Guidelines of the Belgian Hematological Society for newly diagnosed and relapsed follicular lymphoma anno 2019

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On behalf of the BHS-LPD subcommittee

SUMMARY

Follicular lymphoma is the most common low-grade non-Hodgkin lymphoma. Survival rates have been rising over time mainly due to advancing therapeutic strategies. As the last Belgian guidelines date from 2012, we present an update of the scientific evidence regarding diagnosis, staging, treatment and follow-up, and confront these to the Belgian reimbursement rules anno 2019. Follicular lymphoma grade 3B is classified as high-grade lymphoma and treated accordingly, and will not be discussed in this paper. Early stage disease can be treated with involved-field radiotherapy, which has curative potential. Advanced stage disease is virtually incurable, but many treatment options are available with good results. In first line, treatment is mostly based on chemotherapy combined with rituximab; the latter can be continued as maintenance therapy. In relapsed setting, introduction of the newer and more potent anti-CD20-antibody obinutuzumab, also in combination with chemotherapy, can lead to improved survival in high-risk patients. For older patients with comorbidities, rituximab monotherapy is the preferred option. In further lines, PI3K-inhibition with idelalisib and radioimmunotherapy are available. Finally, autologous or allogeneic stem cell transplantation remain an option in a small group of selected patients.

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INTRODUCTION

Follicular lymphoma (FL) is the most common low-grade non-Hodgkin lymphoma and counts for approximately 20% of the non-Hodgkin lymphomas.[1] It mostly results from the translocation t(14,18), leading to an overexpression of B-Cell Lymphoma-2 (BCL-2) and hereby reducing apoptotic activity.[2] Cure is only possible for early stage disease or for selected patients who can undergo allogeneic stem cell transplantation.[3,4] With the exception of follicular lymphoma grade IIIB, which will not be discussed in this paper, the disease has an indolent course and with the current treatments, a mean overall survival of fifteen years is approached. However, it has a relapsing and remitting course, requiring sequential therapies throughout a patient's lifetime.[5] As the last Belgian guidelines date from 2012, we present an update of the scientific evidence regarding diagnosis, staging, treatment and follow-up, and confront these to the Belgian reimbursement rules anno 2019.[6] Levels of evidence [I-V] and grade of recommendation [A-E] are indicated in square brackets.

DIAGNOSIS

Diagnosis of FL is made on excisional biopsy. Other techniques such as fine needle aspiration or core biopsies are less reliable since FL can be heterogeneous, leading to misinter-

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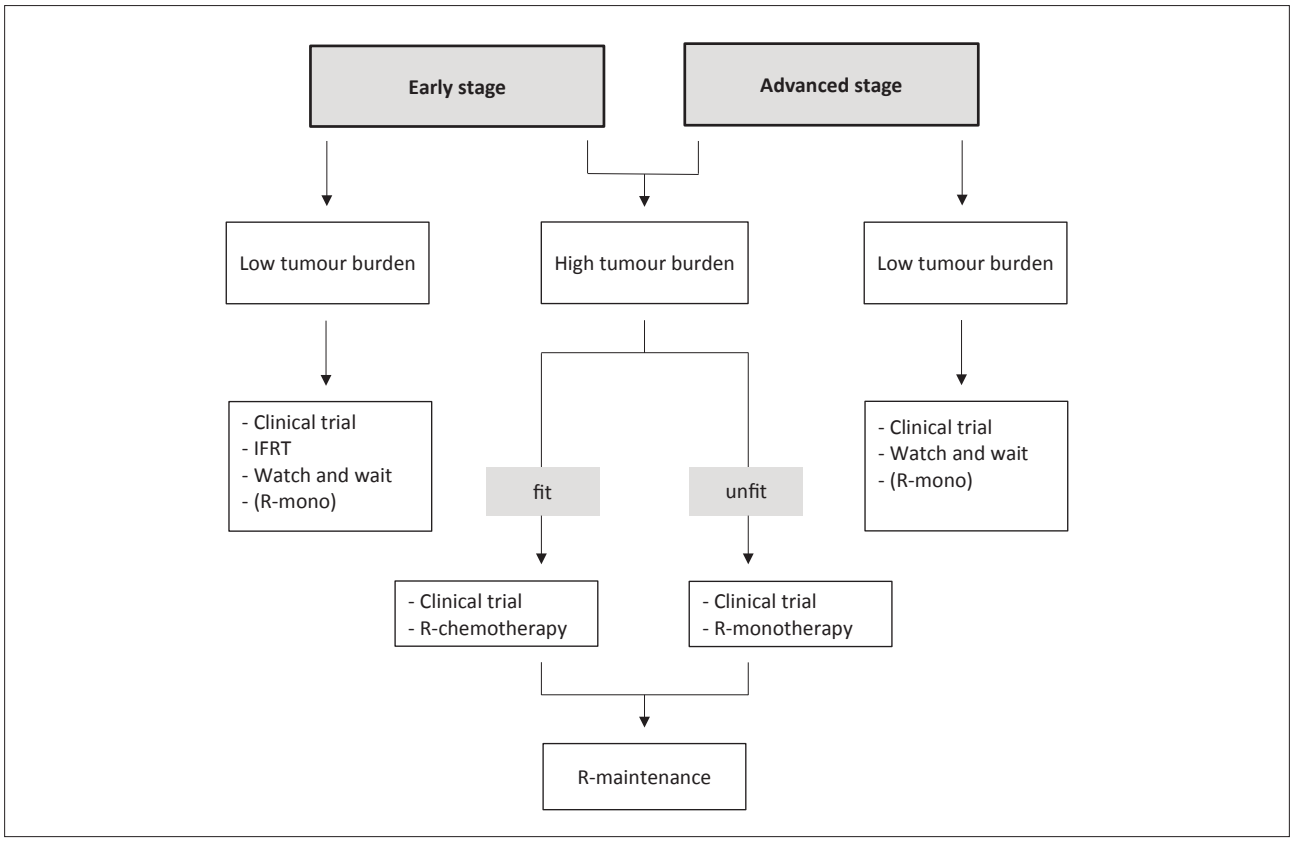

FIGURE 1. Treatment recommendation in first line.

pretation or need for re-biopsy. The neoplastic cells found in the biopsy are centrocytes and centroblasts; the more centroblasts per high power field (HPF), the more aggressive the lymphoma. Based on this, the World Health Organisation (WHO) classification of 2016 provides the following grading system[7]:

- Grade 1-2: 0-15 centroblasts/HPF
- Grade 3A: >15 centroblasts/HPF, also centrocytes visible
- Grade 3B: >15 centroblasts/HPF, lying in sheets, no centrocytes visible. This subtype is classified as high-grade lymphoma and treated accordingly, and will not be discussed further.

Although bone marrow is involved in 70% percent of the cases, other organs are less commonly affected. Given the indolent nature of the disease, B-symptoms and lactate dehydrogenase (LDH) elevation are rather rare.[8] The presence of these is suspicious for histological transformation to high-grade disease, which needs to be confirmed by a new biopsy.[9] This is done by guidance of PET/CT scan.

STAGING AND RISK ASSESSMENT

Staging is performed according to the Ann-Arbor classification. Initial work-up should consist of [10]:

- Blood analysis: complete blood count, chemistry (including LDH, β2-microglobulin and uric acid) and viral serology (human deficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV)) in context of therapy.
- Positron emission tomography / computed tomography (PET/CT): compared to conventional CT, it improves the accuracy of staging [IV, C] and is particularly important in early stage FL where involved-field radiotherapy (IFRT) can be performed with curative intentions.11
- Bone marrow aspirate and biopsy: PET/CT can be false negative, which can cause underestimation of disease stage.

Risk assessment can be done by using the Follicular Lymphoma International Prognostic Index (FLIPI) [I, A] or the revised version (FLIPI2). The revised version is more informative on the progression free survival (PFS) in patients requiring therapy in the era of immunochemotherapy.[12] In the future, extended gene expression profiling could be more useful in predicting the clinical course, and risk scores already have been proposed based on several candidate genes. However, this is not (yet) validated for use in daily practice.[13] Next generation sequencing and liquid biopsy are under investigation but have no role in the management of follicular NHL yet.

A robust marker of poor survival is when there is relapse

TABLE 1. GELF-criteria. ≥1 criteria is considered 'high tumour burden'.

Any nodal or extranodal tumour mass >7 cm diameter
Involvement of at least 3 nodal sites, each with diameter >3 cm
Presence of any systemic or B symptoms
Splenic enlargement with inferior margin below the umbilical line
Pleural or peritoneal serous effusion (irrespective of cell content)
Leukemic phase (> $5.0x10^9$/L circulating malignant cells)
Cytopenia (granulocyte count < $1.0x10^9$/L and/or platelets < $100x10^9$/L)
Compression syndrome (ureteral, orbital, gastrointestinal)

of FL within 24 months of chemoimmunotherapy initiation, a concept known as POD24 (progression of disease), which will occur in 20% of patients. Although there is no method established yet to identify patients at risk for POD24 at diagnosis, the fact of such an early progression is a risk factor for early death (5-year overall survival (OS) of 50% *vs.* 90%).[14]

TREATMENT

An overview of approved treatments is given, although inclusion in a clinical trial always needs to be considered.

FIRST-LINE (*FIGURE 1*)

EARLY STAGE

Only 15-30% of patients with FL are diagnosed in stage I or II. 15 As stated above, the use of PET/CT makes the staging more accurate, leading to more appropriate therapy by using IFRT with curative potential (5-year OS 93%, 10-year OS rates of 75%).[16] Although our guidelines in 2012 recommended a dose of 30-36 Gray (Gy), according to more recent publications a dose of 24Gy is sufficient [II, B].[17-19]

Recently, the combination of IFRT (30-40 Gy) and rituximab was investigated as single arm in the German MIR-trial, showing PFS and OS of respectively 78% and 96% at five years, without compromising the quality of life (median follow-up of 66 months).[20] However, further research needs to confirm this finding before making this approach the new standard.

When potential side effects of radiotherapy need to be avoided or patients refuse radiotherapy, watchful waiting or rituximab monotherapy are alternative options. On the other hand, systemic therapy as used in advanced stage FL can be considered in patients with high tumour burden [IV, B].[21]

ADVANCED STAGE

Most of the patients already have stage III or IV FL at time of diagnosis. These stages are not curable; nevertheless, a group of patients stay stable over a long period or even show a spontaneous regression.[22] Therefore, therapy should only be initiated when certain criteria are met indicating 'high tumour burden', known as the GELF-criteria (*Groupe d'Etude des Lymphomes Folliculaires*) [I, A] (*Table 1*).[21] When asymptomatic, watchful waiting or rituximab monotherapy can be considered. The latter improved PFS but not OS or risk for histological progression.[23,24] Taking into account also the possible toxicity of rituximab itself and the higher cost, the watch and wait strategy is often the preferred option.

Induction

When it is decided to initiate therapy, chemoimmunotherapy is still the first choice.[25-28] The preferred regimens are rituximab (R)-bendamustin and R-CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) [I, B], since R-CVP (cyclophosphamide, vincristine and prednisone) provides a lower 3-year PFS (52% *vs.* 68% compared to R-CHOP, p=0,01). Nevertheless, there is no significant difference in OS, which may make R-CVP more suitable for the elderly.[26,29,30] On the other hand, implementation of an anthracycline should be encouraged in case of histological transformation (histologically proven, or clinically suspected only when biopsy is not possible).[9,31] Furthermore, although there is no proven difference in OS, R-bendamustin is better than R-CHOP in terms of mean PFS and toxicity.[29,32] However, R-bendamustin is not reimbursed in Belgium as first line therapy, so the therapy of choice remains R-CHOP at this moment. Finally, in case conventional therapy is contra-

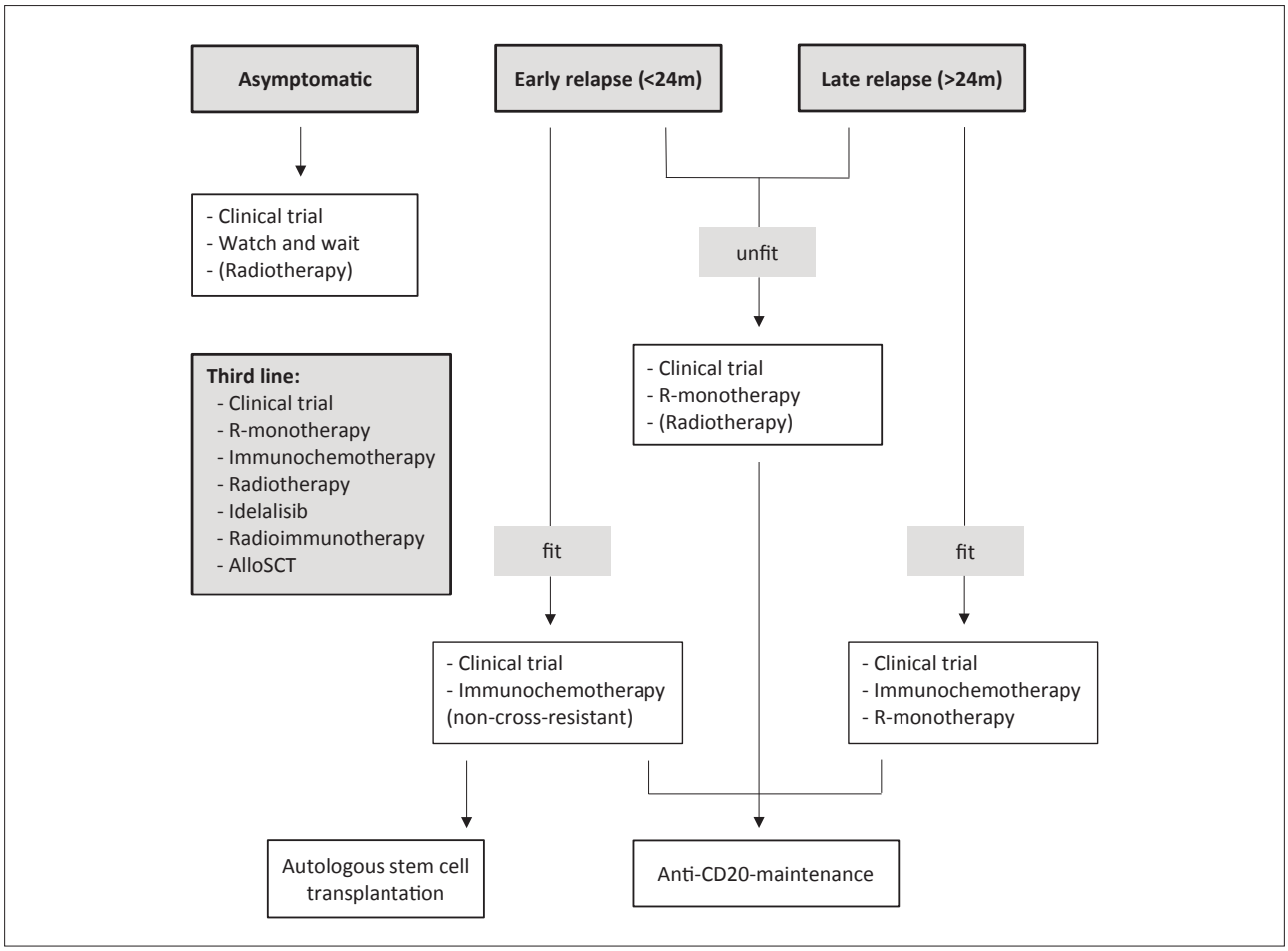

FIGURE 2. Treatment recommendation in relapsed/refractory setting.

indicated, rituximab monotherapy or in combination with chlorambucil can be an alternative [III, B].[33]

Although recently the GALLIUM-trial showed a significant higher 3-year PFS when applying obinutuzumab (O)-chemotherapy compared to rituximab-chemotherapy (80% *vs.* 73,3%), there was a comparable OS and reimbursement in Belgium was rejected.[34]

Finally, a non-chemotherapy strategy has been investigated in the RELEVANCE-trial, where R-chemotherapy was compared to R-lenalidomide with similar results in terms of complete response and PFS but with a different toxicity profile, favouring the use of R-lenalidomide for older patients with more comorbidities.[35] Nevertheless, the trial did not methodologically meet its primary endpoint of superior PFS, with no reimbursement in Belgium at this moment.

Consolidation/maintenance

For patients treated with R-CHOP/R-CVP, rituximab maintenance therapy every two months for two years improves the PFS at six years (59,2% *vs.* 42,7%) and reduces the risk of starting new treatment (HR=0,63). Although OS was comparable in both groups, it is the recommended standard of care [I, B].[36] There is lack of evidence for the benefit of rituximab maintenance following R-bendamustin.

For patients treated with rituximab-monotherapy, maintenance therapy has also proven its benefit in terms of PFS.[37,38] Nevertheless, according to the RESORT-trial, in patients with low tumour burden there is no difference in OS or risk for histological transformation when applying rituximab maintenance therapy compared to retreatment with rituximab when needed. On the other hand, time to cytotoxic therapy was shorter.[39]

Radio-immunotherapy as a consolidation therapy has shown to be inferior to rituximab monotherapy, with no reimbursement in Belgium.[40,41]

Autologous stem cell transplantation improves PFS but not OS, with increasing toxicity and risk of secondary malignancies. Therefore, it is not recommended in first line [I, D].[42,43]

RELAPSED/REFRACTORY DISEASE (*FIGURE 2*)

When confronted with relapsed disease, it is useful to obtain a new PET/CT for staging as well as for performing a new

KEY MESSAGES FOR CLINICAL PRACTICE

1 **Only early stage FL can be treated with curative intention, using involved-field radiotherapy**

2 **In advanced stage FL, treatment initiation is based on the GELF-criteria; in asymptomatic patients and in absence of GELF criteria, watchful waiting remains a valid option.**

3 **First line treatment consists of immunochemotherapy. R-CHOP is preferred, followed by R-maintenance. Although there is better PFS with R-bendamustin and equivalent outcome with R-lenalidomide, these regimens are not yet reimbursed in Belgium.**

4 **In relapsed setting, there is an important difference between early versus late relapse. Early relapse is a poor marker of survival (POD24) and those patients should be treated in clinical trials or with a non-cross-resistant immunochemotherapy such as O-bendamustin, followed by O-maintenance. Autologous stem cell transplantation is also an option. Late relapse can be treated by R-monotherapy.**

5 **Starting from third line, PI3K-inhibition and radioimmunotherapy amplify the available therapeutic options.**

6 **Allogeneic stem cell transplantation remains debatable in the anti-CD20-era, but can be considered in selected patients.**

biopsy. By choosing the most FDG-avid adenopathy, transformation to an aggressive lymphoma can be excluded. As in first line, initiation of treatment is based on the GELF-criteria, and asymptomatic patients with low tumour burden can be observed.[44]

Induction

When decided to start salvage treatment, the regimen depends on prior therapy and patient-specific comorbidities or prior toxicity. In early relapse (<24 months), a non-cross-resistant regimen should be chosen. This applies for the chemotherapy as well as for the immunotherapy: when treated in first line with CHOP and rituximab, switch to bendamustin and the newer anti-CD20 antibody obinutuzumab is preferred [I, B].[45] This approach is reimbursed in Belgium since 2017 for primary refractory disease or very early relapse (<6 months). As obinutuzumab is not reimbursed when relapse after more than six months, rituximab combined with a non-cross-resistant chemotherapy is the only possibility. In case of late relapse (>24 months) or important comorbidity, R-monotherapy can be considered.[46] Recently, combination of rituximab and lenalidomide has shown superiority to R-monotherapy in terms of mean PFS (39,4 months *vs.* 14,1 months).[47] Reimbursement in Belgium will be requested based on these results. When again confronted with relapsed disease after these interventions, idelalisib (PI3K-inhibitor) is reimbursed in Belgium in further lines, with a mean duration of response of 12,5 months. Close monitoring is mandatory because of the high prevalence of neutropenia grades III-IV (27% of patients), as well as elevated liver enzymes, diarrhea and pneumonitis.[48] Also ibritumomab tiuxetan radioimmunotherapy, an anti-CD20 antibody combined with Yttrium-90, is reimbursed in R-refractory disease starting from third line, with a time to progression of 6,8 months.[49] Finally, because follicular lymphomas are very sensitive to radiation, palliative radiotherapy (2x2Gy) can be used when single site disease causes localised symptoms, regardless the chosen regimen.[50]

Consolidation/maintenance

As in first line, rituximab maintenance is applied [I, A], in this context once every three months for two years.[51] Unfortunately, there are no studies that examine the usefulness of rituximab-maintenance when already applied in first line. When obinutuzumab is used, maintenance therapy every two months for two years is recommended.[45,52,53]

Despite several studies, consolidation with autologous or allogeneic stem cell transplantation remains debatable in the anti-CD20 antibody era. Autologous stem cell transplantation can be considered in fit patients with short first remission [I, B]. In carefully selected cases or when relapsed after autologous stem cell transplantation, an allogeneic stem cell transplantation can be beneficial [IV, B].[43,54]

FUTURE PERSPECTIVES

Ongoing trials will lead to new strategies in the treatment of

follicular lymphoma. New anti-CD20-antibodies are being tested, as well as the use of antibody-drug conjugates, Bruton kinase inhibitors, BCL2-inhibitors and immune checkpoint inhibitors. Finally, the very limited results so far with chimeric antigen receptor (CAR) T cells are encouraging.[55]

For instance, frontline use of R-Ibrutinib is now under investigation in a phase III trial (ClinicalTrials.gov identifier: NCT02947347). Furthermore, results of prolonged R-maintenance (four years instead of two) are expected in 2022 (ClinicalTrials.gov identifier: NCT00877214). The recent phase II GALEN trial demonstrated that O-lenalidomide is active in patients with relapsed or refractory follicular lymphoma, including those with early relapse. Randomised trials, for instance versus R-lenalidomide, are warranted.[56]

RESPONSE EVALUATION

The use of PET/CT instead of conventional CT was still investigational in 2012. Evidence now confirms the benefit from using PET/CT at interim evaluation after 3-4 cycles: when less than partial response (PR) is obtained, salvage therapy has to be considered.[57] For the patients not reaching complete remission (CR) at interim evaluation, PET/CT should be repeated at the end of induction therapy [II, B].[58] Nevertheless, partial remission (PR) can still become CR during maintenance therapy.[59]

The role of measurement of minimal residual disease (MRD) by detecting BCL2/IGH rearrangement in the bone marrow is now subject of investigation.[60] As preliminary results look promising, its position compared to end of treatment PET/CT remains to be established in the future.

FOLLOW-UP

History, physical examination and blood examination: every six months. This is based on expert opinion since there is lack of evidence.[6,19,61]

Medical imaging: only when clinically indicated. The routine use of PET/CT is not recommended.[10]

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APPENDIX 1. Levels of evidence and grades of recommendation.

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality or meta-analyses of well-conducted randomised trials without heterogeneity.
II	Small randomised trials or large randomised trials with lower methodological quality, or meta-analyses of such trials with demonstrated heterogeneity.
III	Prospective cohort studies.
IV	Retrospective cohort studies or case-control studies.
V	Studies without control group, case reports, experts' opinions.
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended.
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended.
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages, optional.
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended.
E	Strong evidence against efficacy or for adverse outcome, never recommended.

APPENDIX 2. Follicular Lymphoma International Prognostic Index (FLIPI/FLIPI2).

Levels of evidence	FLIPI	FLIPI2
Nodal sites	> 4	Largest diameter > 6cm
Age (years)	> 60	> 60
Serum marker	Elevated LDH	Elevated β2-microglobulin
Stage	Ann-Arbor III-IV	Bone marrow involvement
Haemoglobin	< 12 g/dL	< 12 g/dL

0-1 risk factors: low risk; 2 risk factors: intermediate risk; 3-5 risk factors: high risk.
LDH: lactate dehydrogenase.