

Guidelines of the Belgian Hematological Society for newly diagnosed and relapsed follicular lymphoma 2012

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Follicular lymphoma is an indolent lymphoma that has occurred more frequently over the last decades. In this article we present an overview of the diagnosis and initial work-up, prognostic scoring system and choice of therapy. For limited stage disease radiotherapy is the treatment of choice, and may have a curative potential. For advanced stages treatment should be initiated upon certain criteria, and is essentially based on immunochemotherapy, rituximab plus chemotherapy. The choice of chemotherapy depends on age, frailty, and specific toxicities of chemotherapy. Maintenance therapy with rituximab after induction has become standard practice. Since virtually all patients relapse eventually, an overview of the treatment in the relapsed setting is given. The treatment is then again based on immunochemotherapy but there is also a place for radio-immunotherapy, or immunotherapy alone. For young patients, high dose chemotherapy with autologous stem cell rescue should be considered. A brief overview on novel agents, and agents that are in the pipeline, is given. We conclude with some recommendations for follow-up.

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Introduction

Follicular lymphoma (FL) is a B-cell non-Hodgkin's lymphoma (NHL), usually with an indolent clinical course. It is the most frequent of the low-grade lym-

phomas, and the incidence is increasing.

The introduction of rituximab in the treatment regimen has changed the picture of the disease, and resulted in an increase of progression-free survival

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(PFS) and overall survival (OS), and durable responses have been observed. Nevertheless, it remains a relapsing disease, and for most patients it is not curable – except maybe for selected patients who can undergo an allogeneic stem cell transplantation.

In this article we present an overview of the diagnostic work-up and treatment for follicular lymphoma. It is based on the 2011 ESMO guidelines and amended for the particular Belgian context of label prescription and reimbursement. Scientific evidence for the use of treatment strategies in label and off-label context are rated by level of evidence as stated in *Table 2*.

Incidence

FLs comprise 29% of NHL.¹ The annual incidence is increasing and current European estimates are at 2.18/100000 inhabitants. This brings the crude incidence in Belgium to 250-400 new cases per year.²

Diagnosis

FL can be diagnosed on bone marrow and excisional node biopsy. Whenever possible, surgical node biopsies should be obtained, since fine needle aspirations and core biopsies can underestimate the grade by lack of representativeness. Flow cytometric analysis of lymph node cell suspensions and bone marrow aspirate has confirmatory but no diagnostic role.³

Pathological classification should be reported as by the WHO 2009 definition. FLs are graded according to the number of centroblasts per high power field. Grade 1 corresponds to less than 5 centroblasts per high power field; grade 2: 6-15 blasts per high power field; grade 3a: more than 15 blasts per high power field, with the blasts intermingled with centrocytes. FL grade 3b also has more than 15 blasts per high power field, but they are in sheets and centrocytes are absent: they are classified with the aggressive lymphomas and treated accordingly. Clinical significance of separation between grade 1 and 2 has been questioned: FL with few centroblasts (less than 15 per high power field) can be graded as low-grade FL and further separation is not required nor recommended.⁴

Transformed lymphoma represents a separate category but there is lack of a uniform definition. It is

considered a histological transformation from grade 1-2-3a FL to a more aggressive histology such as diffuse large B-cell lymphoma or Burkitt/Burkitt-like lymphoma. Sometimes less overt patterns of histological transformation are seen, such as transformation from an FL to a marginal zone lymphoma, or to Hodgkin's disease or dendritic cell neoplasms. Some authors also consider transformation from grade 1-2 FL to grade 3 FL as a transformed lymphoma.

When it is impossible to perform a new biopsy to obtain a histological diagnosis, a clinical picture suggestive of transformation can be considered a transformed lymphoma. Clinical criteria are sudden rise in LDH, rapid nodal growth or rapid growing bulky disease, and the new appearance of previously absent B symptoms. Few studies have directed this patient population as such.⁵

Cytogenetics do not really contribute to the disease management of FL. The most common translocation is t(14;18) which can be diagnosed and followed up by fluorescence in-situ hybridisation (FISH) or polymerase chain reaction (PCR). The occurrence of this translocation is related to tumour grade and site of involvement. It is especially detectable in low-grade lymphoma, and generally absent if FL is arising in extranodal sites such as skin or testis. Thus the t(14;18) translocation can be considered the cytogenetic hallmark in low-grade (grade 1-2) nodal FLs in particular.⁶

Staging and risk factors

Treatment initiation depends on symptoms, disease bulk, staging and progression. Initial staging includes physical examination, CT scan of neck, thorax, abdomen and pelvis, blood sampling, bone marrow aspirate and biopsy. There is no consensus on the interpretation of PET activity of FL. It may be useful to confirm localised stage I/II disease.³ There is level 3 evidence for the negative predictive value of PET scan in FL following induction immunochemotherapy, prior to eventual maintenance.⁷

Blood examination should include complete blood count with white blood cell differentiation, blood chemistry with lactate dehydrogenase, uric acid, beta 2 microglobulin, and virology screening for human immunodeficiency virus (HIV), hepatitis B and C.³

Staging is defined according to the Ann Arbor system, with mention of bulky disease, when appro-

priate. Bulky disease is defined as 1 lymph node of more than 7 cm long, or 3 lymph nodes of more than 3 cm long each, according to Groupe d'Etude des Lymphomes Folliculaires (GELF).⁸

Two prognostic scoring systems are withheld: Follicular Lymphoma International Prognostic Index (FLIPI; based on age, stage, haemoglobin level, number of involved nodal site areas, and LDH), and more recently FLIPI2 (incorporating beta 2 microglobulin, diameter of largest lymph node, bone marrow involvement and haemoglobin level).^{9,10} Their merit is to allow comparison of patient populations treated in different ways, but they have little value in the decision to initiate treatment.

Molecular staging is currently not part of the management of FL. Data on surrogate pathology markers of the tumour micro-environment, such as CD68 positive macrophages and FOXP3 positive T-cells, are not conclusive and can therefore not be advised in routine diagnosis and work-up.¹¹

Treatment

Early stage - curative?

FL tends to be disseminated from the time of diagnosis with only 25% stage I or II. In patients with non-bulky stage I/II disease, involved field radiation therapy (30-36 Gy) has a curative potential in 37-44% of patients, as shown in the follow-up at a single institution.¹² More recent data on more than 6,500 patients confirm a clear advantage to use upfront radiotherapy, within the first year from diagnosis, over alternative approaches, including watch-and-wait strategy, in terms of disease-specific survival and OS.¹³

Rituximab monotherapy as four weekly infusions in low-grade FL also has a high response rate, with low toxicity.¹⁴

The role of adding rituximab to involved field radiation therapy for early stage FL is not documented in large prospective trials. The German MIR trial is addressing this question in a multi-centre prospective phase II trial.¹⁵

The addition of rituximab to radiation therapy has also come under re-appreciation by studies in further advanced stage II-IV FL with no indication for active treatment (see further).

Whereas previous studies have shown that the watch-and-wait policy in this population has no dis-

advantage over treatment with chlorambucil, both with respect to PFS and OS, recent British data show a clear difference in time to initiation of new treatment in patients treated with rituximab or rituximab and maintenance.¹⁶ Three-year PFS was 33% in the watchful waiting group versus 60 and 81% in the rituximab group and rituximab and maintenance group respectively. The percentage of patients not requiring new treatment at three years was 48% in the watchful waiting group, compared to 80% and 91% in the rituximab group and rituximab and maintenance group respectively. This study might change the standard of care for asymptomatic FL patients, if quality of life and long-term toxicity is no worse in the treatment arms.¹⁷

The BHS Lymphoproliferative group recommends involved field radiation therapy with curative intent (30-36 Gy) for localised follicular lymphoma (FL).

It withholds rituximab treatment in disseminated FL not fulfilling GELF criteria for need of therapy as a possible treatment with level I evidence for progression-free survival (PFS) and time to next treatment but with unknown benefit on long-term outcome and overall survival (OS).

Initiation of treatment beyond curative intent

In patients with stage III-IV and stage II non-contiguous disease, current treatments are not considered curative. Nevertheless patients may remain very stable over a long period of time and spontaneous regressions have been described to occur.¹⁸

There is no uniform consensus on the criteria to initiate therapy.

The BHS Lymphoproliferative group recommends to use either the Groupe d'Etude des Lymphomes Folliculaires (GELF) or the German Low grade lymphoma Study Group (GLSG) criteria, since they have been used in validated randomised clinical trials and are the basis for claims made at evidence I level.

Unless these criteria are met, watch-and-wait policy is to be preferred to chemotherapy. Rituximab monotherapy can be considered beneficial to PFS but its impact on long-term outcome is not known.¹⁷

Table 1. GELF and GLSG criteria

GELF criteria ¹⁹	GLSG criteria ²⁰
Nodal/extranodal mass with a diameter >7 cm	Bulky disease (mediastinal lymphomas > 7,5 cm or other lymphomas >5 cm in maximal diameter)
Involvement of ≥ 3 nodal sites	Rapidly progressive disease
Systemic symptoms	Presence of B-symptoms (night sweats, fever or weight loss)
Substantial splenomegaly (≥ 13 cm)	Impairment of normal hematopoiesis, with Hb <10g/dL, granulocyte count <1500/μL, trombocyte count <100000/μL
Pleural or pericardial effusion Ascites Orbital or epidural involvement Ureteral compression Circulating malignant lymphocytes	

If the GELF or GLSG criteria are met, patients should be treated with a combination of rituximab and chemotherapy. Four independent trials support the addition of rituximab to different chemotherapy schedules in first-line therapy: R-CHOP, R-CVP, R-FC and R-MCP.²⁰⁻²³

The value of adding rituximab to chemotherapy is also demonstrated in a randomised trial in the relapsed setting, namely for R-FCM.²⁴

Retrospective comparison in newly diagnosed FL shows an advantage for adding anthracyclines in the initial treatment, in terms of complete remission, OS and failure-free survival (FFS).²⁵

A randomised controlled trial comparing R-CVP, R-CHOP and R-FM for advanced stage FL is conducted by the Italian lymphoma group. Preliminary results show an advantage for R-CHOP and R-FM over R-CVP, with less toxicities in the R-CHOP group than the R-FM group, thus supporting evidence for R-CHOP as the standard treatment for advanced FL needing treatment.²⁶

A phase III comparison between R-CHOP and R-bendamustine in grade 1-2 but not grade 3a FL demonstrates a longer PFS in patients treated with R-bendamustine (90 mg/m² x2 q4wks times 6). The follow-up period of R-bendamustine in terms of late side-effects is short compared to the knowledge on R-CHOP but it has clear advantages in avoiding cardiac and neurological toxicity.^{27,28} Recent results with R-bendamustine suggest at least equivalence to R-CHOP with less toxicity.

R-fludarabine containing regimens are associated with higher CR rates but higher toxicity including second malignancy. They are therefore discouraged in first-line treatment of follicular NHL.

The length of induction treatment is eight cycles for R-CVP, six cycles for R-bendamustine, six cycles for R-CHOP + two cycles of rituximab or eight cycles of R-CHOP, with an interval of 21 days, and six cycles for R-FCM.

In elderly patients there are no separate clinical trials with higher than level 2 evidence. Patients can be treated with rituximab monotherapy, combination of rituximab and chlorambucil or rituximab and bendamustine.

The position of new or alternative anti-CD20 antibodies is still under investigation.

The BHS lymphoproliferative group advises R-chemo in patients with newly diagnosed FL fulfilling the GELF or GLSG criteria. R-CHOP (6+2) or R-CVP (8) should be used in patients up to grade 3a with an advantage for R-CHOP in terms of PFS but not OS. R-CHOP should be preferred in suspected or documented transformed lymphoma.

The therapeutic strategy in case of positive hepatitis serology is part of separate guidelines applicable to all patients with immune suppressive and chemotherapeutic treatment (refer to NCCN).

Maintenance and consolidation

Maintenance

Meta-analysis of interferon alpha maintenance shows an improvement of PFS but not OS but toxicity of this therapy and effect on the quality of life of patients is a concern.²⁹

Maintenance with rituximab for a period of two

Table 2.⁶⁰**Evidence levels in clinical trials**

- Level I: Evidence obtained from at least one properly designed randomised controlled trial.
- Level II-1: Evidence obtained from well-designed controlled trials without randomisation.
- Level II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.
- Level II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.
- Level III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committee.

years improves PFS (75% versus 58% after three years) but as yet no benefit in OS is demonstrated.⁸ Different schedules for rituximab maintenance have been studied, either as an infusion every two months for two years or as four weekly infusions every six months for two years, with comparable results.^{8,30}

There is level I evidence in PFS but not for OS in favour of rituximab maintenance following R-CHOP, R-CVP or R-FCM. In case of infectious complications, Ig levels should be monitored and eventually substituted.

Consolidation

In radio-immunotherapy, radio-isotopes are linked to a monoclonal antibody, and after intravenous infusion this complex binds to all cells expressing the respective antigen. Transient toxicity to the bone marrow, mostly granulocytopenia and thrombocytopenia, is the most common side-effect, and therefore in most studies only patients with less than 25% lymphoma cells in the bone marrow can be included. The most commonly used radio-isotopes are ⁹⁰Y-ibritumomab tiuxetan (Zevalin®) and ¹³¹I-tositumomab (Bexxar®), both based on anti-CD20 antibodies.³¹

Radio-immunotherapy as consolidation after first-line remission-induction prolongs PFS. The FIT trial, comparing one infusion of Zevalin® to observation, in patients in complete or partial remission after chemotherapy-induction, shows a median PFS of 49 months versus 15 months (at a median follow-up of 66.2 months) For the small subgroup of patients who were induced with a combination of rituximab and chemotherapy, there is still an advantage in PFS for the Zevalin® group (>67 months versus 59 months)^{32,33} American studies using Bexxar® consolidation after induction with either CVP, CHOP or fludarabine, show similar results with progression-free survival of 67% at five years. The efficacy of Bexxar® after remission induction with rituximab-containing regi-

mens needs to be further established.³⁴⁻³⁶ Bexxar® has not been developed in Europe for reasons of radioprotection –it is a gamma-emitter- and it is therefore not available in Belgium.

The rate of secondary MDS/AML after radio-immunotherapy seems not to be higher than that observed in patients treated for FL in general.³⁷

The use of radio-immunotherapy in consolidation in first-line has not been compared to maintenance anti-CD20 and data do not yet support superiority. This strategy is off-label and not reimbursed in Belgium.

Consolidation by autologous stem cell transplantation, either following myelo-ablative radiochemotherapy or chemotherapy alone, prolongs PFS.³⁸⁻⁴⁰ There is however no benefit for OS, mainly because it is associated with an unacceptable burden of secondary malignancies (especially myelodysplastic syndrome(MDS)/acute myelocytic leukaemia (AML), with a reported incidence between 4.3 and 12.3%, but also other solid and haematological malignancies)^{41,42} Most clinical trials were conducted in the pre-rituximab-era.⁴³

Autologous stem cell transplantation in first remission is not recommended outside of clinical trials.

Relapsed FL

Relapse eventually occurs in all FL stage III and IV. The histology at relapse can be unchanged or transformed. The risk of transformation to a more aggressive histology is at a steady 3% per year. It has a poor prognosis, with a median post-transformation survival of 1.7 years.⁴⁴ Repeated biopsies are therefore recommended especially in advanced relapse. PET/CT scan may help to determine the optimal site

of biopsy since the majority of transformed lymphomas have a higher SUV uptake, similar to that of diffuse large B-cell lymphoma.⁴⁵ Increasingly higher SUV has a higher specificity for the detection of aggressive disease. An SUV > 10 has a high likelihood for aggressive disease, and an SUV > 13 is virtually indicative of aggressive disease.⁴⁶

Rituximab monotherapy in non-transformed FL was first introduced in relapsed patients in a pivotal trial in 1998.⁴⁷ In the most recent trial an overall response rate (ORR) of 69% was seen, with a median PFS of 15.6 months, after eight weekly infusions of rituximab.⁴⁸

Salvage treatment is however often combined chemo-immunotherapy and as such it is essentially similar to first-line treatment (R-CVP, R-CHOP, R-bendamustine). It can therefore be based on an individual approach, taking into account previous responses and previous individual toxicities in the patient, comorbidities and anticipated tolerance, and perspective of future treatment needs in function of age. Preference may go to a non-crossresistant scheme, e.g. R-Bendamustine after R-CHOP or R-CVP or vice versa.³ In a comparison between BR versus FR shows PFS 30 versus 11 months in follicular and indolent NHL.⁴⁹ In patients who have enjoyed long first-line remissions (e.g. more than two years), the initial treatment schedule can be repeated, taking into account maximum doses of anthracycline if given before.

Rituximab should be added in the rare patient who did not get anti-CD20 in the induction and in patients where previous rituximab containing treatments resulted in a response of at least six months.³ Rituximab maintenance following R-CHOP chemotherapy in relapse prolongs PFS (median, 3.7 years versus 1.3 years) and OS (74% versus 64% after five years), even after antibody containing induction in patients who have not received the antibody as a first line treatment.⁵⁰

In patients with rapid relapse in need of treatment, the rituximab-chemotherapy approach can be followed by autologous stem cell transplantation, especially in younger patients, if the preceding remission is short lived and/or if there are arguments for transformation. Re-treatment with rituximab significantly reduces relapse rate. Autologous stem cell transplantation results in a higher three year overall survival (92% versus 63%).⁵¹

The value of adding radio-immunotherapy in the transplant conditioning is unclear.⁹⁰ Yttrium-ibritumomab tiuxetan has been added to high dose chemotherapy followed by autologous transplant in phase II studies of relapsed B-cell lymphomas (including small numbers of FL patients). Toxicity with this regimen is acceptable, so is the transplant-related mortality rate (0-3%).⁵²

When compared to autologous stem cell transplantation, allogeneic stem cell transplantation has a lower relapse-rate, but shows no advantage in OS, because of a higher transplant-related mortality (24% at one year versus 4-8% at one year for autologous SCT)⁵³ Therefore, allogeneic stem cell transplantation is only to be considered in selected younger patients in the setting of clinical trials. Transplant-related morbidity and mortality may be diminished by reduced-intensity conditioning regimen, but it is unclear if the graft-versus-lymphoma effect is sufficient to control transformed lymphomas with an aggressive clinical course.

At three years, PFS ranges between 20 and 60%, and relapse rates to 40%.⁴³

Radio-immunotherapy as the only treatment represents an alternative to rituximab in the relapsed setting, with higher response rates (80% versus 56%) and higher complete remission rates (30 versus 16%) but somewhat disappointing durations of response. Both modalities have a comparable time to progression of 11.2 months versus 10.2 months.⁵⁴ Patients achieving a complete remission after radio-immunotherapy demonstrate clearly a longer PFS, with remissions lasting for a median of 26.3 months. Radio-immunotherapy is useful in second or third relapse in patients who are not transplant candidates.^{55,56}

The BHS recommends R-chemotherapy followed by maintenance for relapse FL (superior for PFS, OS when including patients not previously treated with rituximab).

There is no superiority for any given chemotherapy regimen and rituximab monotherapy can be proposed in unfit patients or patients with a low tumour burden at relapse.

Autologous transplantation is an appropriate consolidation in the fit patient in second or further remission.

Key messages for clinical practice

1. FL is an indolent lymphoma, for which the treatment may be deferred. Initiation of treatment should be according to GELF/GLSG criteria.
2. Radiotherapy is the therapy of choice in limited stage disease, with a possible curative intent.
3. First-line treatment is essentially rituximab plus chemotherapy. For young and fit patients, R-CHOP is the golden standard, followed by rituximab maintenance for two years. For older patients, R-CVP can be used. Other chemotherapeutic agents like fludarabine and bendamustine are as efficient, but are not reimbursed in Belgium in this indication.
4. Relapse of FL is treated by rituximab monotherapy or rituximab plus chemotherapy, depending on tumour burden. Rituximab maintenance is recommended. Young and fit patients should go to autologous stem cell transplantation in this setting.
5. Rituximab refractory patients should go on clinical trials, or alternatively be treated with bendamustine monotherapy or radio-immunotherapy.

Response evaluation and follow-up

Evaluation by CT scanning should be performed mid-term and after completion of immunochemotherapy. PET/CT scan remains investigational. Minimal residual disease analysis, in particular with PCR for the t(14;18) translocation, has been reported with variable prognostic impact but is as yet no guidance to treatment.

Rituximab refractory patients

An increasing number of patients continue to relapse during their longer periods of OS. The number of patients relapsing within six months of a rituximab containing regimen increases. They are candidates for testing new drugs in FL. The new drugs include other monoclonal antibodies, namely novel anti-CD20 antibodies, such as ofatumumab and GA101; novel antibody-conjugates (anti-CD22,19,79b) proteasome inhibitors like bortezomib; immunomodulatory drugs like lenalidomide that target the micro-environment; proapoptotic small molecules (eg Bcl-2 inhibitors); and inhibitors of the signaling pathway, like mTOR inhibitors, PI3K and Btk-inhibitors.⁵⁷ If they cannot be included in a clinical trial or if they are no transplant candidates, patients can be treated with bendamustine monotherapy (120 mg/

m² D1,2 q28d), and with radio-immunotherapy, both of which are reimbursed in Belgium.^{56,58,59} If they are transplant candidates, they should be treated with high dose chemotherapy followed by autologous transplant, and eventually allogeneic transplant in selected younger patients.

The BHS Lymphoproliferative group recommends that patients who have become rituximab refractory (relapse within less than six months from last dose) should be encouraged to participate in clinical trials. Fit patients in remission are candidates for autologous transplant, and for allotransplant in the context of clinical trials. For other patients, two reimbursed treatment possibilities are available: bendamustine and radio-immunotherapy.

Recommendation for follow-up

Follow-up recommendations are based on consensus rather than evidence.

Clinical evaluation is recommended every three months for two years, than every four to six months for the initial three years and subsequently once a year. This should comprise physical examination,

complete blood count and routine chemistry. Evaluation of thyroid function should be added in patients with irradiation of the neck.

Minimal adequate radiological or ultrasound examination can be done at least every six months for two years and annually after. Regular CT scans are not mandatory outside clinical trials.³

The role of PET/CT scan in follow-up is as yet not supported by prospective data. PET/CT may be useful for prognosis at the end of primary induction treatment, and in the guidance of re-biopsy in patients with relapse.^{7,45}

MRD screening by molecular follow-up has prognostic significance but since current treatment is non-curative and therapies are often delayed until patients are symptomatic or have rapid tumour growth, the high sensitivity of MRD is of no guidance in therapeutic decisions.³

Conclusion

FL is an indolent lymphoma that remains incurable for most of the patients. Based on the 2011 ESMO guidelines we have presented guidelines for diagnosis and treatment, with adjustments to the Belgian situation.

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