular, cytogenetic, and immunophenotypic characterization of follicular lymphoma grade 3B; a separate entity or part of the spectrum of diffuse large B-cell lymphoma or follicular lymphoma? *Hum Pathol*. 2006;37(5):528-533.

13. Bowen JM, Perry AM, Laurini JA, et al. Lymphoma diagnosis at an academic centre: rate of revision and impact on patient care. *Br J Haematol*. 2014;166(2):202-208.
14. Martinez AE, Lin L, Dunphy CH. Grading of follicular lymphoma: comparison of routine histology with immunohistochemistry. *Arch Pathol Lab Med*. 2007;131(7):1084-1088.
15. Barraclough A, Bishton M, Cheah CY, Villa D, Hawkes EA. The diagnostic and therapeutic challenges of Grade 3B follicular lymphoma. *Br J Haematol*. 2021;195(1):15-24.
16. Koster A, Tromp HA, Raemaekers JMM, et al. The prognostic significance of the intra-follicular tumor cell proliferative rate in follicular lymphoma. *Haematologica*. 2007;92(2):184-190.
17. Wang SA, Wang L, Hochberg EP, Muzikansky A, Harris NL, Hasserjian RP. Low histologic grade follicular lymphoma with high proliferation index: morphologic and clinical features. *Am J Surg Pathol*. 2005;29(11):1490-1496.
18. Karube K, Guo Y, Suzumiya J, et al. CD10-MUM1+ follicular lymphoma lacks BCL2 gene translocation and shows characteristic biologic and clinical features. *Blood*. 2007;109(7):3076-3079.
19. Cattoretti G, Chang CC, Cechova K, et al. BCL-6 protein is expressed in germinal-center B cells. *Blood*. 1995;86(1):45-53.
20. Lai R, Weiss LM, Chang KL, Arber DA. Frequency of CD43 expression in non-Hodgkin lymphoma. A survey of 742 cases and further characterization of rare CD43+ follicular lymphomas. *Am J Clin Pathol*. 1999;111(4):488-494.
21. Ott G, Katzenberger T, Lohr A, et al. Cytomorphologic, immunohistochemical, and cytogenetic profiles of follicular lymphoma: 2 types of follicular lymphoma grade 3. *Blood*. 2002;99(10):3806-3812.
22. Pittaluga S, Ayoubi TAY, Wlodarska I, et al. BCL-6 expression in reactive lymphoid tissue and in B-cell non-Hodgkin's lymphomas. *J Pathol*. 1996;179(2):145-150.
23. Cleary ML, Sklar J. Nucleotide sequence of a t(14;18) chromosomal breakpoint in follicular lymphoma and demonstration of a breakpoint-cluster region near a transcriptionally active locus on chromosome 18. *Proc Natl Acad Sci USA*. 1985;82(21):7439-7443.
24. Horn H, Schmelter C, Leich E, et al. Follicular lymphoma grade 3B is a distinct neoplasm according to cytogenetic and immunohistochemical profiles. *Haematologica*. 2011;96(9):1327-1334.
25. Chang ST, Lu YH, Lu CL, et al. Follicular lymphoma in Taiwan: a low frequency of t(14;18), with grade 3A tumours more closely related to grade 3B than to low-grade tumours. *Histopathology*. 2013;63(1):1-12.
26. Bosga-Bouwer AG, van Imhoff GW, Boonstra R, et al. Follicular lymphoma grade 3B includes 3 cytogenetically defined subgroups with primary t(14;18), 3q27, or other translocations: t(14;18) and 3q27 are mutually exclusive. *Blood*. 2003;101(3):1149-1154.
27. Katzenberger T, Ott G, Klein T, Kalla J, Müller-Hermelink HK, Ott MM. Cytogenetic alterations affecting BCL6 are predominantly found in follicular lymphomas grade 3B with a diffuse large B-cell component. *Am J Pathol*. 2004;165(2):481-490.
28. Bosga-Bouwer AG, Haralambieva E, Booman M, et al. BCL6 alternative translocation breakpoint cluster region associated with follicular lymphoma grade 3B. *Genes Chromosom Cancer*. 2005;44(3):301-304.
29. Glas AM, Kersten MJ, Delahaye LJMJ, et al. Gene expression profiling in follicular lymphoma to assess clinical aggressiveness and to guide the choice of treatment. *Blood*. 2005;105(1):301-307.
30. Gallagher CJ, Gregory WM, Jones AE, et al. Follicular lymphoma: prognostic factors for response and survival. *J Clin Oncol*. 1986;4(10):1470-1480.
31. Armitage JO, Weisenburger DD. New approach to classifying non-Hodgkin's lymphomas: clinical features of the major histologic subtypes. Non-Hodgkin's Lymphoma Classification Project. *J Clin Oncol*. 1998;16(8):2780-2795.
32. Solal-Céligny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. *Blood*. 2004;104(5):1258-1265.
33. Martin AR, Weisenburger DD, Chan WC, et al. Prognostic value of cellular proliferation and histologic grade in follicular lymphoma. *Blood*. 1995;85(12):3671-3678.
34. Vitolo U, Ferreri AJM, Montoto S. Follicular lymphomas. *Crit Rev Oncol Hematol*. 2008;66(3):248-261.
35. Pouyiourou M, Meyer A, Stroux A, et al; East German Study Group for Hematology and Oncology (OSHO). First-line treatment with R-CHOP or rituximab-bendamustine in patients with follicular lymphoma grade 3A-results of a retrospective analysis. *Ann Hematol*. 2020;99(12):2821-2829.
36. Marcus R, Davies A, Ando K, et al. Obinutuzumab for the first-line treatment of follicular lymphoma. *N Engl J Med*. 2017;377(14):1331-1344.
37. Hiddemann W, Barbui AM, Canales MA, et al. Immunochemotherapy with obinutuzumab or rituximab for previously untreated follicular lymphoma in the GALLIUM study: influence of chemotherapy on efficacy and safety. *J Clin Oncol*. 2018;36(23):2395-2404.
38. Salles G, Mounier N, de Guibert S, et al. Rituximab combined with chemotherapy and interferon in follicular lymphoma patients: results of the GELA-GOELAMS FL2000 study. *Blood*. 2008;112(13):4824-4831.
39. Rummel MJ, Niederle N, Maschmeyer G, et al; Study group indolent Lymphomas (StiL). Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. *Lancet*. 2013;381(9873):1203-1210.
40. Flinn IW, van der Jagt R, Kahl BS, et al. Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. *Blood*. 2014;123(19):2944-2952.
41. Mondello P, Steiner N, Willenbacher W, et al. Bendamustine plus rituximab versus R-CHOP as first-line treatment for patients with follicular lymphoma grade 3A: evidence from a multicenter, retrospective study. *Oncologist*. 2018;23(4):454-460.
42. Dreyling M, Ghielmini M, Rule S, et al; ESMO Guidelines Committee. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2021;32(3):298-308.
43. Zelenetz AD, Gordon LI, Abramson JS, et al. NCCN Guidelines Insights: B-cell lymphomas, version 3.2019. *J Natl Compr Canc Netw*. 2019;17(6):650-661.
44. Barraclough A, England J, Wight J, et al. Patients with G3B follicular lymphoma experience superior outcomes compared with diffuse large cell lymphoma, but show a continuous pat- tern of relapse [EHA abstract EP1175]. *EHA HemaSphere*. 2020;4(suppl 1).
45. Casulo C, Byrtek M, Dawson KL, et al. Early relapse of follicular lymphoma after rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone defines patients at high risk for death: an analysis from the National LymphoCare Study. *J Clin Oncol*. 2015;33(23):2516-2522.
46. Jurinovic V, Kridel R, Staiger AM, et al. Clinicogenetic risk models predict early progression of follicular lymphoma after first-line immunochemotherapy. *Blood*. 2016;128(8):1112-1120.
47. Schouten HC, Qian W, Kvaloy S, et al. High-dose therapy improves progression-free survival and survival in relapsed follicular non-Hodgkin's lymphoma: results from the randomized European CUP trial. *J Clin Oncol*. 2003;21(21):3918-3927.
48. Sabloff M, Atkins HL, Bence-Bruckler I, et al. A 15-year analysis of early and late autologous hematopoietic stem cell transplant in relapsed, aggressive, transformed, and nontransformed follicular lymphoma. *Biol Blood Marrow Transplant*. 2007;13(8):956-964.
49. Casulo C, Friedberg JW, Ahn KW, et al. Autologous transplantation in follicular lymphoma with early therapy failure: a National LymphoCare study and Center for International Blood and Marrow Transplant research analysis. *Biol Blood Marrow Transplant*. 2018;24(6):1163-1171.
50. Smith SM, Godfrey J, Ahn KW, et al. Autologous transplantation versus allogeneic transplantation in patients with follicular lymphoma experiencing early treatment failure. *Cancer*. 2018;124(12):2541-2551.
51. Khouri IF, McLaughlin P, Saliba RM, et al. Eight-year experience with allogeneic stem cell transplantation for relapsed follicular lymphoma after nonmyeloablative conditioning with fludarabine, cyclophosphamide, and rituximab. *Blood*. 2008;111(12):5530-5536.
52. Jacobson C, Chavez JC, Sehgal AR, et al. Primary analysis of Zuma-5: a phase 2 study of axicabtagene ciloleucel (axi-cel) in patients with relapsed/refractory (R/R) indolent non-Hodgkin lymphoma (iNHL) [ASH abstract 700]. *Blood*. 2020;136(1)(suppl).
53. Assouline SE, Kim WS, Sehn LH, et al. Mosunetuzumab shows promising efficacy in patients with multiply relapsed follicular lymphoma: updated clinical experience from a phase I dose-escalation trial [ASH abstract 702]. *Blood*. 2020;136(1)(suppl).
54. Assouline S, Kim WS, Sehn LH, et al. Updated experience from mosunetuzumab in multiple relapsed follicular lymphoma: promising efficacy from a phase I trial [SOHO abstract IBCL-373]. *Clin Lymphoma Myeloma Leuk*. 2021;21(suppl 1).
55. Horning SJ, Rosenberg SA. The natural history of initially untreated low-grade non-Hodgkin's lymphomas. *N Engl J Med*. 1984;311(23):1471-1475.
56. International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. *N Engl J Med*. 1993;329(14):987-994.
57. Federico M, Bellei M, Marcheselli L, et al. Follicular lymphoma international prognostic index 2: a new prognostic index for follicular lymphoma developed by the international follicular lymphoma prognostic factor project. *J Clin Oncol*.

2009;27(27):4555-4562.
58. Bachy E, Maurer MJ, Habermann TM, et al. A simplified scoring system in de novo follicular lymphoma treated initially with immunochemotherapy. *Blood*. 2018;132(1):49-58.
59. Chau I, Jones R, Cunningham D, et al. Outcome of follicular lymphoma grade 3: is anthracycline necessary as front-line therapy? *Br J Cancer*. 2003;89(1):36-42.
60. Llanos M, Alvarez-Argüelles H, Alemán R, Oramas J, Díaz-Flores L, Batista N. Prognostic significance of Ki-67 nuclear proliferative antigen, bcl-2 protein, and p53 expression in follicular and diffuse large B-cell lymphoma. *Med Oncol*. 2001;18(1):15-22.
61. Tang SC, Visser L, Hepperle B, Hanson J, Poppema S. Clinical significance of bcl-2-MBR gene rearrangement and protein expression in diffuse large-cell non-Hodgkin's lymphoma: an analysis of 83 cases. *J Clin Oncol*. 1994;12(1):149-154.
62. Hadzi-Pecova L, Petrusevska G, Stojanovic A. Non-Hodgkin's lymphomas: immunologic prognostic studies. *Prilozi*. 2007;28(1):39-55.
63. Piris MA, Pezzella F, Martinez-Montero JC, et al. p53 and bcl-2 expression in high-grade B-cell lymphomas: correlation with survival time. *Br J Cancer*. 1994;69(2):337-341.
64. Hallack Neto AE, Siqueira SAC, Dulley FL, et al. Bcl-2 protein frequency in patients with high-risk diffuse large B-cell lymphoma. *Sao Paulo Med J*. 2010;128(1):14-17.
65. Mahmoud HM, El-Sakhawy YN. Significance of Bcl-2 and Bcl-6 immunostaining in B-Non Hodgkin's lymphoma. *Hematol Rep*. 2011;3(3):e26.
66. Barrans SL, O'Connor SJM, Evans PAS, et al. Rearrangement of the BCL6 locus at 3q27 is an independent poor prognostic factor in nodal diffuse large B-cell lymphoma. *Br J Haematol*. 2002;117(2):322-332.
67. Lossos IS, Alizadeh AA, Eisen MB, et al. Ongoing immunoglobulin somatic mutation in germinal center B cell-like but not in activated B cell-like diffuse large cell lymphomas. *Proc Natl Acad Sci USA*. 2000;97(18):10209-10213.
68. Berglund M, Thunberg U, Amini RM, et al. Evaluation of immunophenotype in diffuse large B-cell lymphoma and its impact on prognosis. *Mod Pathol*. 2005;18(8):1113-1120.
69. Höller S, Horn H, Lohr A, et al. A cytomorphological and immunohistochemical profile of aggressive B-cell lymphoma: high clinical impact of a cumulative immunohistochemical outcome predictor score. *J Hematop*. 2009;2(4):187-194.
70. de Leval L, Harris NL. Variability in immunophenotype in diffuse large B-cell lymphoma and its clinical relevance. *Histopathology*. 2003;43(6):509-528.
71. Dogan A, Bagdi E, Munson P, Isaacson PG. CD10 and BCL-6 expression in paraffin sections of normal lymphoid tissue and B-cell lymphomas. *Am J Surg Pathol*. 2000;24(6):846-852.
72. Colomo L, López-Guillermo A, Perales M, et al. Clinical impact of the differentiation profile assessed by immunophenotyping in patients with diffuse large B-cell lymphoma. *Blood*. 2003;101(1):78-84.
73. Ahmed MA, Fowler N, Ma L, et al. SUVmax on pre-treatment FDG PET scan is not predictive of outcome in follicular lymphoma after R-CHOP therapy [ASH abstract 1629]. *Blood*. 2014;124(21)(suppl).