bjh guideline

The investigation and management of follicular lymphoma

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Follicular lymphoma (FL) is a heterogeneous disease. For many it is experienced as a chronic, relapsing, indolent condition with long overall survival (OS). Most people affected have advanced disease at presentation; symptoms may include B symptoms (i.e. fever, night sweats and weight loss), fatigue and the local mass effect of lymph node enlargement. However, many people are asymptomatic at presentation. Some people are observed without treatment according to a 'watch and wait' policy (see section Management of patients with newly diagnosed FL). In contrast to this, over a period of many years, 20–30% of patients will die from refractory FL or following transformation of their disease to high-grade lymphoma.[1] Prognostic indices may help discriminate between risk groups (see section Prognostic factors in FL).

Survival of people with FL has improved over the last 30 years. Single-institution series show up to 30% improvement in 5-year OS.[2,3] A USA population-based registry study of >14 000 patients between 1978 and 1999 showed an increase in median survival from 84 to 93 months.[4] Improvement in failure-free survival (FFS) was only seen following the introduction of anti-CD20 therapy given in combination with traditional chemotherapeutic approaches.

Treatment plans for an individual person should be part of a long-term strategy and planned after multi-disciplinary team review with lymphoma specialist clinicians and nurses, specialist haematopathologists, radiologists and radiation oncologists. Numerous treatment modalities are available, but some may compromise future choices. Risk of long-term complications, such as myelodysplastic syndromes, other secondary cancers, cardiac toxicity and effects on fertility must also be considered, given the extended and increasing survival of many people.

Psychological support from clinical nurse specialists as well as other bodies, such as patient groups, is particularly important in the face of the chronic relapsing nature of this disease and the multiplicity of treatment choices available to the person affected and their physician.

This document represents an update of the inaugural British Society of Haematology guideline, published in 2011, which now merits an update due to significant developments in the understanding and therapy of the condition.

Diagnosis

Morphology

FL is a B-cell neoplasm derived from germinal (follicle) centre cells. Involved lymph nodes show replacement of the normal architecture by closely packed neoplastic follicles that are uniform in size, lack tingible body macrophages and possess poorly formed mantle zones. Reactive germinal centres contain a mixture of centroblasts and centrocytes organised into well-defined zones, whereas germinal centres in FL contain a monomorphic population (usually of centrocytes) and lack any evidence of zonation. Whilst most cases show a uniform pattern of closely packed follicles throughout the involved tissue, the architecture of FL can be variable. In some biopsies there is a mixture of follicular and diffuse areas and in rare cases the architecture is completely diffuse and lacks any identifiable follicular structures.

Approximately half of all FL cases show bone marrow involvement at presentation.[5]

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Immunohistochemistry

Follicle centre cells express B-lineage markers and the germinal centre cell antigens CD10 and B-cell lymphoma 6 (BCL6). The interfollicular component of the node and bone marrow disease often shows down-regulation or loss of these markers.[6] The underlying networks of follicular dendritic cells can be shown with CD21.

Normal germinal centre cells are BCL2-negative; in 85% of cases the neoplastic cells in FL are BCL2-positive. At the molecular level, FL shows a characteristic t(14;18)(q32;q21) translocation which relocates the *BCL2* anti-apoptosis gene so that it is adjacent to an immunoglobulin promoter, leading to over-expression of BCL2 protein. The tumour cells in FL show light chain restriction.

All cases of FL require a histological diagnosis. A fine-needle aspirate is inadequate for the diagnosis; whilst FL cells can be detected in cytology specimens,[7] with confirmation by polymerase chain reaction, fluorescence *in situ* hybridisation and flow cytometric immunophenotyping, histology is needed to grade the tumour and to exclude transformation to diffuse large B-cell lymphoma (DLBCL).

Initial investigations following a confirmed diagnosis of FL

Appropriate investigations following diagnostic biopsy in FL serve a number of purposes. Staging investigations enable an initial assessment of disease extent, including determination of the stage of disease, identification of sites of bulk disease and derivation of prognostic scoring systems, such as the Follicular Lymphoma International Prognostic Index (FLIPI and FLIPI2). Baseline staging also provides a rational basis for treatment, allows appropriate disease monitoring, and facilitates comparative post-treatment assessment.

Imaging guidelines in FL

Use of imaging at diagnosis. Fluorodeoxyglucose-positron emission tomography/computerised tomography (FDG-PET/CT)—Functional and anatomical imaging with FDG-PET/CT, utilising the labelled glucose analogue ^{18}FDG, has become a standard-of-care investigation for several lymphoma subtypes. There is substantial evidence that most cases of FL are visualised on FDG-PET/CT irrespective of grade.[8–13] FDG-PET/CT is the imaging technique recommended as the standard for staging FDG-avid nodal lymphomas in the Lugano classification.[14]

FDG-PET/CT in FL may detect additional nodal and extra-nodal sites of disease, compared with standard CT assessment. One retrospective study was performed on 45 patients with untreated, biopsy confirmed FL who underwent FDG-PET/CT and CT before and after immunochemotherapy induction (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone). FDG-PET/CT detected more nodal (+51%) and extra-nodal (+89%) lesions than CT. FDG-PET/CT modified staging in eight patients (18%). Five patients (11%) initially considered as limited stage (I/II) were upstaged to advanced stage (III/IV).[15]

Specifically, sensitive FDG-PET/CT staging of clinical stage I FL may contribute to the improved prognosis in patients treated with involved field radiotherapy compared to historical cohorts, likely due to better identification of true stage I disease.[15,16]

Recent studies, of variable quality, suggest that up to 45% of people with what is thought to be limited stage FL are upstaged by FDG-PET/CT compared with CT. There are currently no studies reporting on the influence of FDG-PET/CT on FLIPI risk stratification.[17]

There are specific limitations of FDG-PET/CT in FL. It is of limited value for the detection of bone marrow disease; if documentation of marrow involvement is important to the person's ongoing management, then a bone marrow biopsy is required.[11,18] Despite widespread views to the contrary, semi-quantative analysis of uptake does not assist in improving accuracy of FDG-PET/CT for detecting FL transformation. In general, FL as a whole shows lower FDG uptake compared with transformed FL[19], but significant overlap occurs within the histological grade and with transformed disease.

Computed tomography—FDG-PET/CT is preferred but contrast-enhanced CT is also acceptable. It should include the neck, thorax, abdomen and pelvis and extend from the skull base to the pubic symphysis. Imaging of the central nervous system is not routinely required.

In summary, FDG-PET/CT is the preferred staging modality for FL. Contrast-enhanced CT is an acceptable alternative.

Patient assessment

In addition to imaging techniques used to determine the extent of disease and identify areas of bulk, other baseline investigations are required to complete staging, assess underlying fitness and organ function, and inform prognostic scores. The requirement for some tests may vary according to proposed treatment.

A full history and clinical examination should be undertaken to identify significant comorbidities and record performance status. Geriatric tools such as the Cumulative Illness Rate Scale and Activities of Daily Living scores may be useful in frailer patients.[20]

Traditionally, bone marrow aspiration and trephine biopsy (BMAT) has been recommended to complete staging, allow participation in clinical trials and, more recently, for prognosis (see section Prognostic factors in FL). However, its utility for staging FL is questioned when it will not alter management. For example, if the agreed management plan is for initial observation, it is reasonable to delay the procedure until

starting treatment or entry into a clinical trial (please see additional comments below under management of early stage disease). If a BMAT is performed, flow cytometry on the aspirate to identify a germinal centre B-cell population confirms bone marrow involvement and negates the requirement for immunohistochemistry. Similarly, if flow cytometry is not performed but paratrabecular infiltration by small lymphocytes is present in the trephine biopsy sections, then this is sufficient for a diagnosis of bone marrow involvement in an established diagnosis of FL and immunohistochemistry is not warranted. A decision to avoid an initial bone marrow biopsy may affect the ability to accurately calculate prognostic scores, but the information gained should be balanced against the minor risks and potential discomfort and side-effects of the procedure (see below).

When anthracycline-containing chemotherapy is being proposed, electrocardiogram (ECG) and echocardiography should be considered in people aged >70 years and/or with a history of cardiac disease including ischaemic heart disease, hypertension or diabetes mellitus.

The impact of any treatment on fertility should be discussed with men and women prior to commencing chemotherapy. Given that the median age of onset of FL is 65 years this is unlikely to be a consideration for most people. However, if appropriate, males should be offered sperm cryopreservation and females of child-bearing age should be referred to an assisted conception unit to discuss options.

Note that the laboratory studies mentioned below are proposed because they are part of various prognostic scoring tools, or because they reflect end-organ effects of lymphoma or are part of the pre-treatment safety assessment (e.g. hepatitis B assessment).

Recommendations

- **Offer people with newly diagnosed FL imaging with FDG-PET/CT prior to treatment. Contrast-enhanced CT may also be used.**
- **Consider ECG and echocardiography in people aged >70 years and/or with a history of cardiac disease including ischaemic heart disease, hypertension or diabetes prior to anthracycline-containing chemotherapy**
- **Offer the following baseline laboratory tests for people diagnosed with FL prior to immunochemotherapy:**

a Full blood count
b Flow cytometry on blood (or bone marrow aspirate) if peripheral blood lymphocytosis or abnormal lymphocytes seen on blood film
c Urea, creatinine and electrolytes
d Liver function tests including albumin
e Calcium and phosphate
f Urate
g Lactate dehydrogenase (LDH)
h β_2 microglobulin
i Hepatitis B (surface antigen and core antibody), hepatitis C and human immunodeficiency virus (HIV)

- **A staging BMAT is advised in people with newly diagnosed FL. However, this can be reviewed, after discussion with the patient, if it will not alter therapy. The impact of this decision on prognostic score calculations and access to clinical trials should be considered.**

Prognostic factors in FL

In 2004, an international collaborative study evaluated prognostic factors in 4167 rituximab-naïve patients with FL resulting in the publication of the FLIPI.[21] This index includes the following five adverse variables: age ≥60 years, haemoglobin concentration <120 g/l, greater than upper normal value of LDH, stage III–IV and ≥5 involved nodal areas. The FLIPI stratifies patients into three groups (low, intermediate and high risk), well balanced in terms of the proportion of patients in each group and with clearly different outcomes (5-year OS: 91%, 78% and 52% respectively). As well as providing prognostic information, the FLIPI score also identifies people with a higher risk of histological transformation.[22] In an attempt to improve on the FLIPI, a revised version (FLIPI2) has been developed utilising data from >1000 newly diagnosed FL rituximab-treated patients where the following factors predicted for progression-free survival (PFS): β_2 microglobulin greater than upper limit of normal value, bone marrow involvement, age >60 years, haemoglobin concentration <120 g/l and longest diameter lymph node >6 cm.[23] This analysis was made using data that were collected prospectively from patients receiving treatment that included rituximab. Although the original FLIPI was designed in the pre-rituximab era, a large USA national cohort study has recently shown that the FLIPI remains valid in the rituximab immunochemotherapy era and predicts OS as well as PFS.[24] The FLIPI and FLIPI2 were validated recently as a *post hoc* analysis of the PRIMA trial (ClinicalTrials.gov Identifier: NCT00140582). From this analysis, a new simplified scoring system was defined using just two parameters: bone marrow involvement and β_2 microglobulin (the PRIMA-PI [prognostic index]).[25] This defines three risk groups with 5-year PFS rates of 69%, 55% and 37%. However, this has only been applied in the context of treatment with immunochemotherapy and requires all patients to receive a BMAT.

Prognostic indicators at relapse are less well established. Data on the value of FLIPI at the time of relapse are scarce, although its ability to predict survival from progression has been confirmed in retrospective series.[22,26]

Both FLIPI and FLIPI2 provide robust prognostic information for patients treated with antibody-based therapy. Therefore, either FLIPI or FLIPI2 (if BMAT performed) should be calculated and recorded at diagnosis for all patients in routine clinical practice. The FLIPI has not been

validated prospectively to guide therapeutic decisions for patients with FL and, historically, has only been used to inform prognosis and treatment decisions in a clinical trial setting. However, based on clinical trial data, the National Institute for Health and Care Excellence (NICE) guidance has now incorporated the use of FLIPI in a first-line treatment recommendation (https://www.nice.org.uk/guidance/ta513/chapter/1-Recommendations; see section on Management of patients with newly diagnosed FL).

More recently, there has been a move towards determining prognosis based on response assessment and/or the length of initial remission following front-line therapy. Prognostic evaluation includes event-free survival (EFS) at 12 or 24 months,[27] early progression of disease (POD) within 24 months (POD24)[28–30] or the achievement of a complete remission with therapy at 30 months (CR30).[31] All of these endpoints are strongly associated with PFS, POD24 is also associated with inferior OS. A high proportion of POD24 events in the setting of prior bendamustine therapy have been reported to represent disease transformation, which may explain the association with inferior OS.[32] Early POD following initial therapy may lead to a more aggressive approach, including stem-cell transplantation (see section Transplantation in FL), particularly in younger patients and offers an opportunity for clinical trial stratification.

Management of patients with newly diagnosed FL

The management of early stage disease

Full staging is recommended for a suspected early stage disease being considered for radiotherapy, including PET, CT and BMAT to exclude advanced disease, which would require systemic therapy.[33] Conventionally, early stage FL comprising stage I–II disease, where the involved nodes are contiguous and can be easily encompassed within a radiation field, has been treated with local radiotherapy. FL is a highly radiosensitive lymphoma and a number of mature case series in the literature confirm a high response rate with around 80% of patients having long-term disease control at 5 and 10 years.[34–37] Examination of the patterns of relapse in these patients reveals that most relapse outside the irradiated field.[38,39] FDG-PET/CT upstages a significant number of patients, compared to CT.[17] Consequently, outcomes in patients staged by FDG-PET-CT have been evaluated in an international effort, to determine if more accurate staging leads to better patient selection and results. These data suggest that, in the modern era, the outcome following radiotherapy for stage I and localised stage II FL after FDG PET-CT staging is better than in historical series. More than two-thirds of patients remain in remission at 5 years and most relapses occur in distant sites. On multivariate analysis, stage II patients were associated with a less favourable freedom from progression.[15]

Involved-site radiotherapy (ISRT) has become established as the international standard.[40] Regarding the radiotherapy dose, the UK group conducted a randomised trial (FoRT, ClinicalTrials.gov Identifier: NCT00310167) comparing 24 Gy in 12 fractions *versus* 4 Gy in two fractions.[41] The 24 Gy in 12 fractions was the more effective radiation schedule for early stage indolent lymphoma (marginal zone lymphomas as well as FL) with significantly improved local control. Long-term follow-up of this trial was recently presented, in the subgroup treated with curative intent there were 5/119 relapses after 24 Gy and 29/129 after 4 Gy. The 24 Gy in 12 fractions schedule should remain the schedule of choice for curative radiation therapy in FL.

However, in keeping with other published studies, 4 Gy in two fractions was highly effective with little or no toxicity and remains a useful alternative for palliative treatment approaches.[42–48]

Observation without ISRT can be considered in people with limited stage FL who have undergone localised excision and where there may be concerns by the clinician or patient about radiotherapy to a particular site.

Note that early stage disease that is discontiguous or otherwise unsuitable for radiotherapy should be managed as advanced stage disease.

Advanced stage asymptomatic FL

Three randomised studies of varying quality have shown that there is no advantage to immediate treatment in patients with advanced stage *asymptomatic* FL compared with a watchful-waiting approach in terms of OS and disease-specific survival.[49–51]

In the largest study of 309 patients with 16 years of follow-up, the criteria for patients being eligible for a 'watch and wait' approach were defined as the absence of the following: pruritus or B symptoms, rapid generalised disease progression in the preceding 3 months, life-endangering organ involvement, significant bone marrow infiltration resulting in bone marrow depression sufficient to warrant immediate chemotherapy, localised bone lesions, renal infiltration and significant liver involvement. Bulky disease *per se* was not an exclusion criterion.

A more restrictive set of criteria, which defined low tumour burden FL, were established by the Groupe d'Etude des Lymphomes Folliculaires (GELF),[50] largely as criteria for trial entry. Low tumour burden was defined as: largest nodal or extra-nodal mass <7 cm diameter, <3 nodal sites with a diameter >3 cm, absence of systemic symptoms, no serous effusion, no substantial splenic enlargement, no risk of vital organ compression and no leukaemia or cytopenia.

These criteria have been modified in various studies over the years and now specify absence of B symptoms and normal LDH and β2 microglobulin.[52–54] A notable difference between the modified GELF criteria and the UK criteria of low tumour burden is that the latter requires *no more* than

three nodal sites with a diameter >3 cm, emphasising the importance of reviewing the definition of low tumour burden when reviewing study entry criteria.

In clinical practice, a watchful-waiting approach does not need to be limited to patients with low tumour burden, although it is likely that patients with a higher tumour burden will have a shorter interval until disease progression, necessitating treatment.

Watchful waiting is able to defer the initiation of systemic therapy by 2–3 years.[49,50] In the UK study, 40% of patients aged >70 years had neither received chemotherapy nor died of lymphoma at 10 years after study entry. This fell to 16% in those patients aged <70 years. Thus, there is little justification for immediate treatment in patients with advanced stage, asymptomatic FL. Patients who undergo observation do not have an increased risk of high-grade transformation[50,55,56] compared with those who start treatment immediately. The advantage of a watchful-waiting approach is that the toxic side-effects of chemotherapy are deferred or avoided.

Results of a randomised study in patients with advanced stage, asymptomatic FL compared watchful waiting with immediate treatment with rituximab using either the standard 4-week induction or the 4-week induction followed by maintenance rituximab administered twice monthly for 2 years. Results were reported after a median follow-up of 46 months.[57] The primary endpoint was time to initiation of new therapy. At 3 years after randomisation, 46% of patients in the 'watch and wait' arm had not received further therapy, whereas 78% of people in the rituximab induction arm and 88% of people in the rituximab induction and maintenance arm had not initiated new therapy. The difference between the two rituximab arms was not significant. There was no difference in OS with approximately 95% of all patients alive at 3 years. Quality of life was good in most patients with no detriment in the rituximab arms. Significant improvements in quality of life were only seen in some domains in the rituximab induction and maintenance arm, such as people feeling more in control of their situation and less worried about their disease becoming more aggressive or being able to support themselves and their families.[58]

A health economic analysis by the NICE non-Hodgkin Lymphoma Clinical Guideline Committee found that, in comparison to watchful waiting, both rituximab induction and rituximab induction followed by maintenance were cost-effective with rituximab induction being the optimal strategy overall.[59] NICE therefore recommends consideration of rituximab induction for people with advanced-stage FL who are asymptomatic. This is particularly attractive in patients where deferring chemotherapy will be advantageous due to other health reasons. Note that rituximab monotherapy is not licensed in the UK for first-line management of advanced stage asymptomatic FL and is not commissioned for this purpose by NHS England.

Recommendations

- **Offer ISRT to people with limited stage FL that can be encompassed within a radiotherapy field, delivering a dose of 24 Gy in 12 daily fractions.**
- **Consider observation without ISRT in people with limited stage FL who have undergone localised excision and where there may be concerns by the clinician or patient about radiotherapy to a particular site.**
- **In people with asymptomatic, advanced stage FL consider observation alone i.e. no therapy. Induction rituximab monotherapy may also be considered as it is a safe and cost-effective therapy. (Please note that rituximab does not have a UK market authorisation for this indication and is not currently commissioned by NHS England for this purpose).**

Management of patients with newly diagnosed, symptomatic FL

The addition of rituximab to induction chemotherapy represented a landmark in the management of FL[60,61] and remains the only intervention to demonstrate an improvement in OS in previously untreated patients with FL.[62]

Based on these data, it is clear that an anti-CD20 monoclonal antibody should be added to chemotherapy in the treatment of advanced stage, symptomatic FL but there is less consensus as to which chemotherapy regimen it should be paired with. Rituximab plus bendamustine (BR) has been compared with rituximab and cyclophosphamide, hydroxydaunorubicin, vincristine and prednisolone (R-CHOP) in the Study Group Indolent Lymphomas (STiL trial (ClinicalTrials.gov Identifier: NCT00991211).[63] Six cycles of BR (90 mg/m^2 of bendamustine on days 1 and 2 of 28-day cycles) delivered a significant improvement in PFS compared to R-CHOP (hazard ratio [HR] 0·61), although the PFS for the R-CHOP arm was surprisingly lower than would have been expected from other studies (median PFS 40·9 months). BR was associated with a lower rate of toxicities and a favourable side-effect profile compared to R-CHOP. No OS benefit has been reported despite the marked difference in PFS. Further data supporting BR came from the BRIGHT trial (ClinicalTrials.gov Identifier: NCT00877006), which demonstrated non-inferiority of BR compared to rituximab with cyclophosphamide, vincristine and prednisolone (R-CVP) or R-CHOP with an improved overall response rate (ORR) in the bendamustine arm.[64] Neither the STiL nor BRIGHT trials mentioned above used rituximab maintenance after induction (see below). These data have led many clinicians to favour bendamustine over CHOP or CVP as the chemotherapy regimen of choice.[65] The STiL and BRIGHT trials have not reported quality of life data, but the absence of alopecia with bendamustine is one reason for the widespread uptake of this regimen.

Although the STiL trial reported lower toxicity with BR compared with R-CHOP, bendamustine causes prolonged lymphopenia. If this combination is used, it is important to be aware of the risk of clinically significant infections and use anti-infection prophylaxis.

Whilst there is little firm evidence to support choice of chemotherapy regimen, R-CHOP should typically be reserved for situations in which high-grade transformation is confirmed or suspected (see section on FL transformation). Chlorambucil or CVP, with rituximab, is favoured in patients for whom the toxicities of bendamustine are thought to be too high.[66] For many people, bendamustine will be the chemotherapy of choice. The dose of bendamustine is 90 mg/m^2 on Days 1 and 2 of 28-day cycles for up to six cycles, but this can be reduced to 60–70 mg/m^2 or the second dose can be omitted in patients requiring a lower dose on account of frailty or toxicity. All patients receiving bendamustine must receive *Pneumocystis jirovecii* prophylaxis and anti-viral prophylaxis, and consideration should be given to granulocyte-colony stimulating factor (G-CSF) support of the neutrophil count. The CD4 count may be used to determine the duration of prophylaxis required.

Obinutuzumab is an anti-CD20 monoclonal antibody with greater antibody-dependent cellular cytotoxicity than rituximab. In the GALLIUM trial (ClinicalTrials.gov Identifier: NCT01332968), 1202 patients were randomised to obinutuzumab or rituximab plus chemotherapy (bendamustine, CHOP, or CVP) followed by 2 years of maintenance in responding patients. There was a significant improvement in PFS with obinutuzumab [HR 0·66, 95% confidence interval (CI) 0·51–0·85]. The clinically important endpoint of time-to-next-treatment was also longer in the obinutuzumab arm and other endpoints supported the primary endpoint including deeper minimal residual disease (MRD)-negative remissions, more PET-negative remissions as well as reductions in early progression (POD24) in the obinutuzumab arm.[65,67]

There were more toxicities with obinutuzumab compared with rituximab; these were predominantly infusion-related reactions (IRR), but there was also a small increase in the rate of severe neutropenia (46·6% vs. 39·9%) and severe infections (22·2% vs. 18·6%).

Subgroup analyses indicated that the PFS benefit of obinutuzumab was present across many different subgroups including age, stage, presence of bulky disease, gender and chemotherapy backbone. There was less benefit in patients with a low FLIPI score; in 2018, NICE approved obinutuzumab plus chemotherapy for patients with previously untreated advanced stage symptomatic FL with a FLIPI score of ≥2 (NICE TA513).

Caution needs to be taken with the first treatment due to the risk of IRR, and careful monitoring is required during treatment and beyond for neutropenia and infections. Obinutuzumab is currently not available in a formulation that can be delivered subcutaneously, meaning that patients receiving obinutuzumab maintenance require regular intravenous infusions.

Maintenance therapy. The PRIMA trial showed that 2 years of maintenance with rituximab every 2 months led to a significant improvement in 3-year PFS (HR 0·55, 95% CI 0·44–0·68); 10-year follow-up suggests that this benefit is maintained with 10-year PFS 51% vs. 35% (HR 0·61, 95% CI 0·52–0·73).[68] Moreover, 60% of patients in the maintenance arm have still not required another line of therapy at 10 years.

However, maintenance rituximab has not been universally adopted on account of the lack of OS benefit and concern about the increased incidence of infections in patients receiving maintenance. The relative value of maintenance or observation after bendamustine induction has not been addressed in a prospective trial and the toxicities of maintenance after bendamustine were highlighted in the GALLIUM trial, independent of which antibody was used (see above). However, a cross trial comparison by Rummel *et al.*[69], presented in abstract form only, indicates that there is a benefit of maintenance after bendamustine with a similar order of magnitude to that seen in the PRIMA trial.

Maintenance with the same anti-CD20 monoclonal antibody that was used in induction should be considered for patients attaining a partial (PR) or complete response (CR) to induction treatment. Standard dosing is once every 2 months for 2 years. Patients need to be carefully counselled about the benefits and risks. In patients who have experienced severe infections during induction chemotherapy, it may be appropriate to avoid maintenance. There must be a low threshold for stopping maintenance in people who experience recurrent infections. There is no proven role for monitoring serum immunoglobulin levels during maintenance. The subcutaneous formulation of rituximab was approved by NICE in 2014 for use during the maintenance phase and is now widely used instead of intravenous rituximab.[70]

Recommendations

- **Always consider enrolment in a clinical trial, if available.**
- **All people with advanced stage FL should be assessed against the GELF criteria to ascertain if they require treatment.**
- **Offer rituximab or obinutuzumab with chemotherapy for people who require treatment. The chemotherapy with which the antibody should be paired (e.g. bendamustine, chlorambucil, CHOP, CVP) is dependent on patient factors and clinician choice.**
- **For patients responding to therapy (PR or CR), consider maintenance with rituximab or obinutuzumab (whichever antibody was used in induction) for a period of 2 years after discussion with the patient of the risks and benefits.**

Management of relapsed FL

As mentioned, people with relapsed FL who have progressed within 24 months of the previous therapy or who are resistant to both rituximab and an alkylator agent have the worst outcomes.[28] This group represents the greatest area of unmet need in FL. In the relapsed setting, the cumulative effects of previous therapies may be particularly relevant. How best to navigate through the choices of further immunochemotherapy, transplantation, subsequent maintenance antibody therapy and newer agents is suggested below.

Patient assessment

Before commencing therapy in patients with symptoms or signs consistent with relapsed FL, it is strongly recommended that a repeat biopsy for histopathological reassessment be carried out, wherever practicable. This is because of the risk of histological transformation of FL to a more aggressive lymphoma subtype and the adverse prognostic implications of this event.[1,55,71] If histological transformation has been excluded, decisions regarding therapy will depend on a combination of the following factors:

1. The indications for therapy – there is no evidence that intervention will improve outcomes for patients with relapsed but asymptomatic FL. For example, recurrent asymptomatic nodal disease detected on routine clinical examination that shows no signs of rapid progression should not necessarily result in immediate re-treatment.
2. A person's fitness for therapy.
3. Previous treatments received and the duration of response achieved.
4. The person's preference.

Immunochemotherapy

As is the case with front-line therapy, the optimal chemotherapy regimen at the point of relapse has not been determined. The decision to use an anthracycline-based combination should be made on patient characteristics, such as cardiac function, and the response duration of previous therapies. For example, patients who have relapsed late following alkylator-based treatment may be re-treated with an alkylator-rituximab based combination (e.g. R-CVP). This is based on the competitive response rates seen with this regimen in previously untreated people, the concern about potential cardiotoxicity of anthracycline use and its preclusion from further use due to accumulated dose exposure later in the course of the disease or if transformation supervenes. In those patients who are resistant to or who have relapsed early following anthracycline-based chemotherapy or who have contra-indications to their use, alternate agents should be considered.

Cohort studies show that most people who relapse following immunochemotherapy will receive this modality again at the point of first relapse.[72] It should be noted that re-treatment of patients with rituximab is effective in patients who have had disease progression.[73–75]

Therapeutic options for people with relapsed disease are more limited for those who are resistant to rituximab (Rit-R), i.e., people who did not respond or who progressed during or within 6 months after treatment with rituximab or a rituximab-containing regimen. There have been several developments for people in this group. Bendamustine monotherapy has demonstrated efficacy with a median PFS of 9 months in Phase 2 studies.[76] A Phase 3 study[77] has demonstrated evidence for a benefit of obinutuzumab (see section Management of patients with newly diagnosed FL), when combined with bendamustine and followed by obinutuzumab maintenance for 2 years, compared with bendamustine alone. The PFS was 26 months with obinutuzumab and bendamustine, compared with 14 months with bendamustine alone in Rit-R patients. In addition, the depth of response achieved with obinutuzumab plus bendamustine was greater than with bendamustine alone. The number of patients who achieved MRD-negative status following induction was nearly doubled (82% vs. 43%).[78] The combination was associated with an increase in IRR and neutropenia when compared with bendamustine alone. The benefit in PFS achieved with this approach has been reported to translate into an OS benefit in a recent update.[77]

Phosphatidylinositol 3-kinase (PI3K) inhibitors. Idelalisib is a first-in-class, selective, oral inhibitor of PI3Kδ. The latter is critical for activation, proliferation and survival of B cells and is deregulated in FL. At a dose of 100 mg twice-daily or more, responses are observed in approximately 45% of people with FL who have been heavily pre-treated, including those who are Rit-R and alkylator refractory, with the median PFS reported to be 16 months. Subsequent analysis also demonstrated benefit in POD24 patients.[79] Grade 3 adverse events include diarrhoea, fatigue, rash and respiratory complications.

Although rituximab has been used as monotherapy in the relapse setting[80] the response rates and PFS are markedly improved with the addition of chemotherapy. It is therefore recommended that patients who require therapy be treated with the combination of immunotherapy and chemotherapy. For those patients who are intolerant of chemotherapy due to comorbidities or for other reasons, rituximab monotherapy with palliative intent can be considered.

Rituximab maintenance for up to 2 years following a response to re-induction chemoimmunotherapy has a favourable side-effect profile; a meta-analysis demonstrated that maintenance substantially prolongs PFS and OS in relapsed disease, even after antibody-containing induction in people who have not received a monoclonal antibody as first-line therapy.[81] Note that second-line maintenance

treatment has not been investigated in the setting of previous maintenance use in first-line therapy and it should not be used for those patients who had relapsed during their first maintenance period. The benefit of maintenance in the relapse setting for those who completed maintenance in the front-line setting is unknown.

Radio-immunotherapy (RIT) has established efficacy in the relapse and refractory setting. It can be administered as a single therapy even in people with significant co-morbidities and remains effective independent of prior treatment with rituximab.[82] Two RIT agents are licensed for treatment of relapsed or refractory FL: Yttrium Y-90 ibritumomab tiuxetan (Zevalin®) and iodine I-131 tositumomab (BEXXAR®). However, it is important to note that despite its activity and manageable safety profile, few centres are equipped to deliver RIT and wide adoption has been further limited by uncertainty about its place in the FL treatment pathway, and as yet unproven concerns about long-term safety and the impact on subsequent treatment delivery.[83]

Short-course, low-dose radiotherapy (e.g. 2 × 2 Gy) should also be considered in the management of relapsed FL in certain clinical settings where systemic therapy is inappropriate. Response rates are high and toxicity minimal.

Fitter people with relapsed FL should be considered for consolidation high-dose therapy with autologous stem cell rescue (HDT-ASCR) after achieving a second or subsequent remission. This is discussed in the section Transplantation in FL.

Recommendations

- **Offer biopsy, wherever practicable, to people with suspected relapsed FL, to ensure that there is no evidence of high-grade transformation.**
- **Always consider enrolment in a clinical trial; this is especially important for those people with early progression following primary therapy as this group represents a serious unmet need in FL.**
- **Consider observation alone for those people with relapsed disease who are asymptomatic and lack standard indications for therapy.**
- **Offer immunochemotherapy to people with relapsed FL in need of treatment. For those who have achieved a relatively long remission duration, consider repeat therapy with rituximab in combination with the same chemotherapy as administered previously. For those with a shorter remission duration consider rituximab in combination with an alternative chemotherapy regimen from that administered previously. There are insufficient data to comment on the effectiveness of this approach in people with a short remission following bendamustine-based therapy.**
- **Offer bendamustine in combination with obinutuzumab, for those people who are rituximab refractory.**
- **Consider HDT-ASCR for fitter people with relapsed FL who achieve a second or subsequent remission.**
- **Consider up to 2 years of rituximab (or obinutuzumab if this agent was used for induction) maintenance for those people who have relapsed disease who have responded to re-induction therapy, have not received antibody maintenance previously and are *not* suitable for high-dose therapy.**
- **Consider RIT (where available) or idelalisib monotherapy for those in need of treatment. (Please note that idelalasib does not have a UK market authorisation for this indication and is not currently commissioned by NHS England for this purpose).**
- **Consider low-dose radiotherapy for those with relapsed disease, for symptom control.**

Management of the patient with transformed FL (tFL)

As a general rule, in the majority of the cases histological transformation in patients with FL results in a lymphoma that is clinically, histologically and molecularly indistinguishable from DLBCL, so patients should be treated according to recommendations for DLBCL, whenever possible. The management of transformation at diagnosis (also called 'discordant' or 'composite' lymphomas) is outside the scope of these guidelines, as they should be managed as *de novo* DLBCL.

Treatment of anthracycline-naïve patients at the time of transformation

In a similar fashion, patients with tFL who have received no prior chemotherapy (i.e., those managed expectantly or who have received only radiotherapy) should be treated as *de novo* DLBCL [i.e. with R-CHOP (or similar) immunochemotherapy without HDT-ASCR]. Several studies have demonstrated that patients who have not received R-CHOP prior to transformation and receive R-CHOP at the time of tFL do better than those previously treated with R-CHOP.[84] Furthermore, some series have also shown that the outcome of patients with tFL who had not received R-CHOP prior to tFL and receive this regimen at transformation is comparable to that of patients with *de novo* DLBCL treated with R-CHOP.[84,85] Along the same lines, patients who were anthracycline-naïve had a better outcome than those who had been previously treated with anthracyclines among patients not eligible for HDT-ASCR for the treatment of tFL.[86] Having received prior treatment with rituximab is not associated with a worse outcome after tFL in some series,[87] whereas in other series having received rituximab prior to tFL is associated with a worse outcome after radiochemotherapy for tFL, but not after HDT-ASCR for tFL.[86,88]

Treatment of people with tFL who have received anthracyclines previously

The treatment of patients with tFL previously exposed to anthracyclines with or without rituximab is varied and, in general, involves second-line regimens used for DLBCL in patients who are eligible for consolidation with HDT-ASCR. As in the relapsed DLBCL setting, there is no evidence that one regimen is superior to the others.[86,88,89]

Role of stem cell transplantation

Given the poor outcome of patients with tFL in the pre-rituximab era, the general recommendation was to consolidate the response with HDT-ASCR in fit patients. Data from registry studies show that the outcome of patients who had HDT-ASCR for transformed lymphoma is comparable to that of patients who received HDT-ASCR for an indolent lymphoma or for an aggressive lymphoma.[90] However, in the rituximab era, HDT-ASCR does not result in a better outcome than R-chemotherapy in chemotherapy-naïve patients treated with R-chemotherapy for tFL, whereas, in previously treated patients, the inclusion of HDT-ASCR as part of the management of tFL is associated with a better outcome in terms of PFS.[88] Other retrospective studies have suggested an advantage of HDT-ASCR over R-chemotherapy.[91] Importantly, therefore the benefit of HDT-ASCR applies specifically to patients who have previously been treated for FL or tFL, and not those who have never received systemic therapy.

Treatment for patients not eligible for HDT-ASCR

The management of patients not eligible for HDT-ASCR should focus on a palliative/symptomatic approach aiming at a durable remission with good quality of life. Ideally, these patients should be included in clinical trials, if available.

Is there a role for maintenance rituximab in the management of tFL?

Patients with tFL have been excluded from randomised trials analysing the role of maintenance rituximab in patients with FL. The role of maintenance rituximab in patients with DLBCL has been analysed in several randomised trials, either after initial therapy with R-CHOP or after HDT-ASCR.[92–94] In none of these studies did the addition of maintenance rituximab result in a better outcome. Of note, the study performed by the Groupe d'Etudé des Lymphomes de l'Adulte included patients with 'transformation at diagnosis'.[93] A recent retrospective study from the British Columbia Cancer Agency analysed the outcome of patients with 'composite or discordant' lymphoma according to whether they receive rituximab maintenance or not after R-CHOP induction. There were no differences in PFS, freedom-from-progression, freedom-from-indolent-progression or OS among the two groups of patients.[95]

Recommendations

- **Always consider enrolment in a clinical trial, where available.**
- **Offer R-CHOP to people with tFL who are anthracycline-naïve and can tolerate this therapy.**
- **Offer second-line salvage chemotherapy regimens used for DLBCL in tFL who have received prior anthracycline and are fit for HDT-ASCR.**
- **Consider HDT-ASCR in tFL patients previously treated with R-chemotherapy, who respond to salvage therapy and are fit for HDT-ASCR.**
- **There is no evidence to support the use of HDT-ASCR for patients with tFL who have not previously received systemic therapy.**
- **There is insufficient evidence to support the routine use of maintenance rituximab in patients with tFL.**

Transplantation in FL

No completed prospective trials comparing modern immunochemotherapy at relapse *versus* HDT-ASCR have been performed in rituximab-exposed patients and, to date, the evidence base in the rituximab era comes primarily from large, heterogeneous, retrospective data.

Three randomised trials[96–98] have assessed first remission HDT-ASCR (all using cyclophosphamide-total body irradiation [TBI] conditioning). No OS advantage was demonstrated and secondary malignancy rates were higher in HDT-ASCR patients.[99] This approach is therefore not recommended.

HDT-ASCR for FL

A number of large, international data sets report HDT-ASCR outcomes in FL. Briefly, these studies are difficult to compare given their retrospective nature, variable inclusion criteria, differing timing of HDT-ASCR and conditioning protocols, number of prior lines of treatment and rituximab exposure.

Across these studies, patients are younger than the unselected relapsed FL population-based registries (median age 45–55 years vs. 58 years in more inclusive relapsed/refractory [R/R] FL databases[28]). Carmustine, etoposide, cytarabine, melphalan (BEAM) is the dominant conditioning regimen used (1808/3196 patients [56·6%] in the studies outlined; Table I).[1,100–104,113–116,121] Transplant-related, non-relapse mortality (NRM) is typically low, with 100-day NRM of 1–2% and 1–3-year NRM of approximately 3%. TBI-based conditioning is associated with a higher NRM and a concerning 8–12% rate of secondary myeloid malignancies.[1,100] Outcomes broadly suggest a possible PFS plateau at 5-year

Table I. Outcomes after ASCT for FL as first transplant approach.

Centre(s), patient number, study design, study time period	Age, years, median (range)	Conditioning (%)	Line(s) of prior therapy, *n* (%) or median (range)	Survival	NRM	Comment	Reference
N = 280 Multi-centre, international prospective trial: 1999–2006	51 (26–70)	BEAM (100) +/− R purging and then +/− R maintenance	2 (79) 3 (15)	Median PFS 2·64 years (no R) Median PFS 4·18 years (R purge only) Median PFS 7·46 (maintenance R only) Median PFS not reached (R purge and maintenance)	0·4% at 100 days	Trial stopped early due to under recruitment No difference in OS at 10 years across four groups. Plateau emerging at 6 years	Pettengel *et al.*[121]
N = 626 Multi-centre, national Spanish registry (GELTAMO): 1989–2007	47 (18–73)	BEAM (53) BEAC (22) TBI-based (17)	1 (55) 2 (41) ≥3 (4)	Median PFS 9·7 years 12-year PFS 63%	2·7% at 100 days	Second cancers: 6·7% at 5 years and 12·8% at 10 years	Jimenez-Ubieto *et al.*[113]
N = 240 Multi-centre, international registry (CIBMTR): 2002–2014	56 (23–79)	TBI-based (12) BEAM or similar (71) CBV or similar (14) Bu/Mel or Bu/Cy (3)	2 (1–6)	3-year PFS 45% 5-year PFS 38%	5% at 5 years	All patients were early treatment failure (POD24) AutoSCT vs. MSD 5 year OS: 5-year OS 70% (64–76) vs. 73% (64–81)	Smith *et al.*[104]
N = 175 Multi-centre, international registry (CIBMTR and NLCS): 2002–2012	53 (22–69)	TBI-based (13) BEAM or similar (68) CBV or similar (15) Bu/Mel or Bu/Cy (3)	2 (1–6)	PFS not reported 5-year OS 73%	Not reported	All patients were early treatment failure (POD24) POD12 (*n* = 123) ASCT had higher 5-year OS than no ASCT (73% vs. 60%, *P* = 0·05)	Casulo *et al.*[102]
N = 136 Multi-centre national prospective cohort (NCCN): 2001–2009	55 (29–70)	BEAM (28) CBV (53) TBI-based (18)	3 (2–8)	3-year FFS 56% 3-year OS 86%	1% at 100 days 3% at 3 years	MVA: age >60 years and >3 prior lines: adverse factors for OS 0, 1, 2 factors: 3-year FFS: 72%, 47%, and 20% (*P* = 0·0003), and 3-year OS: 96%, 82% and 62% (*P* < 0·0001)	Evens *et al.*[101]
N = 63 Follow up study from GLSG 1996 and GLSG 2000 trials	48–53 (22–63)	BEAM (51) TBI-based (27)	2 (100)	5-year PFS in ASCT group: 52% (vs. 27% in non-ASCT group)	2% at 100 days	70% (113/162) patients POD24 in overall population: 83% (52/63) of ASCT patients: in POD24, ASCT: 5-year PFS 51% *versus* no-ASCT 19% (*P* < 0·0001)	Jurinovic *et al.*[114]

Table I. (*Continued*)

Centre(s), patient number, study design, study time period	Age, years, median (range)	Conditioning (%)	Line(s) of prior therapy, *n* (%) or median (range)	Survival	NRM	Comment	Reference
N = 726 Multi-centre, international registry (EBMT): 1998–2005	53 (21–73)	BEAM (78) Cy + TBI (16)	<3 (55) ≥3 (45)	1-year PFS 77% 3-year PFS 57% 5-year PFS 48%	2% at 100 days 3% at 1 year	Non-direct comparison with RIC alloSCT: 1-year NRM 15% vs. 3% for ASCT. 5-year relapse rate: RIC alloSCT 20% vs. ASCT 47% 5-year PFS: RIC alloSCT: 57% vs. ASCT: 48% No difference in OS	Robinson *et al.*[103]
N = 693 Multi-centre, international registry (EBMT)	45 (17–68)	TBI-based (58) BEAM (24) BEAC (6) CBV (2)	1 (30) 2 (62) ≥3 (8)	5-year PFS 44% 10-year PFS 31%	6% at 1 year 9% at 5 years	MVA: older age ($P < 0{\cdot}001$), refractory disease ($P < 0{\cdot}001$) and TBI ($P = 0{\cdot}04$) were associated with a higher NRM. 34 of 39 tMDS/AML had TBI-conditioning (8·5% TBI cases)	Montoto *et al.*[1]
N = 250 Multi-centre, international registry (CIBMTR): 2000–2012	54 (22–79)	TBI-based (14) BEAM or similar (68) CBV or similar (14)	3 (1–5)	3-year PFS 51% 5-year PFS 41%	5% at 5 years	All patients rituximab exposed Grade 1–2 patients only	Klyuchnikov *et al.*[115]
N = 136 Multi-centre, international registry (CIBMTR): 2000–2012	57 (27–76)	TBI-based (15) BEAM or similar (73) CBV or similar (15)	3 (1–5)	3-year PFS 42% 5-year PFS 36%	4% at 5 years	All patients rituximab exposed Grade 3 patients only	Klyuchnikov *et al.*[116]
N = 121 Multi-centre, retrospective international cohort: 1985–1992	43 (24–61)	CY + TBI (100)	2 (74) 3 (20) ≥4 (6)	5-year FFP 55% 10-year FFP 48%	Not reported	15 tMDS/AML cases (12%) OS for ASCT after 2 prior lines longer than ≥3 lines ($P = 0{\cdot}004$)	Rohatiner *et al.*[100]

BEAM, carmustine, etoposide, cytarabine, melphalan; BEAC: carmustine, etoposide, cytarabine, melphalan, cyclophosphamide; Bu/Cy, busulfan and cyclophosphamide; Bu/Mel, busulfan and melphalan; CBV, cyclophosphamide, carmustine and etoposide; CY, cyclophosphamide; ASCT, autologous stem cell transplantation; NLCS, National LymphoCare Study; GLSG, German low grade study group; EBMT, European Bone Marrow Transplant; CIBMTR, Centre for International Blood and Marrow Transplant Research; GELTAMO, Grupo Español de Linfoma y Transplante Autólogo de Médula Ósea; tMDS/AML, treatment related myelodysplastic syndrome/acute myeloid leukaemia; FFP, freedom from progression; R, rituximab; HR, hazard ratio; NRM, on-relapse mortality; POD24, progression of disease within 24 months; Allo-SCT, allogenic stem cell transplantation; RIC, reduced intensity conditioning.

follow-up in approximately 30–40%. Patients receiving HDT-ASCR earlier in their treatment pathway have an improved PFS[100,101] and possibly OS.[102] In summary, HDT-ASCR remains a standard option in relapsed FL, with outcomes improved when performed at second remission.

HDT-ASCR for POD24 FL

Recent retrospective series have assessed the benefit of HDT-ASCR in patients with early treatment failure (ETF; also see POD24 above) following frontline immunochemotherapy.[28] A recent non-randomised survival analysis compared 174 ETF patients treated with a non-HDT-ASCR approach with 175 patients receiving HDT-ASCR.[102] A planned subgroup analysis showed those with ETF of ≤ 1 year (n = 123) treated with HDT-ASCR had higher 5-year OS than with a non-HDT-ASCR approach (73% vs. 60%, P = 0·05). A similar analysis showed a significant PFS and OS advantage for HDT-ASCR *versus* non-HDT-ASCR in POD24 patients (5-year PFS 51% vs. 19%, P < 0·0001; 5-year OS 77% vs. 59%, P = 0·031 respectively). Although numerous caveats apply from these unmatched comparisons, the emerging evidence suggests that HDT-ASCR is an effective therapeutic option in ASCT-eligible, high-risk ETF patients.

HDT-ASCR versus *allogeneic haematopoietic stem cell transplantation (allo-SCT) as first transplant in FL*

Allo-SCT provides a lymphoma-free graft devoid of chemotherapy-induced DNA-damage, with the potential to mediate a graft-*versus*-lymphoma effect. Allo-SCT as the first transplant procedure was associated with a 3-year relapse rate of approximately 20%, and a 3-year NRM of 20–30%, with a resultant 3-year PFS and OS of 55–65% and 60–70% respectively (Table II).[103,104,115–120] The risk of acute and chronic graft-versus-host disease (GVHD) is difficult to fully assess across studies given the variable reporting of timing and grade; however, it is reputed to be 25–45% and 40–60% respectively. The largest series of patients receiving allo-SCT (n = 1567, prior HDT-ASCR 29%) showed a 3-year OS and PFS of 66% and 58% respectively, with a 3-year NRM of 25% and a relapse risk of 17%. Unsurprisingly, patients with chemo-resistance, older age, heavy pre-treatment, worse performance status and myeloablative conditioning had an inferior survival.

There are non-randomised trials directly comparing reduced-intensity conditioning (RIC) allo-SCT with HDT-ASCR in relapsed FL. Again, the evidence is formed from retrospective studies comparing these approaches in relapsed FL and more recently in ETF. An analysis by the European Society for Blood and Marrow Transplantation compared HDT-ASCR with RIC allo-SCT as first transplant in relapsed FL (54% were rituximab-exposed).[103] Improved disease control after allo-SCT (5-year relapse: allo-SCT 20% vs. HDT-ASCR 47%, P < 0·001) was offset by the 22% 3-year NRM

Table II. Outcomes after RIC-allotransplant for FL as first transplant approach.

Series	Years	N	Prior ASCT, %	Median prior lines, n	3-year NRM, %	3-year RR, %	3-year OS, %	3-year EFS/PFS, %	aGVHD/cGVHD, %
Sureda *et al.*[117]	2001–2011	1567	29	Missing	25	17	66	58	20/45
Klyuchnikov *et al.*[115]	2000–2012	268	0	4	23	19	69	61	28/60
Robinson *et al.*[103]	1998–2005	149	0	3	22	17	68	62	47·2/51·7
Klyuchnikov *et al.*[116]	2000–2012	61	0	3	21	20	61	58	25/53
Smith *et al.*[104]	2002–2014	105 MSD	0	3	MSD 15	MSD 27	MSD 75	MSD 59	MSD 35/54
		95 MUD	0	3	MUD 29	MUD 23	MUD 55	MUD 47	MUD 35/58
Hari *et al.*[118]	1997–2002	120 MAC	6	3	MAC 25	MAC 8	MAC 71	MAC 67	MAC 36/46
		88 RIC	10	3	RIC 28	RIC 17	RIC 62	RIC 55	RIC 44/62
Thomson *et al.*[119] †	1998–2009	82	21	4	15	26	76	76‡	13/18
Laport *et al.*[120] §	2009–2012	65	11	4	16	13	82	71	27/61

NRM, non-relapse mortality; RR, relapse risk; OS, overall survival; EFS, event-free survival; PFS, progression-free survival; MAC, myeloablative conditioning; RIC; reduced-intensity conditioning; MSD, matched sibling donor; MUD, matched unrelated donor; aGVHD, acute graft-*versus*-host disease; cGVHD, chronic graft-*versus*-host disease.

*At 2 years.

†At 4 years.

‡Current PFS.

§Prospective Phase II trial.

compared to 5% 3-year NRM for HDT-ASCR. PFS *beyond* 24 months post-SCT was significantly improved for allo-SCT (relative risk 4·6, 95% CI 2·4–8.7) vs. HDT-ASCR; 5-year PFS: 57% for allo-SCT vs. 48% for HDT-ASCR) with a PFS plateau. However, this did not result in an OS benefit (5-year OS: allo-SCT 67% vs. 72% HDT-ASCR; $P = 0{\cdot}84$).

Allo-SCT following HDT-ASCR

The optimal therapy for patients who relapse after an HDT-ASCR is not established. Data in rituximab-treated, post-HDT-ASCR patients receiving an allo-SCT are more limited, with small subgroups of studies reporting outcomes. The largest study [122] analysed 183 heavily pre-treated young patients (median age 45 years; median four prior lines) who had failed an HDT-ASCR at a median of 30 months prior to the subsequent RIC allo-SCT (47% matched sibling donor [MSD]; 53% matched unrelated donor [MUD]). The 2-year NRM was 27% with no reported difference according to donor source. The 5-year relapse rate, PFS and OS were 16%, 48% and 51% respectively, suggesting allo-SCT remains effective after HDT-ASCR and is able to provide durable disease control, albeit with an unsurprising yet marginally inferior survival compared to outcomes in the HDT-ASCR naïve setting.

HDT-ASCR versus *allo-SCT as first transplant in ETF/POD24*

The first large comparison[104] between allo-SCT (MUD [$n = 95$]; MSD [$n = 105$]) and HDT-ASCR ($n = 240$) patients as first transplant in those experiencing ETF demonstrated no 5-year OS difference between HDT-ASCR and MSD allo-SCT (70% vs. 73%). These outcomes were significantly superior to 5-year OS for MUD allo-SCT, an outcome driven primarily by high 5-year NRM (HDT-ASCR 5%, MSD 17%, MUD 33%; $P < 0{\cdot}001$). Relapse was lower with allo-SCT (5-year relapse: MSD 31%, MUD 23%, ASCT 58%; $P < 0{\cdot}0001$).

Collectively, these data suggest that either RIC allo-SCT or HDT-ASCR is a reasonable option in relapsed FL, particularly in those experiencing ETF. Selection between the modalities represents an ongoing challenge. The enhanced long-term disease control (particularly >24 months) post-allo-SCT needs to be balanced with the NRM risk and morbidity of chronic GVHD, infection and cytomegalovirus reactivation. Available evidence suggests MUD allo-SCT represents an inferior transplant option to HDT-ASCR or MSD allo-SCT. The NRM risk of this approach is prohibitively high and requires careful risk–benefit assessment. Patients with longer first remissions have an age-matched survival similar to the normal population[28] and as such transplantation (with particular reference to HDT-ASCR) should typically be reserved for those with a first remission close to 2–5 years, although the evidence base for selecting such patients is less clear.

Recommendations

- **Do not offer HDT-ASCR in first-line therapy for FL.**
- **TBI conditioning is not recommended for HDT with HDT-ASCR.**
- **Consider early referral for transplantation of fit people with shorter durations of response following first-line therapy.**
- **Offer RIC as the conditioning approach for allogeneic transplantation.**
- **Consider either HDT-ASCR or matched sibling RIC-allogeneic transplantation as an option for younger patients with FL with early relapse, although there is no strong evidence for superiority when comparing these options.**
- **Matched sibling donor allogeneic transplantation and RIC are favoured above matched unrelated donor allogeneic transplantation where a sibling donor is available.**

Experimental agents in FL

Novel agents have an emerging role in the management of FL, with several drugs licensed or in late stages of clinical development including new generation anti-CD20 monoclonal antibodies, small molecule pathway inhibitors of PI3K and Bruton's tyrosine kinase (BTK), and immunomodulatory agents.

Activation of the PI3K/Akt/mTOR pathway is involved in the development and progression of B- and T-cell lymphomas and is a strong prognostic marker in FL.[105] Drugs inhibiting this pathway are among the most active treatments for FL.

Phosphatidylinositol 3-kinase pathway inhibitors (other than idelalisib mentioned in section 6) with USA Food and Drug Administration (FDA) approval for relapsed or refractory FL include the oral dual PI3k δ and γ inhibitor, duvelisib and the intravenous pan-specific inhibitor, copanlisib, with predominant activity in the α and δ isoforms. Approval was based on single-arm Phase 2 trials demonstrating objective response rates of 42% for duvelisib and 58·7% for copanlisib in 83 and 104 patients with R/R FL respectively.[106] The safety profiles were acceptable and consistent with isoform specific off-target effects. The next generation dual PI3k δ and casein kinase-1ε inhibitor, umbralisib, showed promising activity (ORR 53% in 22 patients with R/R FL) in a Phase 1 dose escalation trial with a lower rate of autoimmune-like toxicities compared to other PI3k δ inhibitors. An important consideration of PI3K inhibition is that treatment requires prolonged administration (until disease progression or unacceptable toxicity) and seldom produce CRs.

Lenalidomide is an immunomodulatory drug with direct and immune-mediated mechanisms of action. Single-agent activity and manageable toxicity was reported in early phase

trials of relapsed or refractory indolent lymphoma (ORR 23%)[107] and led to several combination studies. A Phase 2 randomised trial comparing of lenalidomide alone or in combination with rituximab in 91 patients with relapsed FL demonstrated overall responses of 53% (CR 20%) and 76% (CR 39%) for lenalidomide and lenalidomide-rituximab respectively (Cancer and Leukemia Group B [CALGB] [Alliance] 50401 trial; ClinicalTrials.gov Identifier: NCT00238238).[108] Two subsequent Phase 2 single-arm trials of lenalidomide-rituximab (R2) and lenalidomide plus R-CHOP (R2-CHOP) in previously untreated FL yielded high response rates of 95% (CR 72%) and 94% (CR 74%) and treatment was well tolerated (CALGB [Alliance] 50803 trial.[109,110] The RELEVANCE trial (ClinicalTrials.gov Identifier: NCT01650701) was a Phase 3 randomised trial designed to assess superiority of R2 compared to R-chemotherapy. A total of 1030 patients with previously untreated high tumour burden FL were randomised to R2 or R-chemotherapy (CVP, CHOP, or bendamustine) over a 3-year period. The trial failed to show superiority of R2 (ORR 61% [95% CI 56–65]) vs. 65% [95% CI 61–69]) and was not powered to demonstrate non-inferiority. Furthermore, there was no difference in the rate of adverse events although the toxicity profile did differ between regimens; there was a similar rate of neutropenia events, but more febrile neutropenia and more alopecia with chemotherapy and rash was more common with R2. Whilst this regimen may have a role in the future in the management of previously untreated advanced stage symptomatic FL, it is not currently funded in the UK and longer-term follow-up is needed to understand its role as first-line treatment.[111] A more recent Phase 3 randomised comparison of R2 and rituximab-placebo in relapsed or refractory indolent NHL (including 294 patients with FL) perhaps unsurprisingly demonstrated superior outcomes for R2 (median PFS 39·4 vs. 14·1 months; HR 0·46, 95% CI 0·34–0·62; $P < 0·0001$) (AUGMENT trial, ClinicalTrials.gov Identifier: NCT01938001),[112] and it is uncertain whether these data will change practice in the UK where rituximab monotherapy is not widely used to treat relapsed FL.

The use of chimeric antigen receptor (CAR) T-cell therapy is an innovative and important therapeutic development for those with various types of B-cell lymphoma, including those with tFL. Its role in the treatment of those with relapsed FL is evolving.

Follow-up and monitoring of patients with FL

Follow-up of patients undergoing watchful waiting

There is no agreed follow-up strategy for patients undergoing watchful waiting; follow-up is aimed at detecting the development of symptoms or significant disease progression. The schedule of follow-up appointments after initial diagnosis is determined by the rate of disease progression. For most people, 3–6 monthly intervals suffice. Note that up to 20% of people with FL will attend clinic but still not have required therapy at 10 years after diagnosis. It is important to have a system in place for people with FL to access the clinic earlier, if symptoms that suggest disease progression supervene.

At each visit an enquiry about symptoms should be made as well as performing a physical examination. Any concern may warrant repeat imaging. Standard indications for considering therapy are described above. LDH measurement is discouraged as this is not an indication to initiate therapy and may generate anxiety and unnecessary investigations. What is most difficult to define is the degree of lymph node enlargement that would warrant the initiation of therapy if the patient remains asymptomatic. The GELF criteria mentioned above (section Management of patients with newly diagnosed FL) are important considerations in making the decision to offer therapy.

Follow-up of previously treated patients, including surveillance for late effects of therapy

Due to considerable variability in the rate of progression of FL, there are no set standard guidelines for routine patient follow-up after therapy. The frequency of follow-up visits and the means used to monitor disease progression should therefore be tailored to the individual patient's disease and expectations, as well as possible subsequent treatment modalities. Progress imaging should only be considered if the disease is difficult to assess by clinical means, e.g. prominent but asymptomatic abdominal disease may warrant progress imaging during the monitoring phase.

Approximately 80% of treated patients achieve a first remission of >2 years and have a gender and age-matched survival comparable to the normal population.[28] As such, it is important to focus on survivorship, to empower these patients to adjust to living with a low-grade lymphoma over many years, which will carry an excellent prognosis. With this in mind, long-term adverse effects of chemo-immunotherapy must also be carefully considered in the front-line treatment decision. Patients receiving chemotherapy regimens or HDT-ASCR need to be monitored for the development of myelodysplasia and the late effects of cardiotoxic agents.

Recommendations for follow-up of patients with FL

- **Offer clinical assessment with history and clinical examination regularly, modified according to the disease behaviour.**
- **Consider performing a full blood count, urea and creatinine, liver function tests at each clinical visit. A LDH level should not be performed routinely.**
- **Offer thyroid function testing yearly in patients who have undergone irradiation of the neck.**
- **Offer cross-sectional imaging following treatment only on suspicion of relapse requiring therapy (e.g. the advent of clinically significant lymphadenopathy, not**

attributable to another cause, or B symptoms). There is no role for routine scanning of patients following therapy.

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Conflict of Interest

The BSH paid the expenses incurred during the writing of this guidance. All authors have made a declaration of interests to the BSH and Task Force Chairs which may be viewed on request. None of the authors have conflicts of interest to declare.

Review Process

Members of the writing group will inform the writing group Chair if any new pertinent evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be archived and removed from the BSH current guidelines website if it becomes obsolete. If new recommendations are made an addendum will be published on the BSH guidelines website (https://b-s-h.org.uk/guidelines/).

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