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Diagnosis and treatment of follicular lymphoma: an update

Bargetzi Mario[a], Baumann Reto[b], Cogliatti Sergio[c], Dietrich Pierre-Yves[d], Duchosal Michel André[e], Goede Jeroen S.[f], Hitz Felicitas[a], Konermann Carolin[b], Lohri Andreas[g], Mey Ulrich[h], Novak Urban[i], Papachristofilou Alexandros[j], Stenner Frank[k], Taverna Christian[l], Zander Thilo[m], Renner Christoph[n]

[a] Oncology-Haematology, Kantonsspital Aarau, Switzerland
[b] Roche Pharma (Schweiz) AG, Reinach, Switzerland
[c] Institute of Pathology, Kantonsspital St Gallen, Switzerland
[d] Department of Oncology, Geneva University Hospitals, Geneva, Switzerland
[e] Service and Central Laboratory of Hematology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland
[f] Oncology and Haematology, Kantonsspital Winterthur, Switzerland
[g] Oncology-Haematology, Kantonsspital Baselland, Liestal, Switzerland
[h] Oncology and Haematology, Kantonsspital Graubuenden, Chur, Switzerland
[i] President of the SAKK Project Group Lymphoma, Medical Oncology, Inselspital, University Hospital and University of Bern, Bern, Switzerland
[j] Radio-Oncology, Universitätsspital Basel, Switzerland
[k] Department of Oncology, Universitätsspital Basel, Switzerland
[l] Oncology, Kantonsspital Münsterlingen, Switzerland
[m] Department of Oncology, Luzerner Kantonsspital, Luzern, Switzerland
[n] Onkozentrum Hirslanden & Zürich, Zürich, Switzerland

Summary

Over the last few years, there have been many changes in the management of patients with follicular lymphoma, resulting in improvements in progression-free survival and quality of life. In addition to established regimens such as radiotherapy and immunochemotherapy, new treatment options are on the horizon. Furthermore, even the use of established chemotherapy agents has evolved, with new combinations moving to the forefront of the current treatment strategy. Nevertheless, there remains an unmet need for patients who have early relapses, those who are not responsive to anti-CD20 treatment regimens and for those in whom minimal residual disease persists even after immunochemotherapy. This review provides a summary of current developments in the diagnosis, treatment and management of follicular lymphoma, focusing on the clinical issues from a Swiss perspective.

Keywords: *follicular lymphoma, first-line treatment, maintenance treatment, relapse/refractory disease, follow-up*

Introduction

Histogenetically, follicular lymphoma arises from germinal centre B cells. As a low-grade tumour, it is the most commonly occurring subtype among indolent B cell lymphomas in the Western world [1, 2]. Follicular lymphoma is characterised by a relapsing and remitting disease course that may undergo transition to a more aggressive disease. In the past few years, new treatment regimens have made an impact on the management of follicular lymphoma, resulting in more favourable clinical outcomes. The median overall survival has improved dramatically and can now reach 10 to 12 years or more [3, 4]. Immunochemotherapy is currently the standard of care for patients with advanced-stage follicular lymphoma in need of treatment [5].

ABBREVIATIONS

BNLI	British National Lymphoma Investigation
BR	bendamustine-rituximab
CI	confidence interval
CT	computed tomography
CVP	cyclophosphamide, vincristine and prednisone
DLBCL	diffuse large B cell lymphoma
ESMO	European Society for Medical Oncology
FACS	fluorescence-activated cell sorting
^{18}F-FDG	^{18}F-fluorodeoxyglucose
FISH	fluorescence *in situ* hybridisation
FLIPI	Follicular Lymphoma International Prognostic Index
GB	obinutuzumab plus bendamustine
G-CHOP	obinutuzumab plus cyclophosphamide, hydroxydaunorubicin (doxorubicin), Oncovin (vincristine), and prednisone
G-FC	obinutuzumab plus fludarabine/cyclophosphamide
HBV	hepatitis B virus
HCV	hepatitis C virus
HPF	high-power field
NHL	non-Hodgkin's lymphoma
HR	hazard ratio
PET	positron emission tomography
PCR	polymerase chain reaction
R-CHOP	rituximab plus cyclophosphamide, hydroxydaunorubicin (doxorubicin), Oncovin (vincristine) and prednisone
R-CVP	rituximab plus cyclophosphamide, vincristine and prednisone
R-FM	rituximab-fludarabine plus mitoxantrone
SAKK	Swiss Group for Clinical Cancer Research
StiL	the German Study Group Indolent Lymphoma
WHO	World Health Organization

Correspondence:
Professor Dr. med. Christoph Renner,, Onkozentrum Hirslanden,, Witellikerstr. 40,, CH-8038 Zürich,, Christoph.Renner[at]hirslanden.ch

Chemotherapy-free treatment with anti-CD20 antibodies (such as rituximab) is an option for those with a low disease burden. Nevertheless, the majority of patients will experience relapse and require several lines of therapy. There is still the need for effective regimens that achieve disease control with minimal treatment-related toxicity.

This review follows our 2011 publication on the treatment and management of follicular lymphoma [6] and represents an update on the key issues encountered in clinical practice from a Swiss perspective.

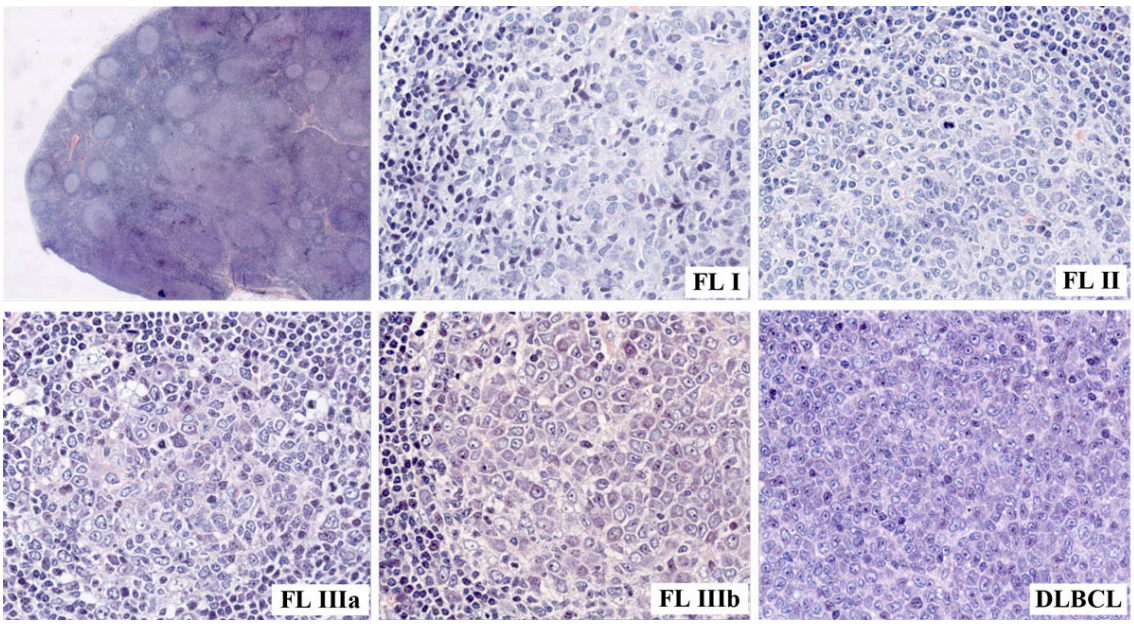
Pathology and staging

Histologically, follicular lymphoma is diagnosed according to the criteria of the 4th World Health Organization (WHO) classification issued in 2008 and updated in 2017 [7, 8]. Follicular lymphoma is defined as a neoplasm composed of germinal centre B cells, namely centroblasts and centrocytes, exhibiting, in most cases at least, a partly follicular growth pattern [8] (fig. 1). Grading of follicular lymphoma is mandatory and is based on the count of centroblasts per high-power field (HPF); in general, tumours with more numerous centroblasts show more aggressive clinical behaviour [8]. Grade 1 (0–5 centroblasts per HPF) and grade 2 (6–15 centroblasts per HPF) tumours with similar clinical characteristics are considered to be of low grade. Grade 3 tumours are considered to be high-grade, and are further divided into 3a and 3b neoplasms; both exhibit >15 centroblasts per HPF but confluent sheets and strands of centroblasts are present in grade 3b neoplasms [9]. Although still under debate, grade 3b follicular lymphoma may be biologically distinct from other follicular lymphomas, with a more aggressive course and with varying molecular and genetic features (table 1) [11], including the absence of the *t(14;18)(q32;q21)* chromosomal translocation, down-regulation of CD10 protein and overexpression of mutated melanoma-associated antigen 1 (MUM-1) protein [12]. Another issue is how to interpret a coexisting tumour component of diffuse large B cell lymphoma (DLBCL) next to follicular lymphoma of any grade of malignancy, recognised by the valid WHO classification as an additional second tumour [10]. This point is key for distinguishing between *de novo* DLBCL and transformation of initial follicular lymphoma, which occurs in approximately 30 to 40% of follicular lymphoma patients [13]. For the clinician, the distinction between grade 3a and 3b follicular lymphoma is crucial and determines prognosis and therapeutic strategy. Clinically, most patients initially present with asymptomatic peripheral lymphadenopathy, affecting the cervical, axillary, femoral and inguinal regions [14, 15]. Although lymph nodes are most commonly primarily involved, the disease may also originate at extranodal sites. The WHO in particular recognises (1) *in situ* follicular neoplasia, (2) duodenal-type follicular lymphoma, (3) testicular follicular lymphoma and (4) diffuse follicular lymphoma as four distinct variants, and furthermore classifies cutaneous follicle centre lymphomas and paediatric-type follicular lymphoma as two separate entities [8].

Diagnosis

The 2016 European Society for Medical Oncology (ESMO) guidelines provide a summary for the diagnosis of follicular lymphoma [5]. The majority of follicular lymphomas are diagnosed by bioptic lymph node examination; fine-needle aspiration does not provide adequate material for tumour grading. The same is true for trephine biopsies that have to be performed for staging purposes, as follicular lymphoma involves bone marrow in about 60 to 70% of patients [16]. For the definition of bulky disease, which has varied over time, we propose a cut-off of >7 cm diameter, in keeping with the ESMO guidelines [5]. The biological heterogeneity and disseminated presentation of follicular lymphoma makes it difficult to select a site for biopsy. The factors that should be taken into account when choosing a biopsy site are accessibility for surgical removal and

Figure 1: Enlarged cervical lymph node (4 cm in diameter) of a 64-year-old male patient harbouring follicular lymphoma (FL) of varying histological grades, including transformation into a diffuse large B-cell lymphoma (DLBCL).



the diagnostic relevance. A selection based purely on size of the lymph node should be avoided, owing to the possibility of necrosis within large lymph nodes.

In Switzerland, a common practice is to use contrast-enhanced positron emission tomography / computed tomography (PET-CT) to identify the most suitable lymph node for biopsy [17]. Although PET-CT is not yet routinely used for staging at diagnosis, it has been shown that follicular lymphoma is avid for ^{18}F-FDG (^{18}F-fluorodeoxyglucose) and that over 90% of patients are PET-CT positive at initial presentation [18]. For patients with early stage follicular lymphoma who are scheduled for localised radiation, PET-CT can be used to map out the area for involved-field radiation therapy and also to exclude the presence of distal sites of disease [19]. The latest ESMO guidelines state that fluorescence-activated cell sorting (FACS) analysis is an optional procedure for diagnostic work-up [5]; we suggest that if access to FACS is available, FACS analysis on bone marrow aspirates should be done to judge on bone marrow involvement [20]. Of note, trephine biopsy plus immunohistochemistry may be more sensitive than bone marrow aspirates plus FACS to detect bone marrow involvement in follicular lymphoma [21].

The use of polymerase chain reaction (PCR) tests for detecting B cell clonality in follicular lymphoma is associated with a high rate of false negatives, due to ongoing somatic immunoglobulin variable region heavy chain (IgVH) hypermutations [22]. In addition to morphological and immunohistochemical studies, fluorescence *in situ* hybridisation (FISH) is the preferred method to detect the *t(14;18)(q32;q21)* chromosomal translocation, which is most specifically found in follicular lymphoma [23, 24]. FISH analysis may have a great differential diagnostic impact, separating follicular lymphoma from reactive follicular hyperplasia and from lymphomas other than follicular lymphoma.

Routine testing for hepatitis B surface antigen and hepatitis B core antibody at baseline and before therapy is strongly recommended for all patients who will undergo immunosuppressive therapy, to mitigate the risk of hepatitis B virus (HBV) reactivation [25]. If positive, viral load assessment by measuring HBV DNA should be performed and antiviral treatment initiated. HBV vaccination may be considered for patients who are HBV-negative and not in immediate need of treatment.

Prognosis

The Follicular Lymphoma International Prognostic Index (FLIPI) [26] is routinely used as a general prognostic tool. The FLIPI was developed before the rituximab era. The five main prognostic factors are the number of nodal sites (≤ or >4), lactate dehydrogenase (normal vs elevated), age (≤ or >60 years), stage (I, II vs III, IV), and haemoglobin (normal vs <120 g/L). The FLIPI-2 includes age >60 years, elevated β2-microglobulin levels, haemoglobin <120 g/l, bone marrow involvement, and lymph node diameter >6 cm as independent risk factors for progression-free survival in the era of rituximab chemotherapy. The FLIPI-2 so far has not gained acceptance and is still investigational. The recent m7-FLIPI index integrates the mutation status of seven clinically relevant genes together with the FLIPI and Eastern Cooperative Oncology Group (ECOG) performance status, in order to identify the subset of follicular lymphoma patients who are at greatest risk of treatment failure [27]. None of these scoring indexes provide guidance on when to initiate therapy.

First-line treatment

The trigger point for starting treatment remains a difficult question. A key driver for beginning treatment is the presence of symptomatic disease. The criteria outlined by the Swiss Group for Clinical Cancer Research (SAKK) for starting treatment includes the presence of at least one of the following: B symptoms; symptomatically enlarged lymph nodes or spleen; clinically significant progression of lymphadenopathy, splenomegaly or other follicular lymphoma lesions; involvement of at least three nodal sites larger than 3 cm, presence of bulky disease, haemoglobin <100 g/l, and platelets <100 × 10^9/l [28]. According to the British National Lymphoma Investigation (BNLI), bone lesions may also be regarded as a trigger for initiating treatment. The SAKK criteria for initiating treatment are summarised in table 2, alongside the criteria for the Groupe d'Etude des Lymphomes Folliculaires and the BNLI groups for comparison. Symptomatic bone marrow involvement is also a criterion for beginning treatment. However, the decision to start treatment often has to be individualised and is reached upon mutual agreement between the patient and clinician.

Around 10% of low-grade follicular lymphomas are diagnosed in early stage I or II [31]. Radiation therapy is the treatment of choice for these patients, with the possibility of long-lasting remissions and curative potential [32]. The treatment volume has evolved over the past decades from the earlier extended-field to involved-field and, more recently, to involved-site radiotherapy. Involved-site radiotherapy treats the affected nodes with a clinical target volume margin of a few centimetres. The reduced toxicity linked to involved-site radiotherapy comes at the cost of a potentially higher recurrence rate in untreated adjacent areas. Nowadays, primary radiation therapy is given at a dose of 24 Gy, which is significantly lower than the doses delivered in the past (30–40 Gy). This development is the result of a randomised trial comparing 24 Gy to 40 Gy in

Table 1: Features that distinguish grade 3b follicular lymphoma from grades 1–3a [9, 10].

	Grades 1–3a	Grade 3b
WHO grading scheme	Grades 1–2 ≤15 centroblasts per high-power field* Grade 3a >15 centroblasts per high-power field	>15 centroblasts per high-power field Presence of solid sheets of centroblasts
Genotype	*t(14;18)(q32;q21); BCL2-IGH* in 90% of cases	*t(14;18)(q32;q21); BCL2-IGH* in 50% of cases *t(3;14)(q27;q32);BCL6-IGH* in 10% of cases
Immunohistochemistry	Expression of CD10	Down-regulation of CD10 Expression of MUM1
Clinical behaviour	Indolent	Aggressive, resembling DLBCL

DLBCL = diffuse large B cell lymphoma; MUM-1 = mutated melanoma-associated antigen; WHO = world Health Organization * high-power field defined as 0.159 mm^2

indolent lymphomas, demonstrating similar efficacy with both doses [33]. Reports from patient cohorts that were treated with low-dose radiotherapy of 2 × 2 Gy, mostly for palliation of advanced disease, showed promising results [34, 35]. Therefore, a randomised trial was carried out to compare 2 × 2 Gy with the standard dose of 24 Gy in follicular lymphoma [36]. Preliminary results demonstrated a significantly higher rate of progression in the low-dose group, so the 4 Gy dose should not be adopted for treatment with curative intent. Importantly, toxicity in the 24 Gy group was low, with <3% grade III acute reactions, demonstrating the safety of modern schedules of radiation therapy with limited treatment volumes and radiation doses. However, the preferred 24 Gy dose is not accepted by all groups and some use a minimum of 30 Gy [37].

It should be noted that most of the relapses in patients with early-stage follicular lymphoma occur outside the irradiated fields [38]. Indeed, an important finding from the LymphomaCare study was that rigorously staged patients had superior progression-free survival compared with patients who had not undergone a rigorous staging process [31]. In a retrospective study conducted in 310 patients with localised follicular lymphoma, excellent outcomes were obtained after radiotherapy in patients who were PET-CT staged (5-year overall survival: 95.8%) [39]. This reiterates the importance of accurate staging using PET-CT prior to radiation therapy, in order to define the areas to be irradiated and to rule out occult disease [38, 40].

Besides radiotherapy alone, the combination with rituximab for early stage follicular lymphoma has been tested in the MIR trial [41, 42]. Preliminary data show an excellent progression-free survival of almost 80% at 5 years after treatment [42]. A comparison of various first-line treatment strategies in 471 patients with stage I follicular lymphoma who participated in the LymphomaCare study showed that the different approaches resulted in similar outcomes [31]. Recent data from a randomised controlled trial in 150 patients with stage I–II follicular lymphoma indicated that treatment with six cycles of CVP (cyclophosphamide, vincristine and prednisone) or rituximab-CVP after involved-field radiotherapy significantly improved progression-free survival compared with radiotherapy alone (10-year progression-free survival 58 vs 41%, respectively) [43]. This suggests that systemic therapy may prevent progression outside of the radiation fields. However, it is not yet clear if the combination of radiotherapy plus rituximab-based systemic therapy will become standard of care in the future.

Watchful waiting remains an acceptable approach in selected patients in the rituximab era, with no detrimental effects on overall survival [44–46]. However, better indices are needed to identify patients who may benefit from early intervention. There is also no conclusive data on whether watchful waiting affects the incidence of transformation of follicular lymphoma. For elderly patients and those with poor performance status, watchful waiting can be considered in selected cases [47].

For patients with symptomatic stage I–II disease without the option to undergo radiotherapy and those with advanced disease (stage III–IV), the treatment approach is similar. Current standard of care for first-line treatment of advanced follicular lymphoma consists of immunochemotherapy with the anti-CD20 monoclonal antibody rituximab (MabThera®/Rituxan®) in combination with a chemotherapy component [5]. Although the ESMO guidelines place equal emphasis on the use of bendamustine and CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone), bendamustine has increasingly been used combined with rituximab [15]. A randomised, multicentre phase III trial by the Study group Indolent Lymphoma (StiL) compared rituximab-CHOP (R-CHOP) with bendamustine-rituximab in 549 treatment-naïve patients with indolent and mantle cell lymphoma. In the subgroup of patients with follicular lymphoma, median progression-free survival was significantly better in the bendamustine-rituximab group compared with R-CHOP (median progression-free survival not reached vs 40.9 months; p = 0.007). Furthermore, the bendamustine-rituximab regimen had fewer adverse effects [48]. Results from the BRIGHT study indicated that bendamustine-rituximab was non-inferior to R-CHOP or R-CVP in terms of complete response (31 vs 25%, respectively; p = 0.0225) and overall response (97 and 91%, respectively; p = 0.0102) in 447 patients with indolent non-Hodgkin's lymphoma

Table 2: Comparison of criteria for starting treatment in follicular lymphoma patients.

Group	Criteria
Swiss Group for Clinical Cancer Research (SAKK) [28]	• Presence of B symptoms • Symptomatic enlarged lymph nodes or spleen • Clinically significant progression of lymphadenopathy, splenomegaly or other FL lesions (50% increase in size over a period of at least 6 months) • At least 3 nodal sites involved (>3 cm) • Presence of bulky disease (>7 cm) • Haemoglobin level <100 g/l • Platelet level <100 × 10^9/l (due to bone marrow infiltration or splenomegaly)
British National Lymphoma Investigation (BNLI) [29]	• 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 a haemoglobin level <100 g/l, white cell count <3.0 × 10^9/l, or platelet count <100 × 10^9/l in the absence of other causes) • Localised bone lesions • Renal infiltration • Macroscopic liver involvement
Groupe d'Etude des Lymphomes Folliculaires (GELF) [30]	• Largest nodal (or extranodal) size >7 cm • At least 3 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 leukaemia or blood cytopenias

(NHL) or mantle cell lymphoma [49]. The safety findings of the BRIGHT study differed from the StiL study in that bendamustine-rituximab was found to have a distinct safety profile compared with R-CHOP or R-CVP, but the overall tolerability of the bendamustine-rituximab regimen was favourable in this clinical setting [49]. A recent 5-year update of the BRIGHT study identified a higher risk of secondary cancers (mainly skin cancers) in the bendamustine-rituximab arm and it was speculated that this could have been due to rituximab maintenance (which was used in 43% of the patients) [50]. It should be kept in mind that there is less long-term follow-up data for bendamustine-rituximab compared with R-CHOP; this is especially relevant when weighing the treatment options for younger patients.

Although the findings from the StiL and BRIGHT studies point towards bendamustine-rituximab as the treatment of choice for follicular lymphoma patients with grade 1 and 2 disease, the optimal treatment for patients with grade 3a disease remains unclear: these patients were not included in either study. The FOLLO5 trial assessed R-CHOP, R-CVP and rituximab, fludarabine and mitoxantrone (R-FM) as front-line treatment in 534 patients with advanced-stage follicular lymphoma [51]. The overall response rates were 88, 93 and 91% for R-CVP, R-CHOP and R-FM, respectively ($p = 0.247$). The 3-year progression-free survival rates were 52, 68 and 63% ($p = 0.011$), respectively, and 3-year overall survival was 95% for the whole series. The authors concluded that R-CHOP and R-FM were superior to R-CVP in terms of 3-year time to treatment failure and progression-free survival, but R-CHOP had a more favourable risk-benefit profile [51]. These findings were recently confirmed, with 8-year progression-free survival rates of 57 and 59% for R-CHOP and R-FM, compared with 46% for R-CVP [52].

In Switzerland, bendamustine-rituximab is widely used as a front-line treatment option in patients with grade 3a follicular lymphoma, although R-CHOP is also used in Switzerland [53]. Many clinicians regard R-CHOP as overtreatment for low-grade follicular lymphoma, but whether grade 3a is considered high- or low-grade disease is still a matter of debate [54]. The results from the StiL and BRIGHT trials, alongside the findings of several other studies with bendamustine-rituximab [55, 56], indicate that the bendamustine-rituximab combination may be preferable to R-CHOP or R-CVP for the front-line treatment of follicular lymphoma patients with low-grade disease who need therapy. The findings from the FOLLO5 study indicate that R-CHOP still holds a place in the first-line treatment of patients with high-risk characteristics, including those with evidence of bone marrow involvement and high levels of β_2-microglobulin [57].

For patients who are in need of treatment but who may not be able to tolerate chemotherapy, or for those with a low disease burden, rituximab monotherapy provides a safe and effective first-line treatment option, with the potential for lasting molecular responses [58, 59]. The SAKK tested rituximab monotherapy in chemotherapy-naïve and pretreated follicular lymphoma patients, resulting in overall response rates of 67 and 46%, respectively [60]. Data from the SAKK 35/98 trial indicated that the independent factors predictive of response to treatment with single-agent rituximab were: low disease bulk (<5 cm), follicular histology, normal haemoglobin levels and low lymphocyte counts [61]. At long-term follow-up, 35% of patients did not show disease progression after 8 years [28]. This number was 45% in the subgroup of previously untreated patients who responded to rituximab induction and who were given prolonged rituximab maintenance [28]. Despite the fact that single-agent rituximab is widely accepted both in Switzerland and internationally [28], and is recommended in the latest ESMO guidelines [5], rituximab monotherapy is still not on the Swiss Specialties List and this is considered off-label use in Switzerland. Within the SAKK, the aim is to develop further regimens using anti-CD20 antibodies as a backbone, in combination with new molecules such as immunomodulatory drugs (e.g., lenalidomide; SAKK 35/10 trial), or Bruton's tyrosine kinase inhibitors (ibrutinib; SAKK 35/14 trial), as well as the BCL-2 inhibitor venetoclax (SAKK 35/15 trial). Further details on the ongoing SAKK trials can be found on www.sakk.ch/en/sakk-provides/our-trials/. The combination of lenalidomide with rituximab (also known as R2) has shown good potential for the treatment of indolent lymphomas, including follicular lymphoma [62]. In previously untreated patients with indolent NHL, lenalidomide-rituximab treatment showed good overall response rates (75–96%) and complete response or unconfirmed complete response rates between 36 and 71% [63]. However, a recent phase III trial (RELEVANCE) did not show improved complete response / unconfirmed complete response or progression-free survival when comparing lenalidomide-rituximab with standard-of-care rituximab plus chemotherapy in previously untreated follicular lymphoma patients [64]. Other groups are studying rituximab-ibrutinib in the front-line setting [65].

Recently, Swiss regulatory authorities have approved an alternative anti-CD20 monoclonal antibody (obinutuzumab, Gazyvaro®) plus chemotherapy followed by obinutuzumab maintenance for first-line follicular lymphoma patients. The GALLIUM study compared the efficacy and safety of obinutuzumab-based with rituximab-based front-line regimens head-to-head in 1202 treatment-naïve follicular lymphoma patients with grade 1-3a disease [66]. Responders received either obinutuzumab or rituximab maintenance. Results from pre-planned interim analyses showed that obinutuzumab-based regimens resulted in better progression-free survival. After a median follow-up of 34.5 months, there was a 34% reduction in the risk of disease progression or death with obinutuzumab-based induction regimens and maintenance. Three-year progression-free survival rates in the obinutuzumab and rituximab arms were 80 and 73.3%, respectively (hazard ratio [HR] 0.66, 95% confidence interval [CI] 0.51–0.85; $p = 0.001$); overall survival rates were similar in both arms. Unexpectedly, there was a higher incidence of toxicities in patients on bendamustine in both arms, notably infections and second neoplasms [66]. Although the study demonstrated a progression-free survival advantage with the use of obinutuzumab, the higher level of toxicity in the bendamustine arms needs to be better understood before these treatment regimens can be routinely used in the front-line setting. A summary of first-line treatment is shown in figure 2.

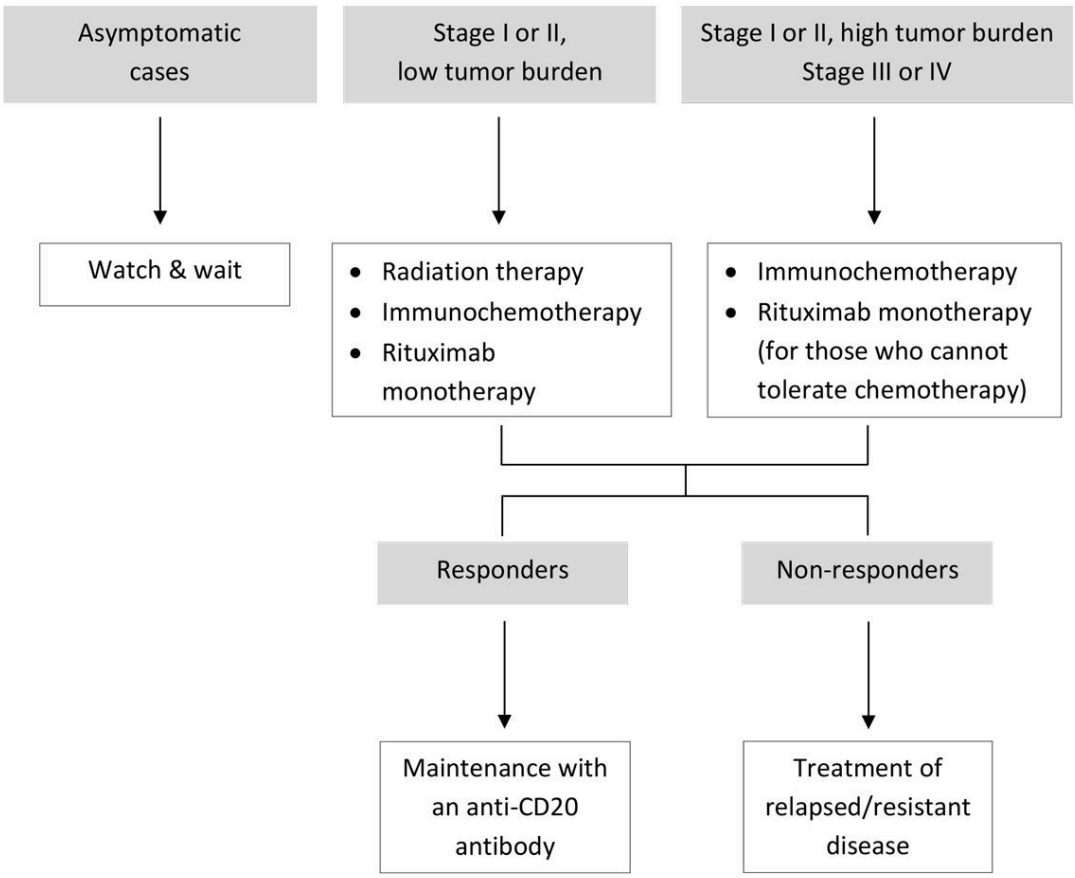
Maintenance therapy

Despite the high efficacy of initial treatment regimens, the majority of patients with follicular lymphoma will experience relapse. The goal of maintenance therapy is to extend the duration of remission obtained with first-line treatment; thus, maintenance is only used for patients who respond to first-line therapy. As a result of its consistent efficacy profile and good tolerability, rituximab has been evaluated in several larger trials as maintenance therapy, leading to controversial results.

The RESORT study focused on the question of whether rituximab maintenance prolongs response duration, compared with rituximab treatment at the time of disease progression, in 408 untreated follicular lymphoma patients with a low tumour burden [67]. Following rituximab induction therapy, responders were randomised to rituximab maintenance or retreatment at disease progression until treatment failure. At a median follow-up of 4.5 years, the estimated median time to treatment failure was 4.3 versus 3.9 years, respectively ($p = 0.54$). Better results were seen for the maintenance arm in terms of 3-year freedom from cytotoxic therapy (95% of patients in the maintenance arm vs 84% in the retreatment arm; $p = 0.03$). However, these benefits must be weighed against the higher amount of rituximab usage in the maintenance arm. The overall survival in both arms was 94% at 5 years, and both treatment regimens were well tolerated. The authors concluded that retreatment at disease progression when single-agent rituximab is used as front-line therapy in patients with low tumour burden is preferable to maintenance rituximab.

Several other studies have evaluated the use of maintenance rituximab in the setting of front-line treatment or relapsed disease [60, 68–71]. The SAKK 35/98 trial included newly-diagnosed and previously-treated follicular lymphoma patients who were given rituximab induction [60]. At the 10-year follow-up, the median event-free survival was 24 months for the rituximab maintenance arm, compared with 13 months for the observation arm ($p < 0.001$) [28]. Multivariate Cox analysis indicated that prolonged rituximab treatment was the only favourable prognostic factor, leading the authors to suggest that this maintenance regimen could be used regardless of other factors including prior treatment, disease stage or Fc-receptor phenotype [28]. The findings from the SAKK 35/98 trial provide guidance on the rituximab dosing schedule for maintenance therapy (375 mg/m^2 every 2 months) [60, 72]. Data from the PRIMA study supported the benefits of this rituximab maintenance schedule for patients who achieve remission after front-line therapy with several immunochemotherapy regimens [73]. The recent 6-year fol-

Figure 2: Algorithm for first-line treatment of follicular lymphoma.



low-up results of the PRIMA study confirmed these earlier findings [74]. With a median follow-up of 73 months, 6-year progression-free survival was 42.7% in the observation arm versus 59.2% in the rituximab maintenance arm, (HR 0.58, 95% CI 0.48–0.69; p <0.0001). Preplanned subgroup analyses showed that the effect of rituximab maintenance was consistent regardless of age, gender, FLIPI score, induction regimen used and response to induction treatment. There were no unexpected toxicities and the 6-year overall survival rate was similar in both study arms (88.7% in the observation arm vs 87.4% in the maintenance arm).

However, the duration of maintenance therapy is still a matter of discussion. Recent results from the SAKK 35/03 trial provide clarification [75]. This study compared short-term rituximab maintenance (one infusion every 2 months, for a total of four administrations) with a long-term maintenance schedule (one infusion every 2 months for a maximum of 5 years, or until relapse, progression or unacceptable toxicity) in 270 patients with untreated, relapsed, stable, or chemotherapy-resistant follicular lymphoma who had received rituximab induction monotherapy (375 mg/m^2). At a median follow-up of 6.4 years, the median event-free survival was 3.4 years (95% CI 2.1–5.3 years) in the short-term arm and 5.3 years (95% CI 3.5 years to not available) in the long-term arm (p = 0.14). A sensitivity analysis focusing on late events showed a statistically significant increase in event-free survival in favour of the long-term maintenance regimen (7.4 years, 95% CI 5.1 to not available compared with 3.5 years, 95% CI 2.1–5.9 years for the short-term arm; p = 0.04). Patients in the long-term arm experienced significantly more adverse effects (p <0.001). No difference in overall survival between the arms was seen. The primary endpoint from this trial showed that long-term rituximab maintenance did not confer a statistically significant benefit in terms of event-free survival compared with the 8-month maintenance treatment schedule.

In Switzerland, rituximab maintenance treatment is frequently used even after a bendamustine-rituximab front-line regimen. The current ESMO guidelines recommend rituximab maintenance therapy according to the schedule established in the PRIMA trial (rituximab 375 mg/m^2 every 8 weeks for 2 years) [5].

Treatment of relapsed/refractory follicular lymphoma

Nearly all patients will experience disease recurrence or progression. There is no conclusive evidence to guide the management of these patients and, in practice, choice of therapy is driven by factors similar to those for first-line treatment. Not all relapses necessitate immediate treatment; asymptomatic cases may be managed with watchful waiting until treatment is needed. When treatment is needed, a variety of strategies are used. These include rechallenge of the initial treatment regimen (when such treatment has led to remission for more than a year), or use of a non-crossresistant chemotherapy with or without rituximab.

Recently, highly effective immunochemotherapy regimens with fewer toxic effects and the expanding array of new agents have shifted the clinical focus away from stem cell transplantation as a routine treatment option in relapsing follicular lymphoma. However, none of the new agents have demonstrated a potential for cure. Valuable time may be lost with the use of palliative treatments during which the time window for high-dose therapy may close for many eligible patients. Accordingly, in patients fit enough to undergo high-dose chemotherapy with autologous stem cell transplantation, this approach should be strongly considered, especially for those with histologically transformed disease. The curative potential of this approach was recently demonstrated in a large retrospective analysis of 655 patients, with durable remissions irrespective of previous rituximab treatment [76]. Furthermore, patients who experience early treatment failure after front-line immunochemotherapy may benefit from the use of autologous stem cell transplantation within ≤1 year of treatment failure [77].

Radioimmunotherapy is an option for patients with low tumour burden and minimal bone marrow involvement; (^{90}Y)-ibritumomab tiuxetan (Zevalin®) has been shown to induce high response rates and durable remissions in relapsed or refractory low-grade follicular lymphoma [78]. Interestingly, radioimmunotherapy given either as a single agent or as consolidation after induction treatment has been consistently shown to cure a certain fraction of patients with follicular lymphoma. Despite this fact, radioimmunotherapy, although available in Switzerland, remains rarely used. The concern over secondary cancers, the lack of high-quality clinical studies and availability of the many new agents may fuel the reluctance of many clinicians to use this potentially curative treatment for follicular lymphoma.

In Switzerland, the majority of patients with relapsed or resistant disease are treated with various immunochemotherapy regimens. The ESMO guidelines define early relapses as those occurring within 12 to 24 months of treatment [5]. In patients with early relapses, use of a non-cross-resistant treatment regimen is recommended [5]. For patients who relapse within 2 to 3 years of initial treatment, the same first-line regimen may be used, unless the initial treatment contained anthracyclines and retreatment would exceed the cumulative threshold of 450 mg/m^2 doxorubicin. Patients with a poor performance status and who showed previous response to rituximab may benefit from rituximab monotherapy [79]. For fit patients with symptomatic disease in need of treatment, several immunochemotherapy regimens may be considered. The bendamustine-rituximab regimen has been used successfully to treat patients with relapsed/refractory follicular lymphoma following one to two previous rituximab-based treatments, resulting in 95% overall response and 80% complete response rates [80]. Fludarabine-based regimens are also often used for patients who relapse after alkylator-based therapies [15]. Nevertheless, bendamustine appears to have a better risk-benefit profile than fludarabine in the relapse setting. The StiL-2 study compared the use of bendamustine-rituximab with fludarabine-rituximab in patients with relapsed or refractory indolent NHL [81]. At a median follow-up of 96 months, median progression-free survival in the bendamustine-rituximab arm was 34.2 months versus 11.7 months in the fludarabine-rituximab arm (HR 0.54, 95% CI 0.38–0.72; log-rank test p <0.0001) [81]. Of note, 11% of the patients in the bendamustine-rituximab arm had previously received the same regimen as first-line treatment.

Currently, there is no information comparing their response with those who were bendamustine-rituximab naïve. Fludarabine-based regimens are also known to have adverse effects such as haematological toxicities and infections, precluding their use in the elderly or in those with comorbidities [82].

In light of the ubiquitous application of rituximab in front-line treatment regimens, the emergence of rituximab-resistant disease is a problem [83]. The GADOLIN trial tested the efficacy and safety of obinutuzumab plus bendamustine against bendamustine alone in 413 patients who had rituximab-refractory indolent NHL [84]. At a median follow-up of 31.2 months, progression-free survival was significantly longer with obinutuzumab-bendamustine (25.3 months) than with bendamustine monotherapy (14.0 months; $p < 0.0001$). The latest update showed a significant overall survival benefit in favour of obinutuzumab-bendamustine versus bendamustine alone (median not reached vs 53.9 months; $p = 0.0061$) [85]. Swiss regulatory authorities have recently approved obinutuzumab plus bendamustine followed by obinutuzumab maintenance therapy for follicular lymphoma patients who previously received a rituximab-based therapy. Also approved and licensed in Switzerland after failure of two prior treatments is idelalisib (Zydelig®), a phosphatidylinositol 3-kinase δ inhibitor [86]. In a phase II open-label study of 125 patients with relapsed or refractory indolent NHL, idelalisib monotherapy showed antitumour activity and acceptable tolerability, including in 72 patients with follicular lymphoma [87]. Several ongoing trials are underway to evaluate idelalisib in combination with rituximab or rituximab plus bendamustine; however, some have been stopped owing to safety concerns related to idelalisib. Another combination that has shown efficacy in the relapse-refractory setting is lenalidomide-rituximab (R2) [63]. Compared with lenalidomide alone, the lenalidomide-rituximab regimen showed a higher overall response rate (76 vs 53%) and longer time to progression (2 vs 1.1 years), with no increased toxicity [88]. The synergistic effects of this combination warrant further investigation. Finally, the use of low-dose involved-field radiation therapy remains a viable option, particularly for patients with localised relapses. A summary of the treatment of patients with relapsed/refractory follicular lymphoma is shown in figure 3.

Post-treatment assessment and patient follow-up

The annual rate of histological transformation in follicular lymphoma patients is around 3%, although this may be slightly lower in the rituximab era [89]. A re-biopsy is strongly recommended upon disease recurrence and before initiating treatment of relapsed disease, to rule out the presence of transformation to a higher-grade histological subtype. The presence of histological transformation in patients who responded to prior immunochemotherapy is associated with poor outcomes and may warrant more aggressive treatment [90]. PET-CT is widely used not only for staging but also for assessment of interim response to treatment and for evaluating response at the end of treatment [91]. The presence of residual FDG-avidity at the end of first-line treatment may be predictive of poorer clinical

Figure 3: Algorithm for the treatment of relapsed/refractory follicular lymphoma. SCT = stem cell transplantation.

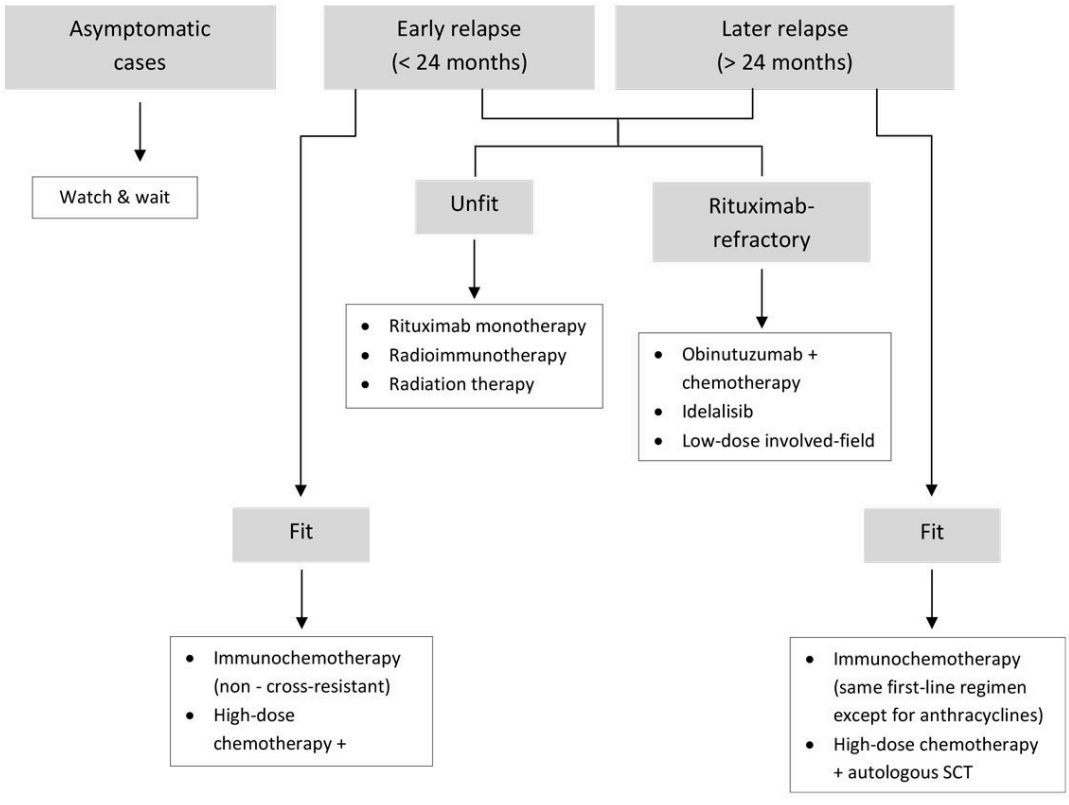


Table 3: Summary of the ESMO guidelines for the follow-up of patients with follicular lymphoma [5].

Examination	Frequency
Medical history and physical examination	After localised radiotherapy Every 6 months for 2 years; thereafter once a year if needed After systemic therapy Every 3–4 months for 2 years; every 6 months for the following 3 years; thereafter once a year
Blood counts and routine chemistry tests	Every 6 months for 2 years; thereafter as clinically indicated
Thyroid function	After 1, 2 and 5 years in patients who received irradiation of the neck
Radiological or ultrasound tests	Every 6 months for 2 years; thereafter once a year up to 5 years (optional)
PET-CT	At mid-term and at the end of chemotherapy induction treatment. *We suggest that PET-CT is also used at diagnosis to identify areas for potential biopsy and to map fields for localised radiation therapy.*

CT = computed tomography; ESMO = European Society for Medical Oncology; PET = positron emission tomography

outcomes [92, 93], although it is still unclear how PET-positivity should guide the choice of subsequent treatment. The use of PET-CT is especially relevant in patients for whom long progression-free survival is a treatment goal; as such, PET-CT may not be necessary in older patients or in those with significant comorbidities, whose treatment goals are mainly symptomatic. There is evidence that the hepatitis C virus (HCV) may be associated with the development of B cell malignancies including follicular lymphoma [94, 95], and that treatment of HCV may be warranted prior to treatment of the lymphoma itself [96, 97]. For patients who will receive R-CHOP or bendamustine-rituximab, antibiotic prophylaxis may be used (sulphonamide/trimethoprim 960 mg 2–3 times per week, or trimethoprim/sulfamethoxazole 160 mg/800 mg 3 times per week).

There is still no conclusive evidence to support adherence to a specific follow-up schedule. The latest ESMO guidelines provide a basis for the minimal follow-up in patients with follicular lymphoma (table 3).

Conclusions

Much progress has been made towards achieving excellent overall survival using immunochemotherapy, particularly in those patients with limited-stage disease who respond to anti-CD20 monoclonal antibody treatment. Indeed, the slow course of the disease is at odds with the rapid pace at which new treatments are being developed. The long follow-up required for clinical trials means that some treatment regimens are out of date before study closure [98]. For example, previous studies on rituximab maintenance did not evaluate the efficacy of maintenance or salvage regimens following front-line treatment with bendamustine-rituximab, simply because this was not standard practice at the time of trial design [98]. Furthermore, it is still difficult to extrapolate trial results to all follicular lymphoma patients, because of the heterogeneous nature of the disease. The most urgent unmet need remains with those patients whose disease is not responsive to anti-CD20 treatment regimens and in whom minimal residual disease persists even after immunochemotherapy, as well as in those with early disease progression after first-line treatment. For these patients, it will be essential to explore the efficacy of novel agents and new combinations to achieve prolonged remission and extended survival.

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