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Follicular Lymphoma

Gopila Gupta and Vikas Garg

Abstract

Follicular lymphoma (FL) is one of the most common type of indolent non- Hodgkin's lymphoma. It originates from germinal center B cells and has characteristic translocation t(11,14) involving immunoglobulin heavy chain gene (chromosome 14q32) and Bcl2 gene (chromosome 18q21) in 90% of patients. FL presents with lymphadenopathy and/or bone marrow involvement. Diagnosis is confirmed by histological examination of lymph nodes. FL is a slow growing tumor with frequent remission and relapses. Follicular lymphoma international prognostic index (FLIPI) and progression of disease within 24 months (POD24) are most important prognostic markers. Early-stage disease is usually treated with radio-therapy. Management of advanced stage depends on disease burden. Patients with advanced stage disease may be observed in case of low burden disease and those with high disease load require treatment with chemo-immunotherapy.

Keywords: Follicular lymphoma, non-Hodgkin's lymphoma, NHL, Low grade lymphoma

1. Introduction - Epidemiology

Follicular lymphoma (FL) is one of the most common forms of indolent lymphoma constituting 20–25% of all non-Hodgkin's lymphoma (NHL) in the United States and Europe. However, it is less common in the African and Asian population accounting for 10% of all NHL [1–4]. There is no known risk factor for follicular lymphoma [5]. It is a disease of the elderly with a median age of 65 years, and the young are only rarely affected [6]. It is an indolent disease that typically manifests as asymptomatic adenopathy. Involvement of the bone marrow is frequent, occurring in up to 80% of cases. B symptoms and high serum lactate dehydrogenase (LDH) levels are observed in approximately 20% of patients. Extranodal involvement is less prevalent, occurring in about 10% of cases [7, 8].

2. Histology

On histopathologic examination, Follicular lymphoma shows densely packed follicles with attenuated mantle zones that obscure nodal architecture. The follicles consist of two major cell types, centrocytes, and centroblasts. Centrocytes are small to medium-sized with scarce cytoplasm, elongated or cleft nuclei, and small nucleoli. Centroblasts are large cells (about three times the size of a lymphocyte) with a basophilic cytoplasm ring, round to oval non-cleaved nuclei, and prominent nucleoli. Histological grading (**Table 1**) is based on the proportion of centrocytes and centroblasts present in the germinal centers. FL grades 1 to 3a is considered a low-grade

Histologic grade	Microscopic features
Grade 1 (follicular small cleaved)	Up to 5 centroblasts per HPF
Grade 2 (follicular mixed)	6–15 centroblasts per HPF
Grade 3a (follicular large cell)	More than 15 centroblasts per HPF
Grade 3b	Solid sheets of centroblasts

HPF high power field.

Table 1.
Histologic grading of follicular lymphoma.

indolent disease, whereas FL grade 3b is considered an aggressive form of lymphoma [9]. Follicular lymphoma has a paratrabecular pattern of involvement in the bone marrow, and the appearance of tumor cells is similar to that found in lymph nodes.

On immunohistochemistry (IHC) Follicular lymphoma cells express B-cell antigens (CD19, CD20, CD22, and CD79a), BCL2, BCL6, and CD10. Surface expression of immunoglobulin is observed in about one-half of cases. BCL2 overexpression is present in the majority of grade 1 FL–2 FL, however, it is less common in grade 3 FL [10]. CD 10 negative FL are commonly high grade, express IRF4/MUMI and BCL 6 but lacks BCL2 expression.

3. Pathobiology

The germinal center B cell expressing CD20 and B-cell leukemia/lymphoma 2 (BCL2) is the cell of origin for follicular lymphoma [11]. The characteristic translocation [t(14,18)] involving the BCL2 gene on chromosome 18q21.3 and immunoglobulin heavy chain gene on chromosome 14q32; q21 is observed in up to 90% of patients. It provides a survival advantage to malignant B cells by upregulation of anti-apoptotic signals [11]. However, BCL2 overexpression alone is insufficient for malignant transformation to FL, and additional hits are required [12]. KMT2D, CREBBP, EZH2, EP300, KMT2C, and ARID1A mutations are commonly identified, although their significance in FL remains unknown [13, 14].

4. Pre-treatment evaluation

The initial evaluation should entail recording a detailed history and completing a comprehensive physical examination. A biopsy of the afflicted lymph node, either excisional or incisional, is required [9, 15]. Biopsy samples should be evaluated by an expert haemato-pathologist. For baseline staging, either contrast-enhanced computed tomography (CECT) of the neck, chest, and abdomen or whole-body positron emission tomography (PET) with computed tomography, should be performed [16, 17]. PET is preferable in early-stage patients and for assessing response at the end of treatment (EOT) [10, 18]. All individuals with early-stage FL should have a unilateral bone marrow biopsy (stages I and II). However, it can be omitted in patients with advanced disease (stage III and IV) as it provides no extra information in such a scenario [19, 20]. For assessment of organ functions and prognostic information, baseline complete blood count, renal and hepatic functions, serology for hepatitis B and C, β2-microglobulin, and LDH are necessary. Patients planned for anthracycline-based therapy should have their cardiac function evaluated by 2D-ECHO or a MUGA scan. Fertility preservation should be discussed with all patients of reproductive age [21].

5. Histologic transformation

Histological transformation of FL to high-grade lymphoma during the natural history of disease is a well-known entity. 15–20% patients demonstrating transformation at 5 years of follow up [22, 23]. Risk of transformation is about 1–3 percent per year. Histological examination reveals loss of follicular architecture and replacement by large-sized cells with a high proliferation index. FL most commonly transforms to diffuse large B cell lymphoma (DLBCL), but other histology like Burkitt's lymphoma, lymphoblastic lymphoma, and Hodgkin's disease have also been reported [24]. Rapidly progressing lymphadenopathy, unusual extra-nodal involvement, constitutional symptoms, elevated lactate dehydrogenase (LDH) and hypercalcemia are clinical pointers of histological transformation. Diagnosis is confirmed by guided biopsy of the highest metabolically active lesion in case of high clinical suspicion [25, 26].

6. Prognostic factors

Age, stage, nodal burden, LDH, hemoglobin, and β2-microglobulin have been recognized as important prognostic factors. Various prognostic models have been developed based on these factors (**Table 2**), including FLIPI (follicular lymphoma international prognostic index), FLIPI 2, and PRIMA-PI (Primary Rituximab and Maintenance study prognostic index). FLIPI is a widely used tool

Prognostic model and risk factors	Risk stratification
FLIPI 1. Age: >60 years 2. Ann Arbor Stage: III–IV 3. Hb concentration: <12 g/dL 4. Number of nodal sites: >4 5. Serum LDH: >ULN	Low: 0–1 risk factors→5-year OS: 92%; Intermediate: 2 risk factors→5-year OS: 78% High: 3–5 risk factors→5-year OS: 52%
FLIPI 2 1. Age: >60 years 2. Bone marrow involvement 3. Hb concentration: <12 g/dL 4. Greatest diameter of largest involved node: >6 cm 5. Serum beta 2 microglobulin concentration: >ULN	Low: 0–1 risk factors→ 3-year OS: 99% Intermediate: 2 risk factors→ 3-year OS: 96% High: 3–5 risk factors→ 3-year OS: 84%
PRIMA-PI 1. Serum beta 2 microglobulin >3 g/L 2. Bone marrow involvement	Low: 0 risk factors→5-year PFS: 69% Intermediate: 1 risk factor→5-year PFS: 55% High: 2 risk factors→5-year PFS: 37%
POD 24 (Progression of disease within 24 months of chemoimmunotherapy)	POD >24 months→ 5-year OS 90% POD <24 months→ 5-year OS 50%

ECOG, Eastern Cooperative Oncology Group; FLIPI, follicular lymphoma international prognostic index; Hb, hemoglobin; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival; POD, Progression of disease; PRIMA-PI, Primary Rituximab and Maintenance study prognostic index; PS, performance status; ULN, upper limit of normal.

Table 2.
Prognostics tools in follicular lymphoma.

developed in the pre-rituximab era, but it has been validated in several prospective trials in patients receiving rituximab [27–29]. PRIMA-PI incorporates only two parameters, serum 2-microglobulin levels, and bone marrow involvement, however it has not been prospectively validated [30]. POD24 (progression within 24 months of therapy) has recently been found as a key prognostic and predictive marker [31, 32]. It may be used method for predicting relapse and aid in therapy selection.

7. Management

Management of FL is based on the stage at presentation, tumor grade, and burden of disease. Early-stage local diseases are treated with curative intent, while in advanced diseases aim is to reduce symptom burden, increase survival, and enhance the quality of life.

7.1 Limited stage FL

Early-stage (stage I and II) patients have an excellent prognosis with median survival approaching 20 years [33–35]. There are several management options available, including radiation, single-agent rituximab, chemo-immunotherapy, and observation. The recommended radiation dosage is involved site radiotherapy (ISRT) with 24 Gy (Gray) administered in 12 fractions [36]. Higher dose does not provide any survival advantage and is associated with greater toxicity [37]. When compared to observation alone, patients who receive RT have better disease-specific survival as well as overall survival [38, 39]. PFS benefit was observed by adding rituximab or chemotherapy to the radiotherapy, however, there was no difference in overall survival [40, 41]. Patients unwilling for treatment may also be considered for observation [42]. High grade (grade 3B) FL patients are managed on the lines of other high-grade NHL like DLBCL (diffuse large B cell lymphoma). Combination chemo-immunotherapy R-CHOP (rituximab, cyclophosphamide, vincristine, doxorubicin, prednisone) is preferred in such cases. If involved sites cannot be encompassed in a single radiation field, patients should be treated as advanced FL.

7.2 Advanced stage FL

Advanced stage FL is a very diverse group, with some patients having an indolent course and long-term survival and others having a more aggressive course, with frequent relapses. Although the majority of patients respond to currently available therapies, relapses are common. The treatment of advanced FL is determined by the histologic grade and disease load [43]. For assessing disease load in advanced FL, Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria are widely employed (**Table 3**). Patient with any of the GELF feature is categorized as high tumor load disease [44].

Patients who do not fulfill any of the GELF features are considered to have a low disease load and can be initially observed. This is based on the results of a randomized trial, which showed no difference in cause-specific survival and overall survival between observation and active treatment with chlorambucil [44]. Another approach is to use single-agent rituximab followed by maintenance. In a randomized trial comparing observation, single-agent rituximab and rituximab followed by maintenance rituximab for 2 years, PFS and time to start of new treatment was better with rituximab treatment. However, there is no survival benefit with

GELF criteria
1. Nodal or extra nodal tumor size: any site >7 cm or ≥ 3 sites >3 cm
2. Presence of B symptoms*
3. Presence of compressive symptoms
4. Palpable spleen below umbilicus
5. Presence of ascites or pleural effusions
6. Presence of leukemic phase (circulating malignant cells >5 × 10^9/L)
7. Presence of cytopenia due to disease: neutropenia (<1 × 10^9/L) or thrombocytopenia (<100 × 10^9/L)

B symptoms are defined as recurrent unexplained fever >38°C, or recurrent night sweats or unexplained ≥10% loss of bodyweight in last 6 months. GELF Groupe d-Etude des Lymphomes Folliculaires.
High tumor load is defined if any one or more risk factors are present.

Table 3.
GELF criteria for assessment of tumor load in follicular lymphoma [43, 44].

rituximab [45]. Similarly, no survival benefit was observed with rituximab maintenance in the RESORT study. In this study, patients received four cycles of weekly rituximab followed by randomization to maintenance rituximab or retreatment on progression [46]. Due to lack of any overall survival advantage with upfront treatment over observation, low burden FL may be kept on close follow-up.

FL with a high disease load warrants immediate treatment with chemo-immunotherapy. Various chemo-immunotherapy induction regimens available for patients with FL are R-CVP (rituximab, cyclophosphamide, vincristine, and prednisone), R-CHOP (rituximab, cyclophosphamide, adriamycin, vincristine, and prednisone), and BR (bendamustine and rituximab). Patients who have a partial or complete remission with the above therapies are further treated with rituximab maintenance. Choice of chemo-immunotherapy regimen is based on patients performance status, pre-existing comorbidities, and side effect profile of drugs as no overall survival advantage has been shown for any regimen above other in a randomized trial. R-CVP has lower response rates and progression-free survival compared to R-CHOP. BR is associated with better progression-free survival and lower rates of neutropenia, infections, neuropathy, and alopecia. However, there was no difference concerning overall survival over R-CHOP and R-CVP [47–49]. Use of newer anti-CD20 agent obinutuzumab has shown improvement in progression-free survival but no overall survival benefit and is associated with higher infusion reactions, neutropenia, and infections [50]. Use of chemotherapy-free regimens using lenalidomide and rituximab (R2) has similar survival with a different toxicity profile compared to chemo-immunotherapy regimens [51].

The role of maintenance rituximab in patients with either complete or partial remission after initial chemo-immunotherapy has not been proven beyond doubt. In the PRIMA (Primary Rituximab And Maintenance) trial, patients were randomized to rituximab maintenance (every 8 weeks for 2 years) or a placebo after initial chemo-immunotherapy. Rituximab arm had higher progression-free survival but at the cost of higher adverse effects (infusion reaction, neutropenia, and infections). However, initial chemo-immunotherapy regimens did not include a bendamustine-based regimen, which is most commonly used in the current era [52]. So these results could not be extrapolated after initial bendamustine-based therapy in absence of prospective evidence. Similarly, there was no survival benefit with rituximab maintenance in patients aged 60–75 years [53].

8. Relapse or refractory follicular lymphoma

FL has a protracted course with multiple remissions and relapses. About 20% of patients do not respond to initial therapy and another 20% of patients relapse within 24 months of initial therapy [54]. Interval between initial treatment and relapse is the most important prognostic and predictive factor for relapsed FL. Those who relapse after 24 months of initial therapy have good long-term outcomes, while those relapsing within 24 months have a dismal prognosis. There is no set consensus on the management of relapsed patients. Multiple options are available including chemo-immunotherapy, novel agents, and stem cell transplant. Choice of therapy depends upon the disease burden, prior therapy, response to prior therapies, duration of previous remission, performance status, comorbidities, and adverse effect profile of the drugs. The goal of therapy is improvement in symptoms, increase survival, and a better quality of life.

Patients who relapse more than 24 months after initial chemoimmunotherapy are considered late relapses. These late relapses have an indolent course and survivals rates can approximate that of the general population [55]. Patients who do not meet GELF criteria have no immediate requirement to initiate treatment and may be observed. An alternate approach is to use single-agent rituximab. Symptomatic FL patients with high disease load may be managed with single-agent rituximab, chemoimmunotherapy, lenalidomide plus rituximab (R2), or novel agents. Single-agent rituximab is preferred in patients with comorbidities and poor performance status [56]. Relapsed FL with good performance status can be treated with anti CD20 monoclonal antibody in combination with chemotherapy or lenalidomide. If the patient has previously received BR-based therapy, R-CHOP, R-CVP, or R2 may be used at the time of relapse. Similarly, if the patient has received R-CHOP-based therapy, he may be considered for BR or R2. If the patient has relapsed during anti-CD20 monoclonal antibody maintenance, it is preferable to use an alternate anti-CD20 agent like obinutuzumab [57, 58]. Radio-immunoconjugates have been used for management of FL in patients with good bone marrow reserve but because of the associated high risk of secondary malignancies and difficult administration have not gained much acceptance [59].

Patients who have progression of disease within 24 months (POD 24) of initial chemo-immunotherapy are considered early relapses and have poor outcomes. 5-year overall survival in this group is 50% compared to 90% for patients who do not progress in 2 years [54]. Histological transformation should be ruled out in these patients with a repeat biopsy. The patient's further therapy is determined by whether he or she is transplant eligible or not. Transplant eligible patients are managed by chemo-immunotherapy followed by autologous hematopoietic stem cell transplant (HSCT). Autologous HSCT in early relapse has shown 20% improvement in 5-year overall survival. There is no survival benefit of allogenic over autologous HSCT [60, 61]. For patients with late relapse autologous HSCT may be deferred for later relapses. Allogenic stem cell transplant may be reserved for fit patients who have persistent marrow involvement, poor mobilizers stem cells for autologous HSCT and failure of autologous HSCT.

Newer drugs in the arena of follicular lymphoma management are PI3K inhibitors (idelalisib, copanlisib, duvelisib, umbralisib). EZH2 (enhancer of zeste homolog 2) mutations are observed in up to 20% of cases of relapsed FL and predict a favorable outcome. EZH2 inhibitor tazemetostat is an oral drug approved in relapsed FL patients in the first relapse in presence of EZH2 mutations and post two lines irrespective of EZH2 mutation status. Responses are observed in approximately 70% of patients with EZH2 mutations and 35% without EZH2 mutations. Adverse effects are mild and include hematotoxicity, hepatotoxicity, and elevation

in serum creatinine [51]. Phosphatidylinositol-3- kinase (PI3K) inhibitors are approved in relapsed FL post multiple lines of therapy. Overall response rates range from 40 to 60%, most of which are partial responses. Common toxicities include fatigue, gastrointestinal toxicity (diarrhea, colitis), hepatotoxicity, pneumonitis, opportunistic infections, and metabolic derangements (hypertriglyceridemia, hyperglycemia). Idelalisib is an oral inhibitor of PI3K delta isoform. Copanlisib is an intravenous drug inhibiting PI3K alpha and delta isoforms. Duvelisib is an oral drug, is a dual inhibitor of delta and gamma isoforms of PI3K. Umbralisib is an oral multikinase inhibitor, acting on PI3K delta and casein kinase [62–65].

Two chimeric antigen receptor T (CART) therapy products have been approved for relapsed/refractory FL post two or more lines of therapy are tisagenlecleucel and axicabtagene ciloleucelis [66, 67]. Response are seen in about 90% of patients with the majority achieving complete remission. Characteristic adverse effects include cytokine release syndrome (CRS), neurotoxicity, cytopenia, infections, and hypogammaglobulinemia.

9. Future directions

Multiple newer therapies are currently under trial in patients with relapsed follicular lymphoma including checkpoint inhibitors, monoclonal antibodies, immunomodulatory drugs, vaccines, and chimeric antigen receptor T cell therapy. Future research should focus on identifying the predictive and prognostic biomarkers to identify patients at risk of early relapse and the role of therapy intensification in such cases.

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