Follicular Lymphoma

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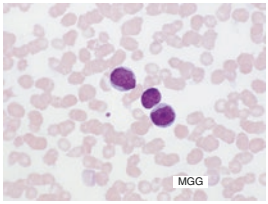
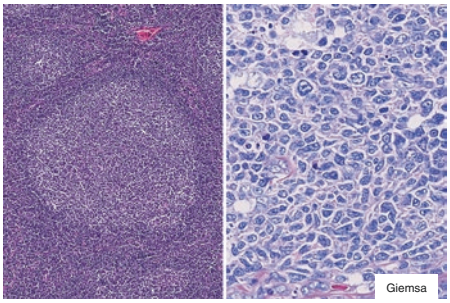
Follicular lymphoma (FL)

Clinical outline
FL typically affects adult patient as a widespread disease involving the lymph nodes, but it can affect extranodal sites. linical features (i.e. pediatric age or anatomic primary site) may define FL subsets with proper biology and behavior.

Cytology	Centrocytes and centroblasts in variable relation; spindle cell morphology rare. In histology, number of centroblast per high power field defines the grading.	Follicular lymphoma, cytology 
Histology	FL recapitulates the cyto-architectural and phenotypic features of germinal centers (GC) but lacking compartmentalization. Diffuse growth possible. Extrafollicular growth of cells with GC-phenotype commonly found. Accompanying sclerosis may be observed. In the bone marrow, infiltrates closely attached to bone trabeculae.	Follicular lymphoma, hystology 

	CD20	CD5	CD23[1]	CD10[2]	BCL6[3]	cyclin D1	CD103	FMC7	IgM	light chains
notes	[1]detects typical dendritic cells too, [2]less frequent in higher grades, [3]less expressed in extrafollicular cells									
other marker	Ki67 variable. BCL2 is typically overexpressed (can undetectable due to mutations or absent in higher grade FL) Other markers of germinal center origin: LMO2, HGAL, GCET. MUM1 positivity in a minority of cases, often with high grade cytology									

■ = majority of cases positive ▨ = variable fraction of cases positive □ = negative

Main differential diagnosis	Benign follicular hyperplasia, Diffuse large B-cell lymphoma (should have lost follicular pattern and show sheets of blasts)

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Key molecular features
IGH genes rearranged, ongoing somatic hypermutation. Frequent overexpression of BCL2 and alteration of TNFRSF14. Frequent translocations: t(14;18)(q32;q21) in approx 85% (less frequent in higher grades), *BCL6* translocation (5-10%). Lymphomas with rearrangements if *IRF4* are separated from FL as a distinct entity despite follicular growth. Frequent copy number alterations: loss of 1p (*TNFRSF14*), 6q, 10q, 17p, gains 1, 6p, 7, 8, 12q, X, 18q. Frequent mutations: *BCL2, KMT2D, TNFRSF14, EZH2, EPHA7, CREBBP, BCL6, MEF2B, EP200, TNFAIP2.*
Precursor lesions
Benign t(14;18)-positive cells in healthy donors, Follicular Neoplasia in situ
Progression
Transformation to diffuse large B-cell lymphoma; less commonly, to high grade B-cell lymphoma or B-lymphoblastic lymphoma / leukemia. Most frequent are relapses of FL not showing histological progression/transformation.

Clinically relevant pathologic features	**Relevance**	**Evidence**
Histologic grading	Prognostic: FL grades I-IIIa harbor no different prognosis. Prognostic: Grade as a prognostic marker only observed in older but not reproduced in more recent studies. Nevertheless, FL IIIb is commonly managed as an aggressive lymphoma.	**A** **B**
Clinico-pathological subtypes of FL (defined by combination of localization, histology and genetics)	Prognostic (favourable): Testicular FL (Confined to testis, frequently younger patients, no t(14;18)(q32;q21) Duodenal-type FL (t(14;18)(q32;q21) positive, confined to duodenum or GI tract, low or no tendency to disseminate or transform) in situ follicular neoplasia (Incidental finding of few t(14;18)(q32;q21) positive cells in GC or lymph nodes enlarged due to other reasons).	
Related diseases	Prognostic (favourable): Primary cutaneous follicle center lymphoma (confined to skin, mostly negative for BCL2 translocation, rarely CD10 expression) Pediatric type follicular lymphoma (nodal, localized stage, cervical region, children, adolescents and young adults, no *BCL2* and *BCL6* translocations)	
***BCL2* rearrangement**	Translocation as a sole bio-marker not prognostic or predictive. Prognostic value of translocation in the context of clinico-pathological subtypes (see above)	**B**
Mutations (*EZH2*, *ARID1A*, *MEF2B*, *EP300*, *FOXO1*, *CREBBP*, *CARD11*)	Prognostic: integration of targeted sequencing for gene panels improves clinical stratification(m7-FLIPI)	**B**
Legend: A = verified in multiple studies, randomized trials and/or integrated in guidelines; B = variable between studies/needs definitive validation; C = preliminary/discrepant results.		

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6.1 Introduction

Follicular lymphoma (FL) represents the most common indolent lymphoma in the Western world. Diagnosis is based on the peculiar histologic nodular pattern and histogenetically it arises from germinal center B-cells. The presence in the same lymph node of a diffuse pattern composed of centroblasts is considered to be in keeping with a progression to a diffuse large B-cell lymphoma.

FL is typically characterized by a relapsing and remitting course of the disease and by the risk of a transformation to a more aggressive disease. The behavior of FL is characterized by a wide heterogeneity. In some cases, the disease can be controlled for many years while in others it follows an aggressive and sometimes chemorefractory course. To date, advanced-stage FL continues to be a treatable but not curable condition. Despite an improvement in the management of patients with FL in recent years, there are still open questions that remain unsolved. In the past 30 years, new treatment approaches have partially modified the management of patients with FL, resulting in more favorable clinical outcomes. Chemotherapy in combination with a monoclonal anti-CD20 antibody is currently the standard of care for patients with advanced-stage FL in need of treatment. The median overall survival (OS) has dramatically improved, in particular, since the advent of rituximab in the treatment armamentarium. Chemotherapy-free approaches based on anti-CD20 antibodies (in particular, rituximab) also represent an option for many patients. Fortunately, for patients relapsing after first-line therapy, there is a wide variety of strategies ranging from targeted therapies up to stem cell transplantation. In this chapter, we review the current knowledge of FL pathology and epidemiology and the critical issues encountered in the clinical practice when treating patients with FL.

6.2 Epidemiology

FL is the second most common lymphoma in the Western world, accounting for approximately 20% of all NHL and up to 70% of indolent lymphomas. The median age at diagnosis is in the mid-1960s. The incidence in Europe is 2.18 cases per 100,000 persons per year [1] and has been stable over time. There is a large variability in terms of incidence, depending in particular on ethnicity: it tends to be higher in Whites than in Black and Asian populations [2]. Numerous potential risk factors have been associated with NHL, even though there is a lack of consensus regarding specific risk factors for the development of FL. Factors traditionally associated with NHL are in particular specific chemical agents (agricultural pesticides, hair dyes), infections (HIV, human T lymphotropic virus type 1 (HTLV-1), Epstein-Barr virus, hepatitis C, *Borrelia burgdorferi*), autoimmune diseases (Lupus erythematosus, rheumatoid arthritis, Sjögren syndrome, Hashimoto's thyroiditis), multicentric Castleman disease, and inflammatory gastrointestinal diseases. Of note, the risk of FL tends to be slightly increased among relatives of a person with FL [3].

6.3 Pathology

FL is diagnosed according to the criteria of the fourth World Health Organization (WHO) classification updated in 2017 [4]. FL is a neoplasm composed of germinal center B-cells exhibiting most frequently a partially follicular growth pattern, which tends to reproduce the architecture of normal germinal centers of secondary follicles. Neoplastic follicles are often poorly defined and usually have attenuated mantle zones. FL is composed of a mixture of centrocytes (cleaved follicle center cells) and centroblasts (large, noncleaved follicle center cells) surrounded by nonmalignant cells including macrophages, T-cells, and follicular dendritic cells. Centroblasts are generally the minority. The presence of diffuse areas composed predominantly of centroblasts is considered to be equivalent to diffuse large B cell lymphoma (DLBCL). Grading of FL is primarily based on the count of centroblasts per high-power field (HPF): grade 1 (0–5 centroblasts per HPF) and grade 2 (6–15 centroblasts per HPF) tend to share similar clinical character-

istics and are considered to be of low-grade. FL of grade 3 are considered to be high-grade and they are further divided into 3A and 3B neoplasms, both exhibiting >15 centroblasts per HPF, with confluent sheets of centroblasts defining grade 3B [5]. Grade 3B cases tend to have a more aggressive clinical course and are biologically distinct from other FL, resembling DLBCL in their clinical behavior and response to therapy. Table 6.1 summarizes the main characteristics distinguishing grades 1–3A from grade 3B.

Histology at the time of transformation is generally in keeping with DLBCL (80%); rarely patients may present with a composite lymphoma (14%) or a lymphoma morphologically similar to a high-grade B-cell lymphoma (6%) [6].

6.4 Immunophenotype and molecular markers

The immunophenotype of FL is usually confirmed by immunohistochemistry or using flow cytometry. Immunophenotyping studies have demonstrated that FL cells are derived from normal germinal B cells. Tumor cells typically express monoclonal surface immunoglobulin and pan-B cell antigens (CD19, CD20, CD79a), complement receptor (CD21 and CD35), and CD10 (60%) and nuclear BCL-6. CD10 expression is often stronger in the follicle than in the interfollicular cells; some cases, in particular grade 3B, tend to lack CD10 but retain BCL6 expression. Unlike small lymphocytic and mantle cell lymphoma, FL lacks expression of CD5 and CD43 (most cases) and there is no staining for MUM1. Cytoplasmic staining for BCL-2 protein is strongly positive in almost all grade 1/2 tumors [7].

FL is characterized by the reciprocal translocation t(14;18)(q32;q21), which is present in 85–90% of cases [8]. This translocation leads to the placement of the B cell lymphoma 2 (BCL2) gene under the inductive influence of transcriptional enhancers associated with IGH, resulting in overexpression of the anti-apoptotic BCL2 protein, in turn leading to increased cell survival. This somatic rearrangement is thought to constitute the first step of lymphomagenesis. Nevertheless, the t(14;18) translocation alone is considered insufficient for the development of FL [9]. The development of FL requires further acquired aberrations in genes controlling the normal germinal center B-cells development. The complexity of the disease is also related to the importance of its interactions with the microenvironment that substantially influence disease development. Moreover, the relevance of normal tumor-infiltrating immune and stromal cells have been recognized to play a crucial role. In a model proposed by Scott et al., FL's neoplastic cells tend to "colonize" reactive germinal center that supports their proliferation and survival, and they "reeducate" the tumor microenvironment to their advantage, escaping immune surveillance [10]. This is well illustrated by the TNFRSF14 and STAT6 mutations which induce this interaction with the microenvironment [11]. In the early stages of development, the neoplastic cells, through the deregulation of a set of genes (KMT2D, MLL2, CREBBP, TNFRSF14, EZH2, RRAGC), acquire specific aberrations that inhibit apoptosis and increase BCR signaling. The acquisition of additional aberrations that enable proliferation (i.e., MYC p53 pathway, FOXO1) changes the nature of the tumor, frequently leading to histologic transformation.

Table 6.1 Grading of follicular lymphoma

Grade 1–2	*0–15 centroblasts per HPF*
1	0–5 centroblasts per HPF
2	6–15 centroblasts per HPF
Grade 3	*>15 centroblasts per HPF*
3A	Centrocytes present
3B	Solid sheets of centroblasts

HPF high-power (40× objective, 0.159 mm^2) microscopic field

6.5 Pathological Variants

In the revised 2017 WHO classification, several variants of FL have been described.

In situ follicular neoplasia (ISFN) is a pathologic diagnosis used to describe the identification of follicles that have a high content of BCL2-rearrangement-positive B cells within a lymph node that otherwise lacks the diagnostic features of FL. ISFN may be associated with progression to overt FL even though the risk is typically considered to be low [12].

Pediatric-type FL is rare, diagnosed mainly in children, and has distinctive clinical and pathological features. It tends to be more frequently localized, and patients typically do not experience a relapse after excision. Pathologically it is characterized by large follicles, with a large number of centroblasts often resembling FL grade 2/3 but lack the t(14;18). The prognosis of pediatric FL appears to be good.

Duodenal-type FL is a distinct subtype from other gastrointestinal FL. It typically presents as solitary or multiple polypoid lesions, which are confined to the mucosa and submucosa of the second part of the duodenum. This subtype of FL tends to have an indolent course and rarely progress into overt FL. Typically is associated with an excellent outcome and may even spontaneously regress [4, 13].

Even though the majority of FL cases harbor the t(14;18) translocation, there is a small subset of cases who do not present this genetic alteration. This entity is described as t(14;18)-negative FL. These patients have similar outcomes as patients with an FL that harbors the translocation, but this entity is associated with a distinct molecular feature that includes the absence of CD10 expression and the presence of BCL6 alterations, IRF4 expression, and proliferation signatures [14].

6.6 Staging

A careful history and physical examination are crucial in evaluating a new patient with FL to define the extent of disease. Treatment decisions depend upon the distinction between early-stage and advanced disease. The majority of patients with FL present with painless lymph nodes enlargement. The most frequently involved sites included cervical, inguinal, and axillary regions. It is also crucial to determine the presence of systemic symptoms (also called "B symptoms") including fever (temperature >38°), night sweats, and unexplained weight loss (>10% of body weight over the past 6 months). B symptoms represent an adverse prognostic factor and their resolution is frequently related to treatment response. Retroperitoneal adenopathies are usually asymptomatic, even though they may lead to abdominal discomfort and obstructive uropathy. Mesenteric or pelvic adenopathy may induce bowel obstruction or perforation.

FL is diagnosed by bioptic lymph node examination; fine-needle aspiration does not provide adequate material for an accurate diagnosis and tumor grading.

Laboratory studies should include a complete blood count, with the examination of the peripheral smear processed to search for circulating lymphoma cells. Lactate dehydrogenase (LDH) and beta2-microglobulin are indirect parameters of tumor load that have independent prognostic value. Serum creatinine and uric acid are essential in identifying risk for tumor lysis syndrome. Impaired renal function may also be related to ureteral obstruction. An isolated elevation in alkaline phosphatase should prompt an evaluation of the skeletal system. A serum protein electrophoresis may reveal a monoclonal gammopathy. It is also recommended to determine several viral serologies, in particular for HIV, hepatitis B (HBV), and hepatitis C (HCV). Although HBV is not crucially related to any NHL, reactivation of chronic hepatitis in patients receiving cytotoxic chemotherapy or immunotherapy is a well-recognized complication. When the hepatitis B surface antigen and hepatitis B core antibody are positive, viral load assessment by measuring HBV DNA should be performed and a specific antiviral treatment initiated, particularly when rituximab is part of the treatment.

Imaging studies represent a key component of the staging evaluation. Moreover, they may help in the selection of the site of biopsy. The preferred imaging modality for staging patients

with NHL depends on the 18F-fluorodeoxyglucose (FDG) avidity of the histologic subtype. Indolent lymphomas are generally characterized by variable FDG avidity. Increasing evidence supports the role of FDG-PET in FDG-avid indolent non-Hodgkin lymphoma, in particular in FL [15]. More recently, formal guidelines for the use of FDG-PET in FL recommend its use for initial staging, evaluation, and response assessment after first-line therapy [16, 17].

FDG-PET may offer several advantages over conventional CT-scan, in particular the potential evaluation of large-cell transformation and the identification of patients at high risk of relapse at the end of therapy. Nevertheless, the exact impact of FDG-PET on outcome in FL remains to be defined and implementation of this tool into clinical management is based primarily on retrospective observations.

FL frequently presents with a bone marrow involvement. Bone marrow assessment should include both an aspirate and biopsy. The aspirate is useful for morphologic analysis, flow cytometry, and cytogenetics.

6.7 Clinical Presentation

The majority of patients with FL present with painless lymphadenopathy in the cervical, axillary, inguinal, and femoral regions [18], while large mediastinal masses are rare. The adenopathy sometimes waxes and wanes spontaneously, but rarely disappears completely. Only a minority of patients (accounting for approximately 15–20%) present with limited-stage disease, namely stage I or II. Despite the presence of widespread disease at diagnosis, the majority of patients are asymptomatic at the time of diagnosis. In contrast to aggressive lymphomas, constitutional symptoms (B symptoms) are rare and are present in approximately 20% of all cases. Only a minority of patients present with an increased LDH or cytopenias in the peripheral blood and no specific laboratory abnormalities have been associated with FL. Central nervous system involvement is rare, even though peripheral nerve compression and epidural tumor masses causing cord compression may be observed.

6.8 Risk Stratification and Prognosis

FL prognosis has evolved over the past decades and the outcome of patients with FL has improved considerably when comparing earlier treatment eras (1960s–1990s, the median survival being in the range of 10 years) to more recent eras, with a median survival in the range of 18 years [19]. This substantial improvement in survival can mainly be attributed to advances in frontline management, namely the use of monoclonal antibodies, superiority in diagnostic measures and supportive treatment and the availability of more active treatments for patients with transformed follicular lymphoma [20].

Several clinical prognostic factors have been identified as indicators of survival in patients with FL at the time of diagnosis.

Histologic grade has historically been an important factor in the determination of patient risk at the time of diagnosis. Low-grade histologies, namely grades 1, 2, and 3A, tend to have a very similar outcome with indolent behavior. However, patients with FL grade 3B tend to have more aggressive disease and they can be potentially cured with anthracycline-based chemotherapy [21].

The Follicular Lymphoma International Prognostic Index (FLIPI) is among the most well-validated prognostic tools in FL [18]. The FLIPI was developed before the rituximab era and it includes five main prognostic factors: number of involved nodal areas >4, LDH (normal vs. elevated), age (≤or >60 years), stage (I, II vs. III, IV), and the hemoglobin level (normal vs. <120 g/l). Patients are classified into the following prognostic groups based on the predicted outcome: low risk (0–1 factors), 90% 5-year OS; intermediate risk (two factors, 78% 5-year OS); high risk (three or more factors, 52% 5-year OS). The FLIPI has subsequently been validated in the rituximab era by the German Low-Grade Study Group in a cohort of 362 patients treated with

rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) [22].

The FLIPI-2 score was derived from a large multicenter study including more than 1000 patients with FL, in need of treatment and receiving rituximab. The FLIPI-2 identified five parameters, some of which overlap with the original FLIPI: age >60 years, serum beta-2 microglobulin level higher than the upper limit of normal, hemoglobin level <120 g/l, bone marrow involvement and greatest diameter of the largest involved node more than 6 cm as independent risk factor for progression-free survival (PFS). Three-year PFS rates of patients with low (0 factors), intermediate (1–2 factors), or high (3–5 factors) FLIPI-2 scores were 91, 69%, and 51%, respectively, whereas 3-year survival rates were 99%, 96%, and 84%, respectively [23]. Prognostic scoring systems are summarized in Table 6.2. A simplified version of the FLIPI-2 based on serum beta-2 microglobulin level and an assessment of bone marrow involvement was proposed using data from the PRIMA study and validated in a separate cohort [24].

The recently proposed m7-FLIPI index combines the mutation status of seven clinically relevant genes (i.e., EZH2, ARID1A, MEF2B, EP300, FOXO1, CREBBP, and CARD11) with the FLIPI and the Eastern Cooperative Oncology Group (ECOG) Performance Status [25]. This model was created using the clinical and genetic data from two studies including patients with previously untreated symptomatic, advanced stage FL treated with either R-CHOP or R-CVP (rituximab, cyclophosphamide, vincristine, and prednisolone). This index was then validated in an independent cohort of 107 patients with symptomatic FL treated with R-CVP.

The French group has investigated the prognostic role of gene expression pattern and identified a 23 gene set identifying a high-risk patient cohort. Again, these results were confirmed in an independent validation set [26].

Both molecular scores represent a first step towards the incorporation of genetic findings in the determination of outcome in patients with FL, but it remains primarily a research tool not applicable to routine clinical practice.

Approximately 20% of patients with FL will experience an early progression of disease (POD) after chemo-immunotherapy, usually defined as progression or relapse within the first 2 years of diagnosis/treatment (POD24). The clinical impact of POD24 was investigated in a pivotal analysis conducted from the National LymphoCare Study (NLCS) including patients with FL treated over 200 locations across the United States. Patients with POD24 had a poorer outcome compared to the reference group (patients without early progression), with 5-year overall survival (OS) at 50% versus 90%, respectively. This finding was maintained even after adjusting for the FLIPI score and was validated in an independent cohort of patients from the

Table 6.2 Prognostic scoring systems in follicular lymphoma

Variables	Risk groups	Number of factors	5-year OS, %
FLIPI [18]			
Age >60	Low	0–1	90
Ann Arbor stage III/IV	Intermediate	2	78
Hemoglobin <12 g/dl	High	3 or more	52
Elevated LDH			
>4 nodal sites			
FLIPI-2 [23]			
Age >60	Low	0	79
Elevated B2M	Intermediate	1–2	51
Lymph node mass >6 cm	High	3 or more	18
BM involvement			
Hemoglobin <12 g/dl			

B2M beta 2 microglobulin, *BM* bone marrow

University of Iowa and the Mayo Clinic [27]. These results highlighted an important and previously under-appreciated population of patients with poor survival.

The prognostic role of POD24 was also separately studied in patients treated with the so-called chemotherapy-free approaches. The Nordic Lymphoma Group recently published the results of two prospective trials including 321 patients with indolent lymphoma (84% with FL) treated with single-agent rituximab (148 randomly allocated to the addition of interferon alfa-2a) with more than 10 years of follow-up. Patients with POD24 appeared to have a significantly worse outcome in comparison to the reference group (10-year survival rate of 59% vs. 81% for those with more prolonged remission) [28]. These results were validated in an independent cohort of patients treated in three Swiss Groups of Clinical Cancer Research (SAKK) trials [29].

In conclusion, at present, the optimal way in which to implement prognostic indexes in FL remains largely unknown and none of these scoring indexes serves as a guide for treatment initiation. In the future, the identification of predictive biomarkers will possibly help to establish the role of individual therapies.

6.9 First-Line Treatment

FL is characterized by a heterogeneous clinical presentation and it is generally considered to be incurable when it presents in an advanced stage. The variability of presentation at the time of diagnosis and the fact that most patients are completely asymptomatic result in differences in strategies for the initial management. Most patients present with slow-growing adenopathies and they do not necessarily need an active treatment at the time of diagnosis. Treatment of FL typically depends on the stage at presentation. Patients with limited-stage (stage I–II) are candidates for radiation therapy, which may be curative in a significant proportion of patients. In contrast, patients with advanced-stage disease (stage III–IV) are considered not to be curable with conventional therapies. For this reason, a pretreatment evaluation is needed to determine the extent of the disease. Moreover, it should provide information concerning the fitness of the patient, in particular, performance status and the presence of comorbidities.

6.10 Initial Treatment of Limited-Stage FL

Approximately 10–20% of FLs are diagnosed at an early stage (stage I or II) [30]. Radiation therapy (RT) has been traditionally the treatment of choice for this group of patients, with the potential induction of sustained remissions [31]. The definition of this particular group of patients is currently more accurate with the use of FDG-PET, which allows the identification of a truly localized disease [32]. Despite the reduced number of randomized clinical trials (Table 6.3.), radiation therapy alone is usually the preferred modality, resulting in 10-year overall survival rates of 60–80% [38]. Alternatively, an initial watchful waiting policy has also been proposed for selected patients, with few retrospective clinical trials reporting similar survival outcomes [30]. Nonetheless, a recent analysis based on the Surveillance, Epidemiology, and End Results (SEER) Program registry suggested a survival benefit in patients with early-stage FL treated with RT in comparison to observation [31]. Systemic therapy with immunotherapy alone (i.e., rituximab) or chemo-immunotherapy has rarely been studied in patients with early-stage FL. McManus et al. conducted a multicenter phase III trial including 150 FL patients with stage I and II. Patients were randomly assigned to RT alone or RT followed by six cycles of chemotherapy. The majority of patients had stage I disease and chemotherapy regimen consisted of CVP with rituximab added after a protocol amendment. With a median follow-up of 9.6 years, the additional chemotherapy appeared to improve PFS (59 vs. 41% at 10 years; HR 0.57, 95% CI 0.34–0.95), even though this was not translated into superior OS [41]. In another prospective phase II study, the combination of involved field radiation and rituximab achieved

Table 6.3 Selected trials including patients with early-stage follicular lymphoma

Author (year)	Stage	*n*	Median RT dose	Survival (%)
Herfarth et al. (2018) [33]	I (56%) II (44%)	85	30–40 Gy	5-year PFS 78 5-year OS 96
Tsang et al. (2005) [34]	I (64%) II (36%)	573	35 Gy	10-year FFTF 48 10-year OS >60
Brady et al. (2019) [35]	I (80%) II (20%)	512	>24 Gy	5-year FFTF 69 5-year OS 96
Vaughan Hudson et al. (1994) [36]	I (100%)	208	35 Gy	10-year FFTF 47 10-year OS 64
Mac Manus et al. (1996) [37]	I (41%) II (59%)	177	35–50 Gy	10-year FFTF 44 10-year OS 64
Wilder et al. (2001) [38]	I (41%) II (59%)	80	40 Gy	10-year FFTF 41 15-year OS 43
Soubeyran et al. (1988) [39]	I (44%) II (56%)	103	35–40 Gy	10-year FFTF 49 10-year OS 56
Guckenberger et al. (2012) [40]	I (47%) II (34%) III (19%)	107	25–45 Gy	10-year FFTF 58 10-year OS 64

PFS progression-free survival, *FFTF* freedom from treatment failure, *OS* overall survival, *Gy* gray

comparable rates of long-term remissions (78% at 5 years) [33]. Similar results have been obtained by adding rituximab to RT therapy: results of a multicenter study conducted in Italy showed that 10-year PFS was significantly longer ($p < 0.05$) in the rituximab RT group (four rituximab courses (375 mg/m^2, days 1, 8, 15, 22) before RT) (64.6%) compared to RT alone (50.7%), whereas the 10-year OS projections were not significantly different [42].

The dose and field of RT varied largely among studies. The radiation field has been gradually narrowed based on nonrandomized evidence, but rather following the publication of trials showing similar outcomes [40]. The standard dose for involved-field radiotherapy (IF-RT) is 24 Gy, which is significantly lower than the doses delivered in the past (30–40 Gy), and this has been demonstrated in a randomized trial to be as effective as higher doses [43]. Moreover, the first report from patients treated with low-dose RT of 2 × 2 Gy, mostly for palliation of advanced-stage disease, showed very promising results in terms of disease control [44]. This lead to the launch of a prospective randomized trial, which aimed to compare 2 × 2 Gy with the standard dose of 24 Gy in patients with limited-stage FL. The preliminary results demonstrated a significantly higher rate of progression in the low-dose group and this lead to the recommendation to not adopt low-dose RT for the treatment of patients with limited stage with a potential curative intent [45].

It should also be considered that most of the relapses in patients with early-stage FL occurred outside the irradiation fields [46]. This highlights the fact that all patients with early-stage FL need to be rigorously staged before treatment start.

6.11 Initial Treatment of Advanced-Stage FL

For patients with advanced-stage disease (stage III, IV or stage II not suitable for radiotherapy) treatment decisions must be individualized according to disease and patient's specific factors. As said, advanced-stage FL is still considered to be an incurable condition, even if the disease is responsive to various treatment modalities such as chemotherapy, immunotherapy, radiotherapy, and target-therapies. Once the diagnosis of advanced-stage FL is established, the next step is to determine if the patient needs therapy, as not all patients with FL require treatment at the time of diagnosis. The crucial decision is when to treat and how to treat. Given the fact that most patients with FL will not die of disease, maintaining an optimal quality of life represents

one of the principal goals of therapy. Importantly, the range of therapeutic options should be discussed together with the patient, and the treatment modality is usually selected based on characteristics of the disease, goals of treatment and perceptions of the preferences of the patient.

6.11.1 Advanced-Stage FL with Low Tumor Burden

There is a wide variety of treatment options for FL. These options include watchful waiting (observation), single-agent anti-CD20 antibody (in particular, rituximab), chemotherapy associated with an anti-CD20 antibody (rituximab or obinutuzumab). Several prospective randomized trials [47–50] demonstrated that deferring therapy until the appearance of symptoms was not detrimental in terms of OS, and a prolonged treatment-free period may decrease cost, complications, and potential drug resistance. Moreover, histologic transformation to DLBCL appeared to occur at a rate of approximately 2%/year, regardless of whether FL is treated aggressively or conservatively [51, 52].

A landmark prospective randomized trial validating the role of watchful waiting as an initial management strategy in advanced-stage FL with low tumor burden was conducted by Ardeshna in 2003. More than 300 patients with advanced-stage asymptomatic FL were randomized to active treatment with an alkylating agent (oral chlorambucil) versus delayed therapy until the time of progression or symptomatic disease. With a median follow-up of 16 years, no difference in terms of OS was observed between the two treatment arms. Of note, nearly 20% of patients did not require any active treatment [48]. Even though other randomized trials have addressed the same question and have obtained similar results [47, 53], the fact that these studies were conducted in an era where rituximab (which has been shown to lead to an improvement in OS in patients with FL in need of therapy) was not available should be underlined. Therefore, we do not know how the impact on survival of rituximab in combination with chemotherapy could have affected the natural history of the disease in this population.

A relevant follow-up study was published in 2014 using rituximab as first-line treatment [54]. In this British trial, patients with low tumor burden FL were randomly assigned to receive either (1) rituximab induction given weekly for 4 weeks, (2) rituximab induction followed by maintenance rituximab every 2 months for 2 years, or (3) watchful waiting. The rituximab induction alone arm was closed prematurely due to slow accrual, and the study was subsequently amended to a two-arms study. With a median follow-up of 4 years, there was no difference in time to next treatment between the induction alone versus induction followed by maintenance group (HR = 0.75, $p = 0.33$), even though the amended trial was underpowered for the comparison of the two groups. Rates of histologic transformation and OS were similar between the two approaches. Nevertheless, there was a significant difference in the time to start of new therapy, with 46% (95% CI 39–53) of patients in the watchful waiting group not needing treatment at 3 years compared with 88% [55–64] in the maintenance rituximab group (hazard ratio [HR] 0.21, 95% CI 0.14–0.31; $p < 0.0001$). Rituximab therapy was associated with improved quality of life measures, reflecting a decrease in anxiety in patients receiving active treatment. This study provided the rationale for single-agent rituximab as an option for patients with newly diagnosed asymptomatic FL with low tumor burden, although the lack of an OS benefit indicates that "watchful waiting" remains an appropriate approach in this population.

If single-agent rituximab should be the first line treatment choice, then the next question is, which is the optimal schedule and how to administer it. In the RESORT trial, 289 patients with FL and low tumor burden were randomized after induction with four doses of weekly rituximab to receive maintenance rituximab (one dose every 13 weeks until progression) or retreatment with rituximab only at the time of progression. With a median follow-up of 4.5 years, time to treatment failure (approximately 4 years) and quality of life were similar in the two arms, and a reduced number of rituximab doses were used in the group without maintenance (median 4 vs. 18 doses) [65].

6.11.2 Advanced-Stage FL with High Tumor Burden

In evaluating the best time for treatment initiation, the best approach is to consider the presence or absence of symptoms along with the estimation of tumor burden. The *Groupe d'Etude des Lymphomes Folliculaires* (GELF) criteria have been proposed to identify those patients who would benefit from therapy rather than observation [47]. The GELF criteria are clinical parameters, which represent a surrogate of tumor burden: patients with high tumor burden, according to these criteria, are generally treated upfront with active systemic treatment. In the original GELF study patients considered to have a low tumor burden, were randomly assigned to one of three arms: arm 1, watchful waiting (n = 66); arm 2, prednimustine 200 mg/m^2/day for 5 days per month for 18 months (n = 64); or arm 3, interferon alfa 5 MU/day for 3 months, then 5 MU three times per week for 15 months (n = 63). Watchful waiting approach did not appear to be detrimental in comparison to early treatment. Since then, the subsequent clinical trials conducted by the same group evaluating different regimens of chemo-immunotherapy included patients with high tumor burden based on these criteria. The British National Lymphoma Investigation (BNLI) criteria have also been validated, and they are frequently used to assess the tumor burden and the optimal timing of initial treatment [54]. In the BNLI criteria, osseous lesions and bone marrow infiltration are also considered as a trigger for initiating treatment. Table 6.4**.** summarizes the main criteria for starting therapy in FL.

The current standard approach for patients with advanced-stage FL with high tumor burden consists of immuno-chemotherapy with an anti-CD20 monoclonal antibody in combination with a chemotherapy component (Table 6.5). Systemic treatment with rituximab alone was also shown to be useful as well as other chemo-free combinations, for example, rituximab and lenalidomide. Chemotherapy regimens frequently used are primarily based on alkylating agents (such as CVP, CHOP), based on a purine analog (i.e., fludarabine) alone or in combination with mitoxantrone (FM) or more recently including bendamustine.

The combination of rituximab with chemotherapy represents one of the standard of care for front-line treatment. Four prospective trials comparing different regimens with or without R have shown a significant benefit in PFS and OS in patients treated with rituximab [72–75]. No significant side effects were associated with the addition of rituximab. The question concerning the chemotherapy backbone should be considered has not being put to rest. The FOLL05 trial compared in 534 patients with advanced-stage FL, three most popular regimens, namely R-CVP, R-CHOP, and R-FM. R-CHOP and R-FM exhibited a superior PFS in comparison to R-CVP with a 3-year PFS of 52.68% and 63% (p = 0.011), respectively. Nevertheless, no differences were observed in terms of OS [69, 76].

Table 6.4 Comparison of criteria for starting treatment

Groupe d'Etude des Lymphome Folliculaires (GELF) [47]	Largest nodal (or extranodal) size >7 cm At least three nodal sites of >3 cm Presence of systemic symptoms Presence of serous effusion Substantial enlargement of the spleen Risk of vital organ compression Presence of leukemia or blood cytopenias
British National Lymphoma Investigation (BNLI) [54]	Presence of pruritus or B symptoms Rapid disease progression during the past 3 months Life-threatening organ involvement Significant bone marrow infiltration resulting in bone marrow depression (defined as hemoglobin level <100 g/l, white cell count <3.0 × 10^9 l^{-1} or platelets count <100 × 10^9 l^{-1} in the absence of other causes) Localized bone lesion Renal infiltration Macroscopic liver involvement

Table 6.5 Selected trials including patients with high-tumor-burden follicular lymphoma at diagnosis

Author (year)	Phase	*n*	Treatment	Maintenance	Survival
Rummel et a. (2013) [66]	III	549	R-CHOP R-B	NO	Median PFS 31.2 Median PFS 69.5 m
Flinn et al. (2019) [67]	III	447	R-CHOP, R-CVP R-B	NO	5-y PFS 55.8%, 5-y OS 81.7% 5-y PFS 65.5%, 5-y OS 85.0%
Salles et al. (2011) [68]	III	1217	R-CVP, R-CHOP, R-FCM	NO YES	3-y PFS 74·9% 3-y PFS 57·6%
Luminari et al. (2018) [69]	III	534	R-CVP R-CHOP R-FM	NO	8-y PFS 42%, 8-y OS 85% 8-y PFS 49%, 8-y OS 83% 8-y PFS 52%, 8-y OS 79%
Marcus et al. (2017) [70]	III	1202	R-CHOP, R-B, R-CVP G-CHOP, G-R, G-CVP	YES	3-y PFS 73%, 3-y OS 92.1% 3-y PFS 80%, 3-y OS 94.0%
Morschhauser et al. (2018) [71]	III	1030	R-CHOP, R-B, R CVP R^2	YES	3-y PFS 78%, 3-y OS 94% 3-y PFS 77%, 3-y OS 94%

PFS progression-free survival, *OS* overall survival, *R-CHOP* rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, *R-CVP* rituximab, cyclophosphamide, vincristine, and prednisolone, *R-B* rituximab and rituximab, *G* obinutuzumab, R^2 rituximab and lenalidomide, *m* months, *y* years, *w* weeks

For patients without evidence of histologic transformation, bendamustine has become an important agent. Rummel et al. conducted a randomized prospective clinical trial, including patients with advanced-stage untreated indolent and mantle cell lymphoma treated with bendamustine and rituximab (B-R) or R-CHOP. The B-R combination appeared to improve PFS in this population and induced less alopecia, cytopenia, and infections in comparison to R-CHOP [66]. There was no difference in OS (70% vs. 66% at 10 years), and the number of second malignancies was similar between the two treatment arms (39 vs. 47 cases).

A similar study was conducted in the United States (the BRIGHT trial) and evaluated the B-R combination in comparison to R-CHOP and R-CVP as an upfront treatment for 447 patients with indolent and mantle cell lymphoma. B-R appeared not to be inferior to the other two regimens in terms of complete response (CR) rate (31 vs. 25%, respectively; $p = 0.0225$) and overall response (97–91%, respectively; $p = 0.0102$) [77]. In the updated 5-year follow-up analysis, PFS for patients treated with B-R was 65% (95% CI, 58.5–71.6) compared to 55.8% (95% CI, 48.4–62.5; HR = 0.61 95% CI, 0.45–0.85; $p = 0.0025$) for the entire group. There was no significant difference in OS between the groups. Of note, patients with grade 3A FL were excluded from this trial. In terms of toxicity profiles, B-R was associated with higher rates of nausea/vomiting, secondary malignancies, and lower rates of peripheral neuropathy/paresthesia and alopecia. Patients treated with R-CHOP/R-CVP had more hematological toxicity than B-R, even though the infection rate appeared to be higher in the latter group [67].

In conclusion, B-R appeared to be a valid option for those patients who want to avoid alopecia or severe neutropenia. Moreover, the schedule of B-R given for two consecutive days but less frequently (every 4 weeks), might be interesting to some patients for logistical reasons. Obinutuzumab is a type II anti-CD20 monoclonal antibody, which has been recently approved in combination with chemotherapy for first-line patients with FL. The approval followed the results published of the prospective randomized GALLIUM trial, including 1202 patients with untreated follicular lymphoma in need of therapy. Patients were randomized to an obinutuzumab-based induction and maintenance strategy versus a rituximab-based induction and maintenance. Participating centers were free to select one of the following chemotherapy regimens associated with the anti-CD20 antibody for induction: bendamustine (57%), CHOP (33%), or CVP

(10%). Responding patients were then allocated to receive up to 2 years of maintenance with the same antibody they received during induction. Results from the preplanned interim analysis showed that the experimental arm was associated with an improved PFS (3-year PFS 83 vs. 79; HR 0.68, 95% CI 0.54–0.87). After a median follow-up of 34.5 months (range, 0–54.5 months) similar results were seen concerning ORR, CR, OS, and rates of histologic transformation. Nevertheless, the obinutuzumab-based strategy was also associated with a higher rate of grade 3/4 adverse events (75 vs. 68%), in particular, infusion-related reactions (59 vs. 49%), febrile neutropenia (6.9% vs. 4.9%) and grade 3/4 infections (20% vs. 15.6%). Unexpectedly, several fatal events were observed in both arms (4% and 4.3% for patients receiving obinutuzumab and rituximab, respectively). Moreover, a higher incidence of grade 3/4 toxicity was observed in patients treated with bendamustine in both arms, in particular infections and secondary malignancies [70, 78]. In conclusion, although these results suggest an improvement in PFS with the use of obinutuzumab, it is currently not clear whether this will translate into a survival benefit after a longer follow-up. For the time being the use of either anti-CD20 antibody appears to be reasonable.

Besides the combination with cytotoxic agents, several patients may also be treated successfully with "chemotherapy-free" approaches. Single-agent rituximab appears to be an adequate initial treatment, in particular for those patients with comorbidities and/or with disease progressing slowly over a long time. Rituximab has low toxicity profiles, and in general, it induced reasonable response rates. The SAKK investigated the role of rituximab monotherapy in newly diagnosed patients and pretreated patients with FL. Rituximab monotherapy given at the dose of 375 mg/m^2/week for a total of four doses followed by four additional doses administered every 2 months, induced an overall response rate ranging from 46% to 67% for patients at relapse or treatment-naïve, respectively [79]. With the long-term follow-up of 9.5 years, it appears that 35% of patients with previously untreated FL who responded to rituximab induction and were treated with four doses of rituximab maintenance did not progress after 8 years [80]. To better define the optimal duration of rituximab maintenance, the same group compared a long-term approach (maximum of 5 years or until disease progression or unacceptable toxicity) versus a short-term schedule (four administrations administered every 2 months). Long-term rituximab maintenance did not appear to improve event-free survival (EFS), which was the primary endpoint of the trial [81].

Another chemotherapy-free approach using rituximab (*R*) as a backbone is the combination with lenalidomide, also known as the R^2 regimen. Three prospective phase II trials conducted in the United States and Europe demonstrated that the R^2 regimen induces a high rate of CR in treatment-naive patients with FL with 3-year PFS with 2-year PFS 86% [82–84]. These promising results led to the launch of an international open-label phase III trial (the RELEVANCE trial), which accrued 1030 patients with advanced-stage FL in need of treatment. Patients were randomly allocated to receive R^2 (lenalidomide given at a dose of 20 mg/day on days 2 through 22 of each 28-day cycle for six cycles, followed by lenalidomide at a dose of 10/20 mg/day for 12 cycles) or chemotherapy with rituximab, which consisted of either CVP, CHOP, or B, depending on the investigator's choice. In each treatment arm, patients were treated for a total of 30 months. With a median follow-up of 38 months, no significant differences were observed in terms of CR rates (48% (95% CI, 44–53) vs. 53% (95% CI, 49–57), p 0 = 0.13), PFS at 3 years (77% vs. 78%; HR 1.1, 95% CI 0.85–1.43), and OS at 3 years (94% vs. 94%; HR 1.16, 95% CI 0.72–1.86). In terms of toxicity, a higher percentage of patients in the rituximab chemotherapy arm presented with grade III/IV neutropenia (32% vs. 50%) and febrile neutropenia of any grade (2% vs. 7%). Patients treated with R^2 presented more rash (43% vs. 24%), diarrhea (37% vs. 19%), and tumor flare reaction (6% vs. <1%) [71]. In conclusion, based on these results, the R^2 regimen represents a new treatment option for previously untreated patients with FL, but has been not yet registered in the first-line indication.

6.11.3 The Role of Maintenance Therapy

Disease relapse represents a matter of concern of patients with FL, and the identification of further ways to extend the period of remission continues to be an essential goal for clinicians and investigators. A possible strategy to achieve this objective is with the implementation of the so-called maintenance therapy, to be proposed after successful induction therapy. Anti-CD20 monoclonal antibodies appear to be an attractive option for maintenance therapy because they are associated with only limited acute toxicity and no significant long-term or cumulative toxicity. Moreover, the long half-life of these compounds allows for spaced treatments while maintaining long-term drug exposure. The role of maintenance therapy has been investigated in patients with either low and high tumor burden, after first-line treatment and in the relapse setting. The RESORT trial included only patients with low tumor burden treated with an induction therapy of 4 weekly doses of rituximab. Patients were then randomized to receive either maintenance rituximab every 3 months indefinitely or rituximab re-treatment upon progression. At a median follow-up of 4.5 years, PFS in both study arms were comparable but patients receiving maintenance therapy were less likely to require cytotoxic chemotherapy even though the estimated OS at 5 years was similar in both groups (94%) and no difference in terms of rate of histologic transformation was observed [85]. Nevertheless, the benefit in terms of disease control must be weighed against the higher amount of rituximab used in the maintenance arm.

Other clinical trials have assessed the role of maintenance rituximab after an induction based on single-agent rituximab. The SAKK 35/98 trial included newly diagnosed and previously treated FL. Patients were treated with a rituximab induction (4 weekly doses) and then randomized to receive either maintenance rituximab given every 2 months for four infusions or no further treatment. With a median follow-up of 10 years, the median EFS was significantly longer in the rituximab maintenance arm in comparison to the observation arm (24 months vs. 13 months, $p < 0.001$) [80]. In a subsequent trial conducted by the same group (the SAKK 35/03 trial) 270 patients with untreated, relapsed, stable, or chemoresistant FL were treated with an induction therapy which was identical to the previously described study and were then randomly assigned to receive a short-term maintenance (rituximab every 2 months for four additional doses) or a long-term maintenance (rituximab every 2 months until progression or unacceptable toxicity for a maximum of 5 years). No differences were seen in terms of the primary endpoint (EFS), and slightly more adverse events were observed in the long-term schedule [81].

In patients responding to an induction therapy based on immune-chemotherapy (i.e., R-CHOP, R-CVP, and rituximab fludarabine cyclophosphamide), the role of maintenance rituximab was primarily addressed in the PRIMA trial. In this trial, 1019 patients with previously untreated FL, demonstrating an initial response to induction, were randomly assigned to maintenance rituximab (375 mg/m2 administered every 2 months for 24 months) or placebo. Improvement in PFS was observed in the maintenance arm at a median follow-up of 36 months (74.9% vs. 57.6%), but no difference could be demonstrated in terms of OS. Rituximab maintenance was also associated with a higher percentage of patients in CR or unconfirmed CR at 24 months (72% vs. 52%), but was associated with a higher overall rate of severe (grade III/IV) adverse events (24% vs. 17%) and a higher percentage of infection (39% vs. 24%) [68]. With a longer follow-up of 73 months the PFS benefit in the maintenance arm was maintained (42.7% vs. 59.2%; HR 0.58, 95% CI 0.48–0.69; $p < 0.0001$) and no unexpected toxicity were observed. Nevertheless, the use of maintenance rituximab did not translate into an improvement in OS even with a longer follow-up [86].

In a large meta-analysis including seven trials evaluating rituximab maintenance after chemotherapy or chemo-immunotherapy (a total of 2315 patients with FL), maintenance rituximab appeared to improve the PFS (HR 0.57; 95% CI 0.51–0.64) and OS (HR 0.79; 95% CI 0.66–0.96)

even though it was associated with a greater risk of adverse events (34% vs. 24%) [87].

It continues to be a matter of debate if these results should also be applied for patients treated with B-R as induction therapy. Several trials reported a higher rate of mortality not related to lymphoma, in particular in patients receiving maintenance after bendamustine-based combinations [70, 88], and the main cause of mortality in these patients was *Pneumocystis jirovecii* pneumonia. Nonetheless, it should be underlined that in this trial, the chemotherapy backbone was not randomly assigned. Moreover, the optimal duration of maintenance therapy is mostly unknown and continues to remain a matter of discussion. Many clinicians decide to administer maintenance with a schedule established in a specific phase III trial, such as that used in the PRIMA study (rituximab every 2 months for a total of 2 years). As previously described, trials that have investigated longer duration of maintenance have observed increased toxicity towards the end of the planned treatment. From a practical point of view, it is recommended to administer long-term prophylaxis for *Pneumocystis jirovecii* if giving rituximab maintenance after B-R induction.

6.12 The Role of High-Dose Chemotherapy and Autologous Stem-Cells Transplant

High-dose chemotherapy (HDT) followed by autologous stem cell transplant (ASCT) represents a treatment strategy that has been extensively investigated in patients with FL. Nonetheless, given the toxicity of this approach and the overall favorable outcome generally observed in patients with FL, the identification of the right timing for this procedure has always been a challenge.

Several randomized clinical trials have investigated the role of HDT, followed by ASCT in patients with FL. Three randomized trials conducted in the pre-rituximab era and one in the rituximab era have evaluated the role of upfront ASCT consolidation versus observation alone in patients with advanced-stage FL, in remission after first-line therapy. All these trials demonstrated a benefit in terms of PFS in comparison to observation alone, indeed suggesting that this approach induced improved disease control, but none showed an OS benefit [89–91]. Based on these results, HDT and ASCT are currently not recommended as consolidation in patients with FL in the first remission.

For patients with FL at relapse, the results of a single prospective trial conducted in the pre-rituximab era showed that ASCT might be superior to conventional-dose therapy. In this trial, 140 patients with refractory FL were randomized to receive chemotherapy alone versus chemotherapy, followed by ASCT using unpurged or purged stem cells. With a 69-month median follow-up, the authors could demonstrate a 2-year PFS (26% vs. 55–58%, $p = 0.0037$) benefit and 4-year OS benefit for patients who underwent ASCT (46% vs. 71–77%, $p = 0.079$) [92]. Despite these positive results, ASCT was not widely adopted as a standard of care for patients with relapsed FL, due to concern regarding early and late toxicity. Moreover, this study was performed before the advent of rituximab, when the median survival of patients with FL was shorter in comparison to the present time.

Several retrospective studies have compared the outcome of patients treated with ASCT or chemo-immunotherapy in a more recent era. Sebban et al. published a retrospective analysis including 254 patients with relapsed FL treated in two successive randomized studies with the same treatment: patients treated with HDT and ASCT presented with a higher rate of 5-year EFS (51% vs. 24%) and OS (70% vs. 42%), in comparison to patients treated with conventional therapy [93]. Similar results supporting the use of ASCT regardless of front-line rituximab exposure have been found by Le Gouill et al. in an analysis including 175 FL patients from the FL2000 [94]. A retrospective analysis using data from the National LymphoCare Study and the Center for International Blood and Marrow Transplant Research reported on the outcomes of 349 patients who progressed within 2 years or did not respond to initial rituximab-based therapy. In

a planned subset analysis, the patients receiving ASCT within 1 year of treatment failure had superior OS at 5 years (73% vs. 60%) [95]. Similarly, the follow-up analysis of two prospective first-line trials confirmed the overall survival benefit in young patients who had relapsed within 24 months after a CHOP-like induction [96]. The European Group for Blood and Marrow Transplantation (EBMT) published a project which aimed to define indications for HDT and ASCT in patients with FL in the rituximab era in Europe following a RAND-modified Delphi consensus method. In patients with first chemosensitive relapse, the consensus was that HDT with ASCT represents an appropriate option to consolidate remission, especially in patients with a short response after immuno-chemotherapy or with high-risk FLIPI [97].

Even though HDT and ASCT may provide a sustained remission and possibly a cure for many patients, it is also essential to recognize the fact that this procedure is associated with significant acute and late toxicity. A primary concern is related to the risk of developing secondary malignancies, in particular, myelodysplasia (MDS) or acute myeloid leukemia (AML). A population-based cohort study including more than 7000 patients treated with ASCT, the risk of secondary malignancies appear to be moderately increased (standardized incidence ratios (SIR) 1.4) compared with the general population but was significantly elevated for MDS/AML (SIR = 20.6) [55]. For this reason, patients should be counseled regarding this risk and other related potential late effects.

6.13 The Role of Allogeneic Stem Cell Transplantation

Allogeneic stem cell transplantation with myeloablative conditioning was associated with a lower relapse rate but higher transplant-related mortality and finally, a similar OS [56]. This observation suggested the presence of graft versus lymphoma effect. To decrease the toxicity of allo-SCT reduced-intensity conditioned (RIC-alloSCT) has been developed. Several clinical trials demonstrated the feasibility of this approach also in patients who were early pretreated [57, 58]. The outcomes following a RIC-alloSCT showed a 5-year PFS rate ranging from 50% to 85%. No prospective trials have compared the efficacy of RIC-alloSCT and myeloablative conditioning alloSCT in patients with FL. RIC-alloSCT is currently the most frequently employed approach for patients over the age of 50 and with comorbidities [97].

The decision to consider either ASCT or alloSCT in patients with refractory/relapsed FL remains to be defined. There is only one prospective randomized trial addressing this issue and unfortunately, it was closed prematurely due to poor accrual [54]. Thus, based on the beforementioned European consensus, alloSCT is being recommended to be preferably discussed for patients that have relapsed after ASCT [97].

6.14 Radioimmunotherapy (RIT)

Radioimmunotherapy (RIT) is based on the use of monoclonal antibodies linked to radioisotopes. Ibritumomab tiuxetan is a murine anti-CD20 monoclonal antibody conjugated to the radioisotope yttrium-90 that is approved by the US Food and Drug Administration (FDA) for the treatment of patients with relapsed/refractory FL. Several prospective trials of RIT (mostly phase II trials) demonstrated response rates ranging from 60% to 80%, with a median PFS less than 1 year. The majority of patients who achieve a CR following RIT remained in remission for more than 3 years [59, 60]. No randomized trials have compared RIT to immuno-chemotherapy. Ibritumomab tiuxetan appeared to be safe; the most common side effects are related to the potentially prolonged hematological toxicity.

The high response rate achieved with this approach makes RIT an attractive treatment option, even though it is currently not commonly employed due to the complexity of administration.

Alternatively a consolidation approach resulted in an improved PFS in an international first-line trial [61]. However, this approach seems

to be inferior to a prolonged rituximab maintenance for 2 years [62].

6.15 Management of Relapsed FL

Although the median OS for FL has improved substantially in comparison to the past decades, most patients will eventually relapse, and they will require successive treatments. The optimal approach to patients with relapsed FL remains undefined. It is crucial to recognize high-risk patients, in particular, patients presenting with a histologic transformation or those presenting with early treatment failure. The latter group is classically composed of patients with FL progressing within 24 months of initial immunochemotherapy [27]. These patients are classically treated with more aggressive approaches because they tend to have a worse outcome. For young patients without significant comorbidity, the best plan may include HDT followed by ASCT especially in early relapses. On the other hand, patients with asymptomatic relapsed FL do not necessarily require immediate treatment. The indications for treatment initiation are generally similar as used for first-line therapy. A repeated biopsy is whenever possible recommended at the time of relapse, to rule out histologic transformation to diffuse large B-cell lymphoma. Bone marrow biopsy is in general reserved for patients with significant cytopenia. The clinical feature that may be associated with histological transformation are in particular rapid discordant growth of a single nodal site, the presence of B symptoms, hypercalcemia, and increased LDH. The choice of subsequent lines of therapy largely depends on several factors, including the type of previous treatment, age, the presence of comorbidities, the duration of remission, and the patient preference. The different options available are a re-challenge with the initial treatment regimen (in particular for patients presenting with long remission), the use of non-cross resistant chemotherapy regimens or the administration of new targeted agents. The goal, in young and fit patients, is to induce a long-lasting remission. In elderly patients presenting with comorbidities, treatment for patients with relapsed FL aims to obtain a better quality of life and to reduce lymphoma-associated symptoms. As said, for patients presenting with early relapse, the use of a non-cross resistant treatment is generally recommended. Patients relapsing after a long period of remission and presenting with comorbidities may benefit from single-agent rituximab [63]. For relapsing patients having received regimens with alkylating agents, a combination including bendamustine may be considered. Several regimens have demonstrated clinical activity in this setting, but there is a limited number of randomized trials. At first relapse after immunochemotherapy, treatment option includes an anti-CD20 monoclonal antibody in association with CHOP, CVP, bendamustine, or lenalidomide, depending on the patient's history and prior therapy. In particular, the combination of bendamustine plus obinutuzumab may be preferred in patients previously treated with R-CVP or R-CHOP, if the relapse occurs less than 6–12 months from the last rituximab administration. The other way round, CHOP may be preferred for patients with previously treated with a bendamustine-based regimen.

Two phase II trials have assessed the activity and safety of combinations with bendamustine in patients with relapsed/refractory NHL (14% with FL): median PFS was in the range of 2 years and the most common side effect was hematological toxicity (in particular, leukopenia and thrombocytopenia) [64, 98]. In a randomized, noninferiority, phase III trial including 230 patients with relapsed indolent NHL and mantle cell lymphoma, fludarabine-based chemotherapy with rituximab was compared to B-R. Patients treated with the latter regimen exhibited a higher response rate and an improved PFS and OS, suggesting that this combination may be one of the preferred treatment options for patients with relapsed indolent lymphoma [99].

The decision to use rituximab maintenance at the time of relapse should be based on whether the patients are refractory to this compound. For patients considered to be rituximab refractory, rituximab maintenance is in general not proposed. In this regard, the GADOLIN trial

included patients with rituximab refractory indolent NHL and randomized patients to receive either obinutuzumab (G) and bendamustine in induction followed by G maintenance or single-agent bendamustine without maintenance. The updated results of this trial showed that the G-B induction plus G maintenance significantly improves PFS and OS in comparison to bendamustine alone [100].

6.16 Novel Agents in the Management of FL

6.16.1 Lenalidomide

New compounds are frequently reserved for patients presenting with multiple relapses, but there are compounds that are now being investigated in the first-line (Table 6.6). One example is lenalidomide, which was assessed as a single agent in patients with relapsed/refractory indolent lymphoma (mostly FL) in the NHL-001 including 43 patients and showing a promising ORR of 23% (CR 7%) with a median PFS of 4.4 months [109]. The combination of lenalidomide and rituximab (also known as the R^2 combination) was tested in several phase II trials [82, 84] and subsequently in a large randomized international phase III trial (the AUGMENT trial) showing a significant clinical activity in comparison to rituximab alone [101]. In the first-line setting, the RELEVANCE trial demonstrated that the R^2 combination was comparable in term of efficacy to standard immuno-chemotherapy (R-CHOP, B-R, R-CVP) [71]. The role of lenalidomide in maintenance is currently investigated in the MAGNIFY study, a phase IIIB multicenter open-label study, where responding patients are randomized to receive either maintenance

Table 6.6 Selected trials including patients treated with "chemotherapy-free" regimens

Author (year)	Phase	*n*	Setting	Treatment	ORR	ORR, survival
Ghielmini et al. (2004) [79]	II	202	First-line FL Relapsed FL	R	46–67%	Median EFS 12–23 m
Taverna et al. (2016) [81]	II	165	First-line FM	R		
			Relapsed FL	Short-term maintenance R Long-term maintenance R	62%	Median EFS 3.4 y Median EFS 5.3 y
Zucca et al. (2019) [84]	II	154	First-line FL	R R^2	57% 78%	Median PFS 2.3 y Median PFS 5.0 y
Leonard et al. (2019) [101]	III	358	Relapsed FL	R R^2	53% 78%	2-year PFS 36% 2-year PFS 58%
Gopal et al. (2014) [102]	II	125	Relapsed indolent NHL	Idelalisib	57%	NA
Dreyling et al. (2017) [103]	II	142	Relapsed indolent NHL	Copanlisib	59%	Median EFS 11.2 m
Schmidt et al. (2018) [104]	II	98	First-line FL	Ibrutinib + obinutuzumab	90%	1-y PFS 80%,
Ogura et al. (2014) [105]	II	39	Relapsed FL	Vorinostat	49%	PFS 20 m
Morschhauser et al. (2019) [106]	II	95	Relapsed FL	Tazemetostat	74%[a]	PFS 60 w[a]
Palanca-Wessels et al. (2015) [107]	I	34	Relapsed indolent NHL	Polatuzumab vedotin	55%	Median PFS 5.7 m
Davids et al. (2017) [108]	I	106	Relapsed indolent NHL	Venetoclax	38%	Median PFS 11 m

FL follicular lymphoma, *NHL* non-Hodgkin lymphoma, *PFS* progression-free survival, *EFS* event-free survival, *R* rituximab, R^2 rituximab and lenalidomide, *m* months, *y* years, *w* weeks

[a]Mutant *EZH2* tumors

lenalidomide plus rituximab or rituximab alone (ClinicalTrials.gov Identifier: NCT01996865).

6.16.2 Phosphatidylinositol 3-Kinases (PI3K) Inhibitors

PI3K inhibitors are heterodimeric enzymes that have regulatory and catalytic subunits. Idelalisib is a selective P110δ PI3K inhibitor. In the phase I study, including heavily pretreated patients with indolent NHL, idelalisib showed an encouraging activity with an ORR of 48% [110]. Based on these promising results a subsequent phase II trial including 125 patients with indolent NHL considered to be refractory to rituximab and alkylating agents were treated with 150 mg twice daily of idelalisib until progression or unacceptable toxicity. The ORR among FL patients was 57% (95% CI 0.42–0.66) with 7% CR, and after a median follow-up of 9.7 months, the median PFS was 11.0 months, substantially longer in comparison to the PFS achieved after the previous therapies [102]. Despite the promising activity, toxicity associated with this agent has frequently been problematic. Idelalisib has been associated with immune-mediated toxicity such as transaminitis, diarrhea, and pneumonitis related to the infiltration of CD8 positive lymphocytes. Moreover, in a subsequent phase III clinical trial, an excess of mortality attributed to an increase in opportunistic infection (in particular *Pneumocystis jirovecii* pneumonia and cytomegalovirus reactivation) was observed in the idelalisib containing arm. Therefore, when treatment with idelalisib is considered, adequate pneumocystis prophylaxis and cytomegalovirus monitoring are highly recommended.

Copanlisib is another pan-class PI3K inhibitor with potent activity against PI3K-alpha and PI3K-delta isoforms which was recently approved by the FDA for the treatment of patients with relapsed FL. In a phase II study, 104 patients with FL treated with copanlisib exhibited an ORR of 59% with 12% CR and a PFS of 11.2 months [103].

6.16.3 Bruton's Tyrosine Kinase Inhibitors

Ibrutinib is an irreversible inhibitor of Bruton's tyrosine kinase (BTK), and it has a pro-apoptotic effect, disrupting cellular adhesion and migration. Two phases II studies were performed enrolling subjects with relapsed/refractory FL. Forty patients received 560 mg daily of ibrutinib until progression or unacceptable toxicity. With a median follow-up of 6.5 months, ORR was 30% (CR 2.5%), and the median PFS was 9.9 months [111]. In the second trial, 110 patients were treated with the same therapy, and after a median follow-up of 27.7 months, the median PFS was 4.6 months [112]. In a first-line trial the combination of obinutuzumab and ibrutinib was well tolerated, but rate of ongoing remissions at 1 year were inferior to conventional treatment approaches [104].

6.16.4 Epigenetic Therapies

Histone deacetylases (HDAC) represent a class of enzymes that remove acetyl groups from an ε-N-acetyl lysine amino acid on a histone, and consequently, they regulate gene transcription. HDAC inhibitors induce hyperacetylation of histones and hence the activation of the mechanism of tumor suppression and apoptosis. One of the agents which was tested in patients with FL is vorinostat. In two phase II trials, which included 17 and 39 patients, respectively, with relapsed/refractory FL, vorinostat appeared to induce an ORR of 47–49% with a median PFS of 15.6 and 20 months [105, 113].

Another compound is tazemetostat, a first-in-class oral enhancer of zeste homolog 2 (EZH2) inhibitor, which was tested as a single-agent treatment for relapsed or refractory patients with FL or DLBCL grouped by EZH2 mutational status, and demonstrated an objective response rate of 92% in FL with EZH2 mutation and 26% in FL with wild-type EZH2 [106].This may represent an example of personalized medicine in FL which may be applied more frequently in the future.

6.16.5 Antibody–Drug Conjugates

Polatuzumab vedotin is an anti-CD79B monoclonal antibody conjugated to monomethyl auristatin E (MMAE). The recommended dose, which was defined in a phase I trial, is 2.4 mg/kg. The results showed promising activity with ORR of 55% with a median PFS of 5.7 months. The most common grade 3–4 toxicities were hematologic and peripheral neuropathy [107].

6.16.6 Bcl-2 Inhibitors

Bcl-2 family proteins play as regulators of apoptosis in cancer cells. BH3-only proteins have interaction with Bax and Bak, and they induce cellular apoptosis. Venetoclax (ABT-199) is a small molecule BH3-mimetic. Venetoclax was investigating in 106 patients with relapsed/refractory B NHL treated in a phase I study, and ORR was 38% (11/29) and for CR (14%) in patients with follicular lymphoma [108]. Other studies using this compound in combination with other targeted agents are currently ongoing.

6.17 Conclusions

The optimal treatment approach for patients with FL remains undefined. In this chapter, we reviewed the current spectrum of treatment options for patients with newly diagnosed and relapsed FL. The trend observed over the last years is characterized by a shift towards more biological and targeted treatments. A plethora of new targeted agents are currently under investigation and there is a high expectation that these agents will be part of the treatment armamentarium against FL.

The management of patients with relapsed FL largely depends on patient and disease characteristics. In the next 10 years, FL will likely remain an incurable condition. Nevertheless, new approaches with less toxicity will probably further improve the outcome of those patients. The unmet medical need remains the patient not responding or rapidly progressing to immunochemotherapy. In particular for those patients, it will be crucial to investigate the efficacy of novel agents and new combinations.

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