

Follicular Lymphoma: A Review of Mechanisms, Risk Factors, and Unmet Needs

FOLLICULAR LYMPHOMA (FL) IS an indolent, B-cell lymphoproliferative disorder that accounts for about 20% of all cases of non-Hodgkin lymphoma (NHL).^{1,2} Although findings from most studies point to a declining incidence of FL over the past several decades, certain subpopulations of patients may be at higher risk. In particular, there is a linear relationship between increasing age and risk,³ and unlike other NHL subtypes, FL occurs more commonly in women than men.^{1,3} Nevertheless, because of its low incidence, FL is considered an orphan disease in much of the world.²

Despite having a relatively favorable prognosis in the majority of cases,³ FL is associated with considerable clinical heterogeneity and molecular and morphologic diversity.¹ Correspondingly, older age^{2,4} and more advanced stage at the time of diagnosis² are associated with increased mortality rates. The hallmark translocation t(14;18), which is identified in 75% to 90% of cases,^{1,5} leads to overexpression of BCL2, an anti-apoptotic protein that promotes cell survival. On its own, BCL2, however, is not considered to be sufficient for lymphomagenesis.⁵⁻⁷

Because of the heterogeneous disease course of FL, decisions to initiate treatment for patients with the disorder are usually individualized and may be based on the patient's performance status and individual characteristics.⁸ Watchful waiting is commonly employed in frontline settings for individuals with asymptomatic, low tumor-burden FL,⁸ whereas chemoimmunotherapy, usually with the addition of rituximab, is generally preferred when treatment is initiated.⁹⁻¹¹ From a historical perspective, the introduction of rituximab to the treatment armamentarium for FL has significantly improved clinical outcomes,¹²⁻¹⁴ with median survival in the chemotherapy era approaching 20 years and median progression-free survival (PFS) greater than 7 years.¹² Unfortunately, however, about 20% of patients with FL experience disease progression within the first 2 years of first-line therapy, which, in turn, is associated with poor survival.^{10,12} Additionally, it has been found through long-term follow-up that about 60% to 70% of patients will experience a relapse despite initial response to therapy.⁸ Histologic transformation to a more aggressive lymphoma occurs in about 2% to 3% of cases per year and is associated with poor survival.⁵

Beyond the clinical implications, progressed FL has consequences for healthcare costs and impact on patients' quality of life. In one study, the 12-month cumulative costs associated with FL were approximately 3.5 times higher for patients with progressive disease than for individuals without progressive disease (\$30,890 vs \$8704), which was driven in large part by the use of rituximab-containing combination chemotherapy regimens. Patients with progressive FL had more total outpatient visits and laboratory procedures, as well as more frequent chemotherapy visits per month, than individuals with non-progressive disease.² Although decrements in quality of life outcomes have been reported for patients with FL, relapsed disease is associated with a more profound impact on quality of life, increased anxiety

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and depression, and greater loss of work productivity.²

Recent advances in the understanding of FL biology and pathogenesis have identified several somatic mutations and host immune factors thought to drive oncogenic signaling pathways that may be targetable with novel therapeutic approaches.⁸ This article reviews the pathogenesis, prognosis, state of treatment, and unmet needs of patients with FL.

Etiology and Pathogenesis

The family of NHL subtypes comprises about 90% of malignant lymphomas, with significant etiologic variation among NHL subtypes and differences in clinical presentation and course.¹

Genetic susceptibility and environmental factors have been shown to play a role in the etiology of FL, although the exact role of each and the extent of their influence on each other have yet to be elucidated.¹ Because some degree of genetic instability is integral for normal lymphocyte differentiation, progenitor B cells are particularly susceptible to acquiring chromosomal translocations and other oncogenic mutations.

Genome-wide association studies are helping to elucidate the role of genetic diversity in the etiology of various NHL subtypes, including FL, and to identify susceptibility variants in human leukocyte antigen (HLA) class 1 and 2 regions that may predispose lymphocytes to acquiring hallmark translocations. One study that used SNP2HLA as a reference reported that homozygosity in HLA class 2 loci—but not in any HLA class 1 loci—were associated with increased risk of FL.¹⁵ Because HLA class 1 and 2 molecules have distinct functions within the immune system, these data provide at least suggestive evidence that differing immune pathways are relevant for initiation and progression among the separate NHL subtypes.¹⁵ Perhaps related, single-nucleotide variants (SNVs) in the coding region for CXCR5, a receptor involved in B-cell migration and activation, are more strongly associated with risk for FL than other NHL subtypes.⁸ For instance, alterations in CXCR5 may alter host immune functions, potentially influencing FL initiation and progression.^{6,16} SNVs have also been identified in the HLA region, and 5 have been identified in non-HLA loci that are near genes coding for BCL2, offering evidence that SNVs may contribute toward predisposition for acquisition of t(14;18).^{5,6,17}

A complex series of pathways are suspected to perpetuate FL precursor cells to pathogenesis, including epigenetic dysregulation, increased stimulation of survival pathways, and immune evasion.⁵ Disruption of histone-modifying enzymes occurs through genetic lesions, which permit FL precursors to undertake rapid transcriptional and phenotypic alterations during the

differentiation process and enhance various survival pathways.⁵ Aberrant DNA methylation is recognized as an additional mode of epigenetic dysregulation in FL pathogenesis.⁵ In the context of cells already resistant to apoptosis due to BCL2 overexpression, such epigenetic dysregulation serves to perpetuate proliferation programs and genetic instability.⁵ Under normal conditions, BCL signaling drives formation and maintenance of the germinal center, whereas it must be downregulated to permit B cells to exit the germinal center and progress toward terminal differentiation. Constitutive expression of BCL locks B cells in a germinal center-derived phenotype, while also making the arrested B cell susceptible to DNA damage.⁵ In turn, “chronic active” B-cell receptor signaling affects activation of a variety of additional pathways, including NF- κ B, MAPK, and PI3K-AKT, that directly or indirectly promote cell survival.⁵ Finally, the skewing of T-cell composition within the FL microenvironment toward an immunosuppressive phenotype drives tumor growth by activation of B-cell receptors through paracrine secretion of protumor cytokines and by fostering escape from immune surveillance.⁵

Epidemiology

NHL is more common in developed countries; it is recognized as the 10th most common malignancy worldwide while ranking seventh in the developed world.¹ In a review of data from the National Cancer Data Base, which accounts for approximately 70% of newly diagnosed cancer cases in the United States and Puerto Rico, 596,476 cases of NHL were diagnosed between 1998 and 2011, of which 17.1% were FL.¹⁸ Rates appear to vary according to geographic region. One study reporting on trends in the United States, United Kingdom, France, Italy, the Netherlands, Australia, and Japan found an incidence ranging from 2.1 per 100,000 in France to 4.3 per 100,000 in the United States.² Other studies have found that FL accounts for a lesser proportion of all NHL cases in eastern countries than in the United States.¹⁸

Most evidence points to a trend in declining incidence of FL. Although results from a 2006 study reporting on surveillance, epidemiology and end results data for the period 1974 to 1992 demonstrated a modest increase in the numbers of follicular lymphoma cases,¹ findings from a 2016 study suggest declining incidence of follicular lymphoma from 2001 through 2012.³ The authors of the latter study reported an estimated incidence of 3.4 per 100,000 population (from 2011 to 2012), or about 13,960 new cases per year in the United States.³ The contrast in incidence in different time periods is similar to data for overall lymphoma incidence rates,

which increased steadily during the 1970s and 1980s before leveling off and eventually declining throughout the 1990s.³ One potential contributing factor in incidence trends for FL may be a decline in smoking rates since 2001; a positive association between smoking history and risk of FL has been noted in some studies.³ It has been suggested that tobacco use may induce the t(14;18) translocation, which is found in 70% to 95% of tumor tissue in patients with FL.^{1,5}

Notwithstanding overall trends, certain subpopulations continue to be disproportionately affected by FL. An increasing incidence of FL in individuals from age 30 to 70 years was observed in a large-scale analysis of data from the North American Association of Central Cancer Registries.³ Additionally, in contrast to other NHL subtypes, FL is more common in women than men.^{1,3} Geographic differences do not appear to account for the sex difference; a higher 10-year prevalence of FL among women (26.2/100,000) than among men (24.1/100,000) was reported in a study from the United Kingdom.² Specific risk factors for FL, including autoimmune conditions such as Sjögren syndrome, which is more common in women, may be a factor in a slight preponderance in women (incidence rate ratio, 1.18).³ Other suspected risk factors have been recognized, including smoking history in women and environmental exposure to benzene or solvents.³

Risk Factors

Although family history of NHL, recreational sun exposure, hay fever, and allergies are associated with increased risk across most, if not all, NHL subtypes, there is significant heterogeneity in the risks associated with each subtype.¹⁹ As may be expected, the greatest differences in associated risks are between B-cell and T-cell lymphomas, although there is also significant heterogeneity in risk factors within the family of B-cell lymphomas.²⁰ Moreover, a cluster analysis of risk factors demonstrated that groupings of NHL subtypes share common risks: peripheral T-cell lymphoma and mycosis fungoides/Sézary syndrome; marginal zone lymphoma and Burkitt lymphoma; and diffuse large B-cell lymphoma, FL, chronic lymphocytic leukemia/small lymphocytic leukemia, mantle cell lymphoma, and lymphoplasmacytic lymphoma/Waldenström macroglobulinemia—and within the last group, certain shared risk factors further differentiate FL and mantle cell lymphoma from the others.¹⁹

A pooled analysis of 19 case-control studies, comprising 3530 patients with confirmed FL and 22,639 controls, identified several factors that either positively or negatively impacted risk of FL. In regression analysis, higher risk of FL was associated with

first-degree relative with NHL (odds ratio [OR], 1.99; 95% CI, 1.55-2.54), higher body mass index as a young adult (OR, 1.15; 95% CI, 1.0-1.27 per 5 kg/m² increase), and work as a spray painter (OR, 2.66; 95% CI, 1.36-5.24). A lower risk of FL was associated with presence of an atopic disorder (OR: 0.87; 95% CI: 0.80-0.94), previous blood transfusion (OR, 0.78; 95% CI, 0.68-0.89), increased sun exposure (OR for highest quartile, 0.74; 95% CI, 0.65-0.86), occupation as a baker or miller (OR, 0.51; 95% CI, 0.28-0.93), and occupation as a university/higher education teacher (OR, 0.58; 95% CI, 0.41-0.83).^{19,21} Some sex-specific risk factors were identified in women with Sjögren syndrome and history of cigarette smoking was associated with increased FL risk, whereas history of alcohol consumption, hay fever, and food allergies were associated with decreased risk of FL.^{19,21}

An inverse relationship between sun exposure and risk of FL has been noted in some studies.¹⁹ For example, a case-control study found evidence that early-life sun exposure may be protective against overall risk for NHL. Exploratory analysis found no association between early-life sun exposure and FL, but there was evidence that certain single-nucleotide polymorphisms contained in the vitamin D receptor gene code mediated the effect of early-life sun exposure and NHL risk, including FL.²² Overall, these data suggest that vitamin D deficiency or sunlight-mediated immune modulation may have a role in NHL development. Vitamin D deficiency has also been associated with inferior overall survival (OS) specifically among patients with diffuse large B-cell lymphoma treated with a regimen of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).¹⁹

Clinical Presentation and Classification

Asymptomatic lymphadenopathy, usually occurring with waxing and waning symptoms, is a common presenting sign in patients with FL, and bone marrow involvement is also seen in approximately 70% of patients.²³ Fewer than 20% of patients present with B symptoms or increased serum lactate dehydrogenase.²³ The pathology of FL is characterized by proliferation of centrocytes and centroblasts exhibiting at least a partial follicular pattern.²⁴

Increasing numbers of centroblasts are associated with a more aggressive clinical course.²³ Accordingly, the World Health Organization Classification System, first published in 2001, is widely used to determine the pathologic grade of FL tumors according to the number of centroblasts present per high power field (hpf)²³:

- Grade I: 0 to 5 centroblasts/hpf (follicular small cleaved)

- Grade 2: 6 to 15 centroblasts/hpf (follicular mixed)
- Grade 3: with more than 15 centroblasts/hpf (follicular large cell)
- Grade 3: subdivided into grade 3a (centrocytes are present) and grade 3b (sheets of centroblasts)

In recognition that patients with grade 1 and 2 FL have similar clinical outcomes, these 2 grades were grouped under a single grade (ie, FL1-2) when the guidelines were revised in 2008.²⁵ However, the 2008 guidelines differentiate grades 3a and 3b; thus, FL is still commonly classified into 3 grades for diagnostic purposes: FL1-2, FL3a, and FL3b.²⁵

Prognosis

FL is associated with a relatively favorable prognosis in the majority of cases. The reported 2-year survival rate associated with FL is between 88% and 93%.³ Moreover, with a few exceptions, OS rates across NHL subtypes suggest an improving prognosis over time; compared with the period 1998 to 2000, the rate of 5-year OS for patients with FL improved significantly for new cases diagnosed between 2001 and 2003, with similar rates for new cases diagnosed between 2004 and 2006.¹⁸

Several factors have been suggested to affect clinical outcome. Younger age at diagnosis and earlier disease stage have each been associated with better survival prospects, whereas older age and more advanced stage at the time of diagnosis are associated with increased mortality rates.^{2,4} Despite the generally favorable prognosis associated with FL, a portion of patients will experience a relapse, in some cases, after 8 to 10 years of follow-up.⁸ Within the first 2 years of frontline therapy, 20% of patients may experience FL progression, which is associated with poor prognosis and increased risk of death.^{10,12}

Prognostic Models and Criteria for Planning Treatment

The Follicular Lymphoma International Prognostic Index (FLIPI) is a commonly used clinical tool that uses 5 factors to assess prognosis for FL: aged >60 years, Ann Arbor stage III to IV, amount of involved nodal areas, serum lactate dehydrogenase greater than the upper limit of normal, and hemoglobin <12g/dL.^{23,25} Presence of 0 or 1 risk factors in the FLIPI is considered low risk and is associated with a 98% 2-year OS and an 84% 2-year PFS; presence of 2 risk factors is considered intermediate risk and is associated with 94% 2-year OS and 70% 2-year PFS; presence of 3 or more risk factors is considered high risk and is associated with 87% 2-year OS and 42% 2-year PFS.²³

Length of remission after induction of chemotherapy is considered a strong predictor of outcome, with progression within 2 years associated with a lower rate of survival. A retrospective analysis from the National LymphoCare Study found that about 20% of patients experienced progressive disease within 2 years of receiving R-CHOP treatment; 5-year OS was 50% in the group of patients with early progression, compared with 90% among those without early progression.¹¹

The Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria are frequently used to determine the need to start treatment.²⁶ GELF criteria incorporate the following parameters²³:

- Involvement of ≥ 3 nodal sides, each with a diameter of 3 or more cm
- Any nodal or extranodal tumor mass with a diameter of ≥ 7 cm
- B symptoms
- Splenomegaly
- Pleural effusions or peritoneal ascites
- Cytopenias (leukocytes $< 1.0 \times 10^9/L$ or platelets $< 100 \times 10^9/L$)
- Leukemia ($> 5.0 \times 10^9/L$ malignant cells)

FL tumor grade has been shown to have some prognostic utility for planning treatment.²³ Generally, there is no evidence to support different treatment approaches for grade 1 or 2 FL, and 3a is considered an indolent disease whereas grade 3b indicates a more aggressive disease.²³ Irrespective of tumor grade, interactions between tumor cells and the microenvironment are influential in overall clinical behavior.²³

Evolution of Treatment Paradigms for FL

FL follows a heterogeneous course, with the decision regarding whether to start treatment and which approach to use based largely on the patient's performance status and characteristics of the individual patient's disease.⁸

Frequently, watchful waiting (also called active surveillance or observation) is employed in frontline settings, especially for the approximately 10% to 15% of patients with asymptomatic, low tumor-burden FL.⁸ When treatment is initiated, chemoimmunotherapy regimens are preferred, with the common addition of rituximab.^{9,11} The benefit of adding rituximab to various chemotherapy backbones has been demonstrated in multiple randomized studies, conferring improved PFS and OS rates.^{8,13,14,23} Ardeshtna and colleagues studied the use of single-agent rituximab in a prospective, randomized study in the setting of asymptomatic, advanced-stage, low tumor-burden FL. Compared with observation, single-agent rituximab improved PFS and time to new treatment, but there was no difference in OS between treatment groups.^{8,9,27}

Among patients with advanced-stage, high tumor-burden FL, chemoimmunotherapy with considerations of rituximab maintenance is considered the standard of care.¹⁰ Recent clinical studies attempting to define further refinements in treatment approaches for this population of patients may require some context for interpretation. For example, the StiL study found a greater PFS associated with bendamustine-rituximab (BR) than with R-CHOP (69.5 versus 31.2 months overall, and not reached versus 40.9 months in the FL subgroup)²⁸; the BRIGHT study confirmed these findings while comparing BR to R-CHOP or cyclophosphamide, vincristine, and prednisone (R-CVP) (5-year PFS: 65.5% BR versus 55.8% R-CHOP/R-CVP groups)²⁹; and the PRIMA study found improved PFS associated with maintenance rituximab after R-CVP, R-CHOP, and R-fludarabine, cyclophosphamide, and mitoxantrone.³⁰ However, none of the aforementioned studies reported differences in OS, which may be a by-product of the length of follow-up for the given clinical trials. Some authors have commented that these considerations suggest that future clinical trials looking at novel therapies in frontline settings should focus on therapies that have less associated toxicity, are easier to administer, and confer acceptable PFS compared with current regimens.¹⁰ Meanwhile, treatment in the setting of relapsed FL may be the most appropriate mechanism by which to judge anti-lymphoma activity of such novel agents.¹²

Unmet Need in FL Therapies and the Role of PI3K

Generally, the incorporation of rituximab into first-line chemotherapy regimens has significantly improved clinical outcomes for patients requiring treatment.¹² Due to refinements in treatment protocols over time, median survival in the chemotherapy era is approaching 20 years, with first-line median PFS for chemoimmunotherapy plus rituximab greater than 7 years.¹² However, about 20% of patients with FL experience disease progression within the first 2 years of first-line therapy, which, in turn, is associated with 2-year survival of 68% and 5-year survival of about 50%, compared with 97% and 90%, respectively, in patients who do not experience progression within 2 years of diagnosis.^{10,12} A preferred management strategy for these patients has, so far, proven elusive, although various studies are designed to address this question.

Unfortunately, existing prognostic models, such as FLIPI, have proven limited in their utility for identifying patients at risk for early progression on therapy. Patients who were most likely to have high-risk FLIPI scores were those with early relapsing disease rather than those without early progression (survival >2 years). Those with

early progression were found to have a 5-year survival rate of 50%; however, neither the FLIPI nor its modified version, FLIPI2, reliably predict response to specific treatments, including newer targeted agents.¹²

Advances in treatment have improved the prognosis for patients with FL; it is estimated that about 30% to 40% of patients will not experience relapse even after decades of follow-up, and studies suggest a plateau in relapse rates around 8 to 10 years after starting treatment.⁸ Retrospective analyses of patients treated with radiotherapy for stage I FL indicate that about 50% of patients are free from disease after a 10- or 15-year follow-up.^{9,31} Similar findings were reported in a retrospective review of 107 patients with stage I to III FL treated with either extended field or nodal irradiation, with no apparent differences between the 2 treatments in survival or local control.⁹

Although allogenic and autologous stem cell transplant achieved durable remission for patients in some studies,^{32,33} associated toxicity and issues regarding patients' access to these approaches limits their practical use in clinical settings.⁸ Moreover, an evolved understanding of FL biology has implicated several somatic mutations, as well as the composition and activity of nonmalignant cells within the microenvironment, as influential in driving oncogenic signaling pathways that ultimately impact disease activity.⁸

Specifically, the PI3K pathway has been shown to be hyperactive in many B-cell lymphomas, including FL, with overexpression predicting poor prognosis and higher likelihood of relapse or resistance to treatment.³⁴ Activity within the PI3K/AKT/mTOR pathway is known to have a key role in B-cell survival, proliferation, metabolism, migration, and chemokine secretion.^{34,35} There is evidence that PI3K is one of the most active pathways in several types of cancers³⁶; when activated, the PI3K pathway rescues B-cell receptor-deficient mature B cells from immune surveillance, thereby providing conditions for their proliferation.^{35,37} Novel therapeutics have entered clinical trials for various indications, including among treatment-naïve patients and those with relapsed or refractory FL, that target these and other active signaling pathways in FL. ♦

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