Am J Blood Res 2022;12(4):105-124
www.AJBlood.us /ISSN:2160-1992/AJBR0143811

Review Article

Current trends in diagnosis and management of follicular lymphoma

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Received April 28, 2022; Accepted June 30, 2022; Epub August 15, 2022; Published August 30, 2022

Abstract: Follicular lymphoma (FL) originates from germinal center B cells, is the most prevalent form of indolent non-Hodgkin's lymphoma. Upfront management is based on stage, grade, and disease burden. Radiotherapy may be curative in limited disease while chemoimmunotherapy is preferred in advanced disease. Maintenance therapy is routinely administered but its role is debatable. Relapses are common and interval from initial therapy to relapse is most important prognostic factor for relapsed FL. Management of relapsed patients is based on the initial management, the interval from prior therapies, and the toxicity of available therapies. Multiple agents are available for patients after two or more lines of therapy, but sequencing remains poorly defined.

Keywords: Follicular lymphoma, FL, non-Hodgkin's lymphoma, NHL, chemoimmunotherapy, CART, PI3K, EZH2

Introduction

Follicular lymphoma (FL) is an indolent variety of non-Hodgkin's lymphoma (NHL) originating from germinal center B cells. FL is one of the most prevalent forms of indolent B cell NHL. It has a long disease course due to chronic incurable nature of the disease in the majority of patients. In this article, we will discuss the diagnosis, prognostication, and management of follicular lymphoma in treatment naïve and relapsed patients.

Epidemiology

The incidence of FL is highest in the western population with 3.18 cases per 100,000 people annually in the United States and it constitutes about 20-25% of all NHLs [1-3]. It is less common elsewhere and constitutes about 10% of all NHLs in the Indian population [4-8]. FL has a median age of 65 years and a male-to-female ratio of 1.2:1 [9, 10]. Indian patients with FL have a younger age at presentation (median age 51 years) and higher male predilection (male:female ratio = 2:1) compared to the western population [11, 12].

Pathogenesis

The cell of origin for follicular lymphoma is the germinal center B cell. Malignant cells co-express CD10, CD20, and B-cell leukemia/lymphoma 2 (BCL2). Translocation t (14,18) is characteristic of almost 90% of FL which leads to overexpression of anti-apoptotic BCL2 [13]. The absence of t (14,18) is seen in less than 10% of cases and is frequently associated with grade 3b FL [14]. Genome sequencing has identified mutations in KMT2D, CREBBP, EZH2, EP300, KMT2C, and ARID1A, though the role of these in the causation or disease progression/relapse of FL remains unclear [15-17].

Histology

FL presents as closely packed follicles with attenuated mantle zones and effacement of the nodal architecture. Compared to the reactive germinal centers the malignant follicles lack tangible body macrophages and polarization. Two types of neoplastic cells present in the germinal centers form the basis of histological classification. Centroblasts are large cells with a basophilic cytoplasmic rim, non-cleaved

Table 1. WHO histologic grading of follicular lymphoma

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, WHO World Health Organization.

nuclei, vesicular chromatin, and 1-3 prominent nucleoli. Centrocytes have a small to medium size, scant cytoplasm, elongated or cleaved nuclei, and inconspicuous nucleoli. FL is classified histologically (**Table 1**) based on the number of centroblasts per high power field (HPF) [13].

FL cells are derived from germinal center B-cells and display B-cell antigens (CD19, CD20, CD22, and CD79a), as well as BCL2, BCL6, and CD10; however, CD5 and CD43 are only rarely expressed. Tumor cells express surface immunoglobulin, most commonly IgM (50-60%) with kappa or lambda restriction [18]. CD10 negative FL are histologically grade 3 and lack expression of BCL2. These tumors are positive for IRF4/MUMI and BCL6 [19].

Histopathological transition to high-grade lymphoma is well-known, with 15-20% of patients exhibiting transformation after 5 years of follow-up [20, 21]. The annual risk of transformation is roughly 1-3 percent; the most common histology is diffuse large B cell lymphoma (DLBCL), although other histologies such as Burkitt's lymphoma, and lymphoblastic lymphoma, and Hodgkin's disease have also been described [22-24].

Four variants of FL (**Table 2**) are recognized in WHO 2016 classification. Because FL is primarily a disease in adults and is uncommon in children, pediatric FL is treated as a distinct entity. Primary cutaneous FL is also classified separately.

Clinical features

FL has a chronic indolent course and patients commonly present with asymptomatic peripheral lymphadenopathy. Bone marrow involvement is common (80%), but B symptoms are reported by only 20% of patients. In half of the cases, the liver and spleen are involved, while extranodal involvement occurs only in 10% to 20%. High serum lactate dehydrogenase (LDH) and cytopenia are observed in 20-25% of patients [11, 31]. Clinical features of clinical variants of FL have been described in **Table 2**.

Management

Pre-treatment workup

Initial assessment should include careful history taking, assessing performance status, and physical examination. Excisional or incisional biopsy of the involved lymph node is recommended [32, 33]. Immunohistochemistry (IHC) should be performed in all cases and biopsies should be reviewed by an expert haematopathologist [34]. All patients should have baseline blood count; renal/hepatic function tests; serum lactate dehydrogenase (LDH), hepatitis B serology, human immunodeficiency virus (HIV); and β2-microglobulin.

Contrast-enhanced computed tomography (CECT) of the neck, chest, and abdomen, or positron emission tomography (PET) with computed tomography (CT), should be considered for baseline staging [35, 36]. 18F-Fluorodeoxyglucose (18F-FDG) PET is positive in 95% of FL cases and it is preferable to do PET for initial staging workup in early-stage patients before radiation therapy (RT) and for end-of-treatment (EOT) response assessment [37, 38]. Many patients with limited-stage FL may be upstaged by PET-CT; in such cases, RT may be best avoided. In a retrospective analysis from the FOLL05 trial, 60% of patients with limited-stage FL were upstaged by using PET [39]. Detection of bone marrow involvement by PET is poor prognostic and predictive of PFS and OS [40, 41]. TMTV (total metabolic tumor volume) estimates tumor burden using automated computer software in PET-CT images. Based on retrospective studies TMTV has shown usefulness as a prognostic marker and to differentiate between tumor grades [42, 43].

Staging of FL may be done using either the Ann Arbor staging system or Lugano staging system, which are similar for all NHL [38, 44]. Unilateral bone marrow biopsy should be considered in patients with stages I and II, but it may be avoided in stage III and IV FL as it provides no additional information in such cases [45-47]. Cardiac evaluation using 2D-ECHO or MUGA scan should be done in patients planned

Table 2. Clinical variants of FL and other entities in WHO (WHO World Health Organization) 2016 classification of lymphoid malignancies [13]

Variants of Follicular lymphoma	
In situ follicular neoplasia (ISFN) [formerly named as in situ follicular lymphoma]	Follicle size is normal with preserved nodal architecture. Partial or total colonization of reactive follicles with centrocytes (BCL2 rearrangement positive) confined to germinal center Risk of progression to FL is less than 5%. May co-exist with FL or other forms of B-cell lymphomas In case of ISFN with no evidence of overt lymphoma wait and watch strategy recommended. Excellent prognosis [25]
Duodenal type FL	Incidentally diagnosed as polyps commonly involving second part of duodenum. Most cases present as localized mass (stage IE/IIE) Histological grading and immunophenotype similar to nodal FL t (14,18) is common, 50% have KMT2D mutations < 10% risk of progression to nodal FL Wait and watch strategy preferred. Excellent prognosis [26]
Testicular FL	Common in children, rare in adults Usually histological grade 3a, stage IE disease Lacks BCL2 translocation Surgical excision is sufficient in most cases. Good prognosis [27]
Diffuse follicular lymphoma variant	Diffuse growth pattern Lacks BCL2 rearrangement 1p36 deletion seen in most cases Inguinal involvement Spread to other areas rare
Pediatric type FL	Considered a separate entity Localized clonal proliferation, nodal disease stage I/II Grade 3 histology. Lacks BCL2 rearrangement Children and young adults May not require treatment other than excision. Excellent prognosis [28]
Large B cell lymphoma with interferon regulatory factor 4 (IRF4) rearrangement	New provisional entity Strong expression of IRF4/MUMI and BCL6 Children and young adults Localized mass, mostly cervical lymph nodes and Waldeyer ring More aggressive than pediatric FL Good outcomes with combined immunochemotherapy [29]
Primary cutaneous follicle center lymphoma	Considered a distinct clinic-pathological entity, classified separately Approximately 50% of primary cutaneous B-cell lymphomas Localized or solitary skin lesions presenting as erythematous plaques, nodules or tumors of variable sizes. Common site of presentation is scalp, forehead and trunk with epidermal sparing Most cases do not express BCL2 Radiotherapy for localized lesions and systemic chemotherapy for multi-focal and extensive disease. Excellent prognosis [30]

Table 3. Prognostics tools available in Follicular Lymphoma

Model	Factors	Risk stratification	Prognosis
FLIPI	Age: > 60 years Ann Arbor Stage: III-IV Hb concentration: < 12 g/dL Number of nodal sites: > 4 Serum LDH: > ULN	Low: 0-1 risk factors Intermediate: 2 risk factors High: 3-5 risk factors	5-year OS: 92%; 10-year OS: 71% 5-year OS: 78%; 10-year OS: 51% 5-year OS: 52%; 10-year OS: 36%
FLIPI 2	Age: > 60 years Bone marrow involvement Hb concentration: < 12 g/dL Greatest diameter of largest involved node: > 6 cm Serum beta 2 microglobulin concentration: > ULN	Low: 0-1 risk factors Intermediate: 2 risk factors High: 3-5 risk factors	3-year PFS: 91%; 3-year OS: 99% 3-year PFS: 69%; 3-year OS: 96% 3-year PFS: 51%; 3-year OS: 84%
PRIMA-PI	Serum beta 2 microglobulin > 3 g/L Bone marrow involvement	Low: 0 risk factors Intermediate: 1 risk factor High: 2 risk factors	5-year PFS: 69% 5-year PFS: 55% 5-year PFS: 37%
m7 FLIPI	ECOG PS > 1 FLIPI high risk Mutations in: EP300, CREBBP, CARD11, MEF2B, EZH2, ARID1A, FOXO1		Low risk: 5-year FFS 77.2% High risk: 5-year FFS 38.2%
POD24	Progression of disease within 24 months of chemoimmunotherapy	POD > 24 months POD < 24 months	5-year OS 90% 5-year OS 50%
TMTV	Estimation of tumor volume [50] in PET images using automated software.	TMTV > 510 cm^3 TMTV < 510 cm^3	5-year PFS: 33%; 5-year OS: 85% 5-year PFS: 65%; 5-year OS: 95%

ECOG, Eastern Cooperative Oncology Group; FFS, failure-free survival; FLIPI, follicular lymphoma international prognostic index; Hb, haemoglobin; LDH, lactate dehydrogenase; m7-FLIPI, follicular lymphoma international prognostic index including the mutation status of seven genes; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; PRIMA-PI, Primary Rituximab and Maintenance study prognostic index; PS, performance status; TMTV, total metabolic tumour volume; ULN, upper limit of normal.

for anthracycline-based therapy. All patients of reproductive age should be counseled for fertility preservation [48].

Prognostic factors

In the current era, the prognosis and long-term outcomes of FL have improved with ten-year overall survival of about 80% [49]. Age, stage of diagnosis, tumor grade, number of affected nodal regions, the diameter of the largest node, bone marrow involvement, hemoglobin, β2-microglobulin levels, and LDH are important prognostic factors. More recently other factors such as the mutational profile of various genes based on gene expression profile, the positive end of the treatment PET scan, progression within 24 months of treatment (POD24), and total metabolic tumor volume (TMTV) have been added. Based on these, various prognostic models have been formed (**Table 3**).

FLIPI (follicular lymphoma international prognostic index) was developed before the advent of rituximab, but it has since been validated in prospective studies in patients receiving rituximab [50, 51]. FLIPI2 was developed prospectively in 942 patients treated with rituximab-based therapy and incorporates bone marrow findings and serum β2-microglobulin levels [52]. PRIMA-PI (Primary Rituximab and Maintenance study prognostic index) is a simplified prognostic tool that only considers two variables: serum bone marrow involvement and 2-microglobulin levels [53].

The m7-FLIPI integrates FLIPI with seven common gene mutations in FL including epigenetic modifiers (EP300, EZH2, CARD11, CREBBP, MEF2B); transcription factor (FOX01); and nucleosome remodeling complex member (ARID1A). It reclassifies about half of the patients assigned to high risk according to FLIPI into low risk [54].

Early progression within 24 months of treatment completion (POD24) is considered the most important prognostic marker due to its validation in multiple studies. In National Lympho Care Study, patients progressing within 24 months have five years OS of 50%, compared to 90% in patients progressing later [55, 56]. POD24 is a commonly used tool to predict outcomes at relapse and may help in deciding on therapy.

PET has been used in prognostication at diagnosis, end of treatment, and at time of relapse.

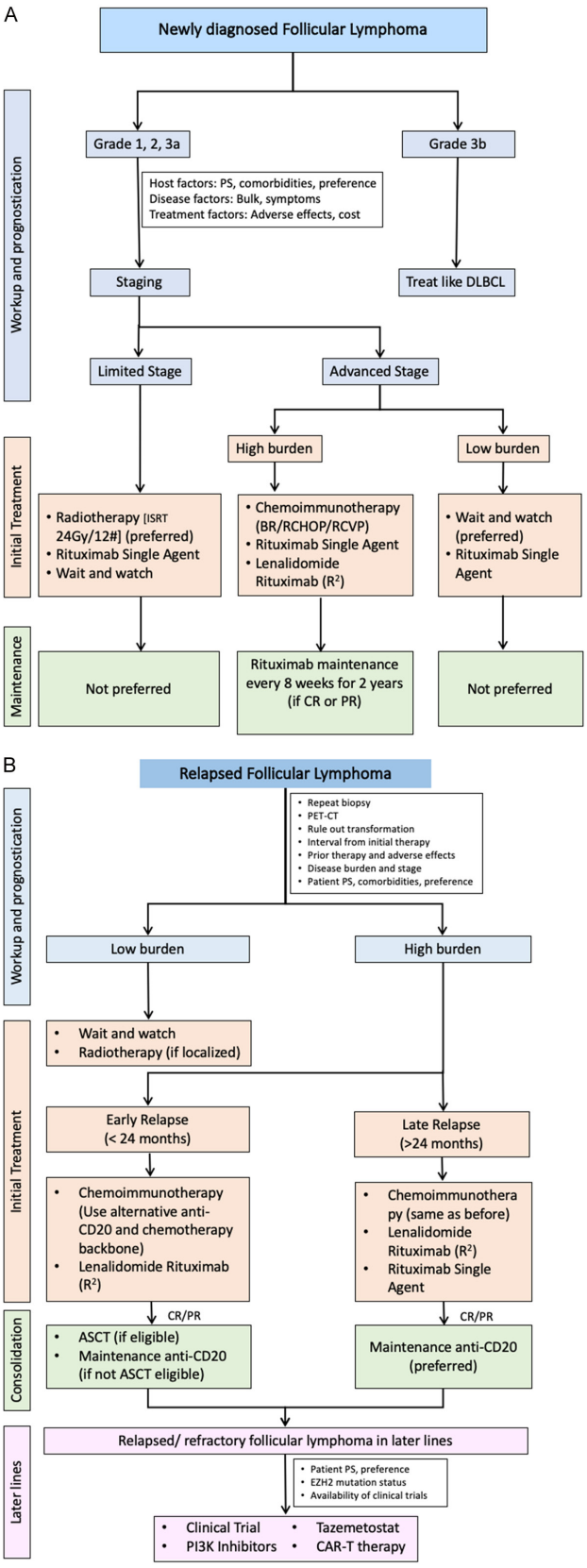

Figure 1. A. Treatment algorithm for newly diagnosed follicular lymphoma. B. Treatment algorithm for relapsed/refractory follicular lymphoma.

Patients with higher TMTV value (> 510 cm^3) on baseline PET imaging have poor five-year PFS and OS independent or FLIPI scores [42]. EOT PET scan is prognostic for PFS and OS, as positive EOT PET has poor outcomes [57]. All these factors provide prognostic information at diagnosis or relapse, however, the utility of these tools in deciding the therapeutic modality or predicting relapse remains limited.

Treatment of follicular lymphoma

Treatment consideration

Before starting therapy for a newly diagnosed case of follicular lymphoma, various factors require due consideration. Host factors include performance status, comorbidities, and toxicity concerns. Important disease-related considerations are the stage of disease, disease bulk, grade, and risk of transformation. Therapy-related factors are adverse effects, cost of therapy, and availability of clinical trials. Treating physicians should counsel patients regarding the goal of the therapy viz. cure, maintaining the quality of life, or improving survival. After considering all these factors further management plan needs to be devised. Treatment algorithms for newly diagnosed and relapsed cases have been depicted in **Figure 1A** and **1B** respectively.

Limited stage FL

Limited stage FL includes stage I and stage II. These patients constitute up to 30% of all cases [58]. They have a very good prognosis with median survival reaching 20 years [59, 60]. These patients may be managed with either radiotherapy, single-agent rituximab, radiotherapy with chemoimmunotherapy (CIT), or close follow-up. The intent of treatment is curative in such a setting. Key studies in limited-stage FL have been summarized in **Table 5**.

Patients receiving radiotherapy (RT) have better overall survival and disease-specific survival compared to observation alone [61, 62]. Wait and watch policy may be employed in selected cases where patients are unwilling for therapy or if there is any contraindication to the use of RT at the disease site [63]. RT is favored if the disease

Table 4. Assessment of tumour burden in Follicular Lymphoma [74, 75]

GELF (Groupe d-Etude des Lymphomes Folliculaires) criteria
1. Nodal or extra nodal tumour 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)
BLNI (British National Lymphoma Investigation) criteria
1. Presence of pruritus or B symptoms
2. Rapid disease progression in preceding 3 months
3. Life threatening organ involvement
4. Bone marrow infiltration causing cytopenia
5. Localized bone lesions
6. Renal infiltration
7. Macroscopic liver involvement

*B symptoms are defined as recurrent unexplained fever > 38°C, or recurrent night sweats or unexplained ≥ 10% loss of body-weight in last 6 months. High tumour burden is defined if any one or more risk factors are present.

sites can be addressed by a single radiation field. In a phase III trial, 24 Gy was non-inferior to 40-45 Gy for within radiation field progression, OS, and PFS [64]. FORT trial compared 24 Gy with 4 Gy, local progression was more common in patients receiving 4 Gy. However, there was no difference observed in OS and PFS [65, 66]. The ideal dose of RT is 24 Gy (Gray) divided into 12 fractions administered as involved site irradiation (ISRT) [67].

The addition of CIT or rituximab to radiotherapy has shown prolongation of PFS, however, no OS benefit is observed. In addition, chemoimmunotherapy was associated with higher hematological toxicities and infections [68-70]. Patients with stage II disease with non-contiguous involvement are managed like advanced stage FL.

Advanced stage FL

The majority (> 70%) of patients with FL present in an advanced stage. The prognosis has greatly improved in the last few decades and OS has reached up to 20 years [51, 71]. However, this is a very diverse group of population with few patients having long-term survival, and others having frequent relapses and shorter survival. Despite responses to therapy, relapses are common, and most of these patients are incurable. Treatment is aimed to decrease symptom burden and morbidity, improve quality of life, and prolong survival [72, 73]. Management of advanced-stage FL is based on the histologic grade and tumor burden. British National Lymphoma Investigation (BNLI) and Groupe d-Etude des Lymphomes Folliculaires (GELF) criteria are commonly used for estimating disease burden in advanced FL (**Table 4**). If one or more risk factors are present, patients are considered high risk. Patients with low disease burden patients may be kept under regular follow-up and therapy may be started at disease progression [74, 75].

In a randomized trial in 309 low-burden FL patients, cause-specific survival, and overall survival (OS) were similar between observation and chlorambucil therapy. In the observation arm, 19% of patients did not require any therapy even after 10 years [75]. Alternatively, single-agent rituximab with or without maintenance can also be used in low-burden diseases. In a three-arm randomized trial, low burden FL were randomized to observation, four cycles of rituximab every week (induction rituximab), or four weekly cycles of rituximab followed by rituximab maintenance every two months for two years (maintenance arm). The primary endpoint was the time to start a new treatment, which was lower for the observation arm but was similar between the two rituximab arms. PFS and quality of life were better with maintenance rituximab but there was no difference in

OS and histologic transformation (HT) [76]. In the RESORT trial, low burden FL was randomized after four cycles of weekly rituximab to maintenance rituximab every three months for three years or retreatment on progression. The primary endpoint was time to treatment failure (4.3 years vs 3.9 years) was similar in both groups. No difference was observed in OS and HR-QOL (health-related quality of life) [77]. Due to the lack of survival benefit with rituximab, we prefer to wait and watch policy in patients with low burden FL. Important studies in the advanced stage, low burden FL have been summarized in **Table 5**.

Patients with a high disease burden require immediate treatment. CIT with BR (bendamustine and rituximab), R-CHOP (rituximab, cyclophosphamide, adriamycin, vincristine, and prednisone), or R-CVP (rituximab, cyclophosphamide, vincristine, and prednisone) followed by rituximab maintenance is the most used approach. None of these CIT have shown OS benefit and choice depending on performance status and comorbidities. Data from major trials have been elucidated in **Table 6**. In phase III FOLL05 trial, patients with advanced FL were treated with either R-CHOP, R-CVP, or R-FM (rituximab, fludarabine, mitoxantrone). R-CVP arm had lower PFS with a higher rate of progression and requirement of additional therapy. R-FM arm was associated with more neutropenia and secondary malignancies [52, 78]. In the StiL trial, PFS was better with BR than R-CHOP (69.5 months vs 31.2 months, HR = 0.58) with no difference in OS. BR had a favorable toxicity profile with lesser rates of neutropenia, infections, neuropathy, and alopecia [79]. In the BRIGHT trial, BR had better PFS than R-CHOP/R-CVP with a similar OS. However, patients in these trials did not receive maintenance therapy [80].

A novel anti-CD20 agent like obinutuzumab has also been studied in this setting. In phase 3 Gallium trial obinutuzumab-chemotherapy was compared to rituximab chemotherapy, PFS advantage was observed but there was no OS benefit. In addition, the obinutuzumab arm has higher neutropenia, infusion reactions, and infections [81].

Chemo-free regimens like lenalidomide/rituximab (R2) have shown encouraging results in early phase trials, however, no PFS or OS benefit was observed in the phase 3 RELEVANCE trial. It is associated with higher skin-related toxicity and lower hematological toxicity compared with conventional chemo-immunotherapy. It may be considered for patients not willing to chemotherapy [82, 83]. Recent updates have suggested that patients with EZH2 mutations or EZH2_mut signature may do better with CHOP/CVP and those without may do better with bendamustine-based treatment [84].

Grade 3B follicular lymphoma

Patients with early-stage grade 3B FL are treated like DLBCL with three to four cycles of R-CHOP followed by radiotherapy, while advanced patients require six cycles.

Maintenance

The role of maintenance rituximab after initial induction therapy has been studied extensively. Rituximab maintenance in limited-stage FL has been already discussed above. Key studies have been summarized in **Table 6**. In the phase 3 PRIMA study, patients who received R-CHOP or R-CVP were randomized to rituximab maintenance (eight weekly for two years) or placebo. At 3 years follow-up rituximab arm had higher PFS and higher rates of complete responses. No OS advantage was seen even at 10-year follow-up and maintenance was associated with more infections, infusion reactions, and neutropenia [85, 86]. In the post hoc analysis of the BRIGHT trial, patients who received maintenance rituximab after bendamustine had significantly improved PFS [87]. In Phase 3 MAINTAIN trial, patients with advanced FL who received six cycles of BR followed by two years of rituximab maintenance were randomized to two more years of rituximab maintenance versus observation. Four years of rituximab maintenance showed no significant improvement in PFS or OS [88].

The debate on the role of maintenance therapy in FL continues due to the lack of OS benefits and added adverse effects. Furthermore, prospective trials evaluating maintenance after initial bendamustine-based therapy are lacking. At present maintenance, therapy may be individualized based on clinical risk factors, toxicity profile, and patients' preferences.

Relapse or refractory follicular lymphoma

FL has a chronic course heralded with multiple relapses. There are multiple options, but there

Table 5. Summary of key studies in follicular lymphoma

Study/Trial	Study population	Treatment	Results	Remarks
Limited stage follicular lymphoma				
Phase III trial, Lowry et al, 2011 [64]	Early stage FL, 640	40-45 Gy in 20-23 # vs 24 Gy in 12 #	No difference in ORR, within-radiation field progression, PFS or OS	Lesser toxicity of lower dose radiotherapy
Phase III FORT trial, Hoskin et al, 2014 [65, 66]	Early stage FL, 614	24 Gy in 12 # vs 4 Gy in 2 #	5 year local progression-free rate 89.9 % vs 70.4 %. No difference in OS and PFS	More alopecia, xerostomia and mucositis with 24 Gy
Phase III TROG 99.03 trial, MacManus et al, 2018 [68]	Early stage FL, 150	30 Gy IFRT alone vs arm 30 Gy IFRT plus 6 cycles CVP/RCVP	10 year PFS 59 % vs 41 %. No difference in OS	Additional hematologic toxicity and infections with chemoimmunotherapy
Italian multicentric study, Ruella et al, 2015 [70]	Early stage FL, 94	RT alone vs Rituximab-RT	10-year PFS 50.7 % vs 64.6 %. No difference in OS	BCL-2/IgH positivity strongly associated with relapse
SEER, Pugh et al, 2010 [61]	Early stage FL, 6568	Observation vs RT	Upfront RT associated with improved OS and disease specific survival	Lymphoma most common cause of death
Advanced stage, low burden follicular lymphoma				
Phase III multicentric trial, Ardeshna et al, 2003 [75]	Asymptomatic, advanced-stage, low-grade non-Hodgkin lymphomas (n = 309)	Immediate systemic therapy with oral chlorambucil 10 mg/day vs initial observation, with systemic therapy on progression	No difference in OS or cause-specific survival	19% patients not requiring therapy even at 10 years
Phase III multicentric trial, Ardeshna et al, 2014 [76]	Asymptomatic patients (aged ≥ 18 years) with low-tumour-burden follicular lymphoma (grades 1, 2, and 3a) (n = 379)	Watchful waiting vs rituximab induction (375 mg/m^2 weekly for 4 weeks), vs rituximab induction followed by a maintenance (12 infusions given at 2-monthly for 2 years.	Significant difference in time to start new treatment. Better PFS with rituximab therapy. No difference in OS and time to histological transformation	12% patients had spontaneous regression. Greater toxicity with rituximab. However, QoL better with maintenance rituximab
Phase III RESORT trial, Kahl et al, 2014 [77]	Untreated low tumor burden FL who responded to four doses of rituximab induction (n = 289)	Re-treatment at disease progression vs rituximab every 3 months until treatment failure	No difference in median time to treatment failure (3.9 vs 4.3 years), QoL, and OS	Maintenance rituximab had longer time to first cytotoxic therapy
Phase III trial, Brice et al, 1997 [74]	Newly diagnosed follicular lymphoma patients with a low tumour burden (n = 193)	No initial treatment vs prednimustine vs interferon alfa	No difference in OS	Based on past chemotherapy regimens not in current use
Advanced stage, high burden follicular lymphoma				
Phase III FOLL 05 trial, Federico et al, 2013 and Luminari et al 2018 [52, 78]	Previously untreated advanced stage FL (n = 534)	R-CHOP vs R-CVP vs R-FM	8 year PFS 49% vs 52% vs 42%. No difference in OS	More grade ¾ neutropenia and second malignancy with R-FM
Phase III StiL trial, Rummel et al, 2013 [79]	Previously untreated stage III/IV indolent non-hodgkin's lymphoma (n = 514)	BR vs R-CHOP	Better PFS with BR. No difference in OS	Less neutropenia, infections, neuropathy and alopecia with BR
Phase III BRIGHT trial, Flinn et al, 2014/2019 [80]	Previously untreated stage III/IV indolent non-hodgkin's lymphoma (n = 447)	BR vs R-CHOP/R-CVP	5 year PFS 70.3% vs 62.0% (p = 0.058). No difference in OS	Higher second malignancy with BR
Phase III GALLIUM trial, Marcus et al, 2017 [81]	Previously untreated advanced stage FL (n = 1702)	Obinutuzumab-Chemo (Bendamustine, CVP, CHOP) vs Rituximab-Chemo. (Maintenance given in both arms for 2 years)	3 year PFS better with Obinutuzumab (80 vs 73.3%)	Greater neutropenia, infections and infusion reaction with Obinutuzumab
Phase III RELEVANCE trial, Morschhouser et al, 2018	Previously untreated advanced stage FL (n = 1030)	R^2 vs BR/R-CHOP/R-CVP (Maintenance given in both arms for 2 years)	At 3 years no difference in ORR, PFS and OS	Greater haematological BR/R-CHOP/R-CVP toxicity with and skin toxicity with R^2

BR Bendamustine-Rituximab, R^2 Lenalidomide-Rituximab, ORR objective response rate, OS overall survival, PFS progression free survival, QoL quality of life, R-CHOP (rituximab, cyclophosphamide, adriamycin, vincristine and prednisone), R-CVP (rituximab, cyclophosphamide, vincristine and prednisone), R-FM (rituximab, fludarabine and mitoxantrone), RT radiotherapy, SEER Surveillance Epidemiology and End Results database.

Table 6. Summary of key studies for maintenance therapy in Follicular lymphoma

Study/Trial	Study population	Treatment	Results	Remarks
Phase III multicentric trial, Ardeshna et al, 2014 [76]	Asymptomatic patients with low-tumour-burden FL (grades 1, 2, and 3a) (n = 379)	Watchful waiting vs rituximab induction vs rituximab induction followed by a maintenance	Significant difference in time to start new treatment. Better PFS with rituximab therapy. No difference in OS	12% patients had spontaneous regression. Greater toxicity with rituximab. QoL better with maintenance rituximab
Phase III RESORT trial, Kahl et al, 2014 [77]	Low burden FL responding to four doses of rituximab induction (n = 289)	Re-treatment at disease progression vs rituximab every 3 months until treatment failure	No difference in median time to treatment failure (3.9 vs 4.3 years), QoL, and OS	Maintenance rituximab had longer time to first cytotoxic therapy
SAKK 35 Trial, Martinelli et al, 2010 [89] Moccia et al, 2020 [90]	FL patients in partial or complete remission post 4 cycles of Rituximab (n = 165)	Short maintenance (4 doses 2 months) vs prolonged maintenance (every 2 months for 5 years)	At 10 year PFS 3.4 years vs 5.3 years (not significant)	
Phase III PRIMA trial, Salles et al, 2011 [85, 86]	Partial or complete response to R-CHOP/R-CVP (n = 1018)	Rituximab maintenance (every eight weeks for two years) vs Placebo	3 year PFS 74.9% vs 57.6%. No OS difference	Higher infections, infusion reaction, and neutropenia with maintenance
Retrospective analysis of BRIGHT trial, Kahl et al 2017 [87]	Stage III/IV FL previously treated with BR (n = 144)	Rituximab maintenance	Improved PFS and trend towards improvement in OS	70% had previous partial response to therapy
Phase III MAINTAIN Trial, Rummel et al, 2017 [88]	Stage II (bulky), III, or IV disease. Post 6 cycles BR and 2 years rituximab maintenance (n = 350)	Rituximab maintenance (every eight weeks for two years) vs Observation	Four years of rituximab maintenance showed no significant improvement in PFS or OS	Compared with data from STIL trial, improvement in PFS

BR Bendamustine Rituximab, FL Follicular lymphoma, ORR objective response rate, OS overall survival, PFS progression free survival, QoL quality of life, R-CHOP (rituximab, cyclophosphamide, adriamycin, vincristine and prednisone), R-CVP (rituximab, cyclophosphamide, vincristine and prednisone).

is no standard management for relapsed FL. Given the likelihood of transformation, a fresh biopsy should be done followed by re-staging, assessment of symptom burden, and prior therapies. Prognostic tools like FLIPI-1, FLIPI-2, and M7-FLIPI can predict survival, but there are no tools to predict the relapse of disease [91]. About 20% of patients who relapse within 24 months of initial therapy are labeled as early relapses and have a worse prognosis than those who relapse later. Five-year survival approximates 50% in such patients compared to 90% in those who relapse later than 24 months [55]. No sequence is defined for managing unfit patients with relapsed refractory FL and post two lines of therapy. The goal of therapy should be the improvement in symptoms and a better quality of life. Many drug combinations, novel agents, and transplant options have been studied and have demonstrated efficacy as discussed below. Management decision is based on disease stage, symptom burden, the interval between initial therapy and relapse, prior therapy, treatment-related toxicities, patients' comorbidities, and preferences. Therapies available for the management of relapsed or refractory FL are discussed in **Table 7**.

Late relapse

Patients who relapse more than 24 months after chemoimmunotherapy (CIT) have an excellent prognosis. Limited-stage patients may be treated with radiotherapy or single-agent rituximab. Patients with relapsed advanced FL who have a high symptom burden require immediate treatment while those with low symptom burden may be kept on observation. Patients initially treated with R-CHOP or R-CVP may be offered bendamustine or lenalidomide-based therapy and vice versa. Obinutuzumab may be favored above rituximab if later had been used in previous lines or rituximab refractory patients [92, 93]. In the phase III GADOLIN trial, 396 patients with rituximab refractory indolent NHL were randomized to six cycles of Bendamustine-Obinutuzumab (BO) followed by two years of obinutuzumab maintenance or to six cycles of single-agent bendamustine. In FL patients BO therapy showed improvement in PFS (median PFS 24.1 months versus 13.7 months) as well as OS (not reached versus 60.1 months) [94, 95]. In the AUGMENT trial patients with relapsed refractory FL/MZL (not rituximab refractory) were randomized to lenalidomide plus rituximab (R2) or rituximab only. R2 showed improved ORR (78 versus 53%) and PFS (39.4 months versus 14.1 months) [96]. Maintenance with anti CD20 monoclonal antibody may improve PFS but has no impact on overall survival [97].

Early relapse

Patients who have progressed within 24 months (POD24) of frontline therapy have poor outcomes with CIT and histological transformation should be ruled out [98]. Progressive lymph node enlargement, extranodal involvement, raised LDH, and hypercalcemia also indicates transformation [99]. If there is clinical suspicion, a PET-guided biopsy of the most metabolically active lesion should be performed. The initial management strategy is like those with late relapse. Fit patients who are responding to re-induction with CIT may be taken for autologous HSCT. In a Center for International Blood and Marrow Transplant Research (CIBMTR) and the National LymphoCare Study (NLCS) analysis patients undergoing autologous HSCT within one year of treatment failure have improved five-year OS compared to no HSCT (73% VS 60%) [100]. Some studies have suggested better outcomes with autologous compared to allogenic HSCT due to higher non-relapse mortality (NRM) [101, 102]. The role of maintenance therapy is unclear post HSCT in such patients.

Novel therapies in the landscape of management of relapsed and refractory FL include phosphoinositide 3'-kinase (PI3K) inhibitors, enhancer of zeste homolog 2 (EZH2) inhibitors, and chimeric antigen receptor therapy (CAR-T) [103-108]. Programmed death receptor ligand 1 (PDL1) inhibitors, BCL2 inhibitors, and Bruton tyrosine kinase (BTK) inhibitors have also been tested in early phase trials and have shown modest efficacy [109-112].

PI3K-AKT axis is important for the proliferation, growth, and survival of the B cells. Idelalisib inhibits PI3K delta isoform and is approved in relapsed/refractory FL post two lines of therapy. It is associated with gastrointestinal toxicity (hepato-toxicity, colitis, and rare intestinal perforation), pneumonitis, hypertriglyceridemia, cytomegalovirus (CMV), and Pneumocystis jirovecii infection [103]. Copanlisib is a parenteral dual inhibitor of PI3K alpha and delta isoforms. In addition to the above toxicities, it is associ-

Table 7. Therapies available for management of relapsed or refractory Follicular lymphoma

Study design	Study population	Drug	Response rates	Survival	Adverse effects
Phase III AUGMENT trial [96]	Relapsed refractory FL or marginal zone lymphoma (n = 358)	Lenalidomide plus rituximab versus placebo plus rituximab followed by rituximab maintenance	ORR 53%, CR 20%	mPFS 39.4 months vs 14 months, No difference in OS	Grade ¾ toxicity: neutropenia (50%) and leukopenia (7%)
Phase III GADOLIN trial [94]	Rituximab-refractory, CD20+ indolent NHL (n = 413)	Obinutuzumab plus bendamustine versus bendamustine followed obinutuzumab by maintenance	NA	mPFS 25.8 months vs 14.1 months	Grade ¾ toxicity: Neutropenia (37.3%), infusion- reactions (11.3%) thrombocytopenia (10.8%), anemia (7.4%)
Multicenter phase II study [103]	≥ 2 prior lines of therapy, double refractory indolent NHL (n = 125)	Idelalisib PI3K delta inhibitor 150 mg twice orally daily	ORR 57%, CR 06%	mPFS 11 months, mOS 20 months	Grade ¾ toxicity: Neutropenia (27%) transaminitis (13%) Diarrhea (13%) Pneumonia (7%) Febrile neutropenia (3%)
Phase II CHRONOS-1 trial [104]	≥ 2 prior lines of therapy in relapsed refractory indolent NHL (n = 142)	Copanlisib PI3K alpha and delta inhibitor 60 mg one-hour infusion day 1, 8, 15 of 28-day cycle	ORR 61%, CR 17%	mPFS 12.5 months, mOS 43 months	Grade ¾ toxicity: Hyperglycemia (40%) Hypertension (24%) Neutropenia (24%)
Phase III CHRONOS 3 trial [105]	≥ 2 prior lines of therapy in relapsed refractory indolent NHL (n = 458)	Copanlisib plus rituximab vs placebo plus rituximab	ORR 81%, CR 34%	mPFS 21.5 months vs 13.8 months	Grade ¾ toxicity: Hyperglycemia (56%) Hypertension (40%)
Phase II Global Unity-NHL trial [107]	≥ 2 prior lines of therapy, double refractory indolent NHL (n = 117)	Umbralisib PI3K delta and casein kinase isoforms. 800 mg daily	ORR 45%, CR 06%	mPFS 10.6 months	Grade ¾ toxicity: Neutropenia (11.5%) Diarrhea (10.1%)
PHASE II DYNAMO trial [106]	≥ 2 prior lines of therapy, double refractory indolent NHL (n = 129)	Duvelisib PI3K delta and gamma inhibitor 25 mg twice per oral daily	ORR 42.2%, CR 1.2%	mPFS 9.5 months, mOS 28.9 months	Grade ¾ toxicity: neutropenia (24.8%), diarrhea (14.7%), anemia (14.7%), and thrombocytopenia (11.6%)
Phase II trial [108]	Relapsed FL with at least 2 prior lines of therapy (n = 99)	Tazemetostat EZH2 inhibitor 800 mg per oral twice daily	EZH2 Mutated ORR 69%, EZH2 wild ORR 35%	mPFS EZH2 Mutated 13.8 months, EZH2 wild 11.1 months	Grade ¾ toxicity: neutropenia (3%), anemia (3%), and thrombocytopenia (2%)
Phase II ZUMA 5 trial [114]	≥ 2 prior lines of therapy in relapsed refractory indolent NHL (n = 153)	Conditioning (cyclophosphamide at 500 mg/m^2 per day and fludarabine at 30 mg/m^2 per day on days -5, -4, and -3) followed by a single infusion of axicabtagene ciloleucel (2 × 10^6 CAR T cells per kg) on day 0	ORR 92%, CR 76%	12 months PFS: 73.7%, 12 months OS: 92.9%	Grade ¾ toxicity: cytopenias (70%), infections (18%), cytokine release syndrome (7%), neurological events (19%)
Phase II, DAWN trial [110]	≥ 2 prior lines of therapy (n = 110)	Ibrutinib BTK inhibitor 560 mg once daily until progression	ORR 20.9%, CR 11%	mPFS 4.6 months, 30 months OS 61%	Diarrhea, fatigue, cough common adverse effects
Phase II trial [111]	Relapsed refractory indolent NHL (n = 39)	Vorinostat 200 mg twice daily for 14 consecutive days in a 21-d cycle	ORR 49%, CR 18%	mPFS 20 months	Grade ¾ toxicity: thrombocytopenia (48%), neutropenia (31%)
Phase II study [112]	Relapse after ≥ 1 prior therapy and rituximab sensitive disease (n = 30)	Pembrolizumab + Rituximab	ORR 80%, CR 60%	mPFS not reached	Nausea, aseptic meningitis, pneumonia. Immune-related toxicity (grade 2) diarrhoea, pneumonitis and skin rash

Double refractory: refractory to anti CD20 antibody and alkylating agent, ORR objective response rate, mOS median overall survival, mPFS median progression free survival, OS overall survival, PFS progression free survival.

ated with hyperglycemia, hypertension, and dermatologic toxicity (due to inhibition of alpha isoform). A recent phase 3 trial has shown improved ORR and PFS when combined with rituximab [104, 105]. Umbralisib, an oral multikinase (PI3K delta and casein kinase) inhibitor has been recently approved and has a similar toxicity profile. Duvelisib was withdrawn from the market by the manufacturer [106].

EZH2 is a histone methyltransferase involved in the germinal center formation and EZH2 mutations lead to its epigenetic silencing and provide a proliferative advantage to germinal center B cells [113]. Up to 20% of patients with relapsed FL have these mutations. Tazemetostat is an EZH2 inhibitor approved for relapsed with EZH2 mutation (after one line of therapy) and without EZH2 mutation (after multiple lines of therapy) [108].

CAR-T therapies may be an option where cost and availability are not an issue, as these are approved in relapsed refractory FL post two or more lines of therapy based on the ZUMA-5 trial. The ORR and CR rates were 94% and 79% respectively. At 12 months PFS was 73.7% and OS was 92.9%. Grade ¾ toxicity included cytopenia (70%), infections (18%), cytokine release syndrome (7%), and neurological events (19%) [114]. Antibody-drug conjugates (Polatuzumab vedotin), bispecific antibodies (Mosunetuzumab, Glofitamab, epcoritamab), and phagocytosis checkpoint inhibitors (anti CD47 "don't eat me signal") are the future agents in the armamentarium [115-119].

Summary and conclusions

FL is one of the most prevalent forms of indolent B cell NHL. It has a long disease course due to chronic incurable nature of the disease in the majority of patients. Patients with de novo localized disease are treated with curative radiotherapy. Asymptomatic patients with advanced disease may be kept on observation. While those with a more symptomatic and high burden disease are treated using systemic chemoimmunotherapy and maintenance Rituximab.

Advances in prognostication and the development of newer agents have changed the treatment paradigm in relapsed patients. Relapsed patients are managed based on POD24. Late relapses are treated like treatment naïve cases and an alternative chemotherapy agent or lenalidomide is used with anti-CD20 therapy. Early relapses are difficult to manage, fit patients should be taken up for the autologous HSCT after reinduction with chemoimmunotherapy. Unfit patients may be offered alternative chemoimmunotherapy, small molecule inhibitors, or CAR-T cell therapy.

The above principles are followed at our institute for the management of FL. Bendamustine is the preferred chemotherapy partner due to better tolerability and PFS benefit compared to other combinations. Maintenance rituximab for two years is considered after discussing possible adverse effects with the patients. Due to a lack of access to clinical trials and newer agents, relapsed patients are usually offered chemoimmunotherapy or lenalidomide-based therapy followed by maintenance Rituximab.

Future directions

With advancements in the therapies for relapsed/refractory therapy in FL, the prognosis has improved. Further research is warranted to identify the clinical and molecular markers to better identify patients at risk of early relapse. Newer chemotherapy-free regimens for the management of untreated and relapsed regimen needs further refinement.

Disclosure of conflict of interest

None.

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