

## *Follicular lymphoma – EML*

The application sought inclusion of medicines used in the treatment of follicular lymphoma in the core list of the Essential Medicines List. In addition, the application sought the addition of rituximab and bendamustine and the Expert Committee's endorsement of cyclophosphamide, vincristine, prednisone and doxorubicin, which are currently included in the complementary list, for use in this indication.

The application, amended to include details of the Expert Committee's considerations and decision, is presented in this section.

### **Introduction**

Follicular lymphoma (FL) is the most common indolent lymphoma and the second most common non-Hodgkin lymphoma – accounting for about 10–20% of all lymphomas in developed countries. The incidence of FL, as of other non-Hodgkin lymphomas, is rising, although it varies between geographical regions and ethnic groups; incidence is lower in Asian and sub-Saharan African countries than in western regions, probably as a result of both genetic and environmental factors (1, 2).

The initial symptoms of FL include painless swelling in one or more lymph nodes, particularly in the cervical, axillary, inguinal and femoral regions. The median age at diagnosis is 55–60 years and there is a slight preponderance in women. The progression of FL varies, in terms of the speed of the tumour's growth and the involvement of other organs. Some people diagnosed with FL will have no symptoms for many years and need no treatment. Approximately 45% of cases (3% of FL patients per year) eventually transform – or progress – to an aggressive disease that resembles diffuse large B-cell lymphoma. Transformation severely worsens outcomes and 10-year survival drops from 75% to 36% for patients with transformed FL (3).

Although prognosis has improved substantially over the past two decades, a cure for FL has remained elusive. Treatment therefore depends upon a person's symptoms, tumour grade, age and general health (4). Most people with FL have widespread disease when first diagnosed; bone marrow involvement is common and present in more than 50% of patients. The vast majority of patients present with advanced (stage III–IV) disease but are often asymptomatic. The disease is usually characterized by an indolent course, response to initial therapy with frequent relapses and shorter duration of response to salvage therapy (5). Because cure is not possible and early treatment does not improve overall survival, treatment should be started on the basis of symptoms associated with tumour burden as determined using Group d'Etude des Lymphomes Folliculaires (GELF) criteria or the Follicular Lymphoma International Prognostic Index (FLIPI), or if there is rapid lymphoma progression.

The standard of care for the treatment of symptomatic disease in high-income countries is combination chemotherapy plus immunotherapy with the humanized monoclonal anti-CD20 antibody, rituximab (R). Chemotherapy is often based on a

combination of cyclophosphamide, vincristine and prednisone (CVP); the cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) combination is sometimes used, particularly in patients with large tumour burden or high-grade disease. All cases of grade 1–3a disease are treated with R-CVP or bendamustine–rituximab (B-R), according to the paradigms for FL and other indolent lymphomas; grade 3b FL is treated as an aggressive B-cell non-Hodgkin lymphoma and may be cured with R-CHOP. For patients with grade 1–3a disease, CHOP offers no advantage over CVP, and has the added toxicity of an anthracycline. Recently, B-R has been shown to be as good as, or superior to, R-CVP. While rituximab is more costly than the drugs of the CVP combination and is more difficult to administer, its availability has been partly responsible for improved median overall survival in patients with FL (6).

### **Public health relevance**

Epidemiological data pertaining to low-grade follicular lymphomas are limited. However, the incidence of general follicular lymphomas is known to account for about one third of non-Hodgkin lymphomas (NHLs) (7). Epidemiological information for NHLs serves as an approximation for follicular lymphomas.

GLOBOCAN estimates global incidence of total NHLs in 2012 to be 385 741 (age-standardized rate (ASR) of 5.0 per 100 000) (8). The incidence of NHLs in more developed regions (190 403 with an ASR of 8.6 per 100 000) was more than twice that in less developed regions (190 811 with an ASR of 3.6 per 100 000). According to GLOBOCAN, NHLs seem to affect North America, South Africa and the United Kingdom more than other regions. The 2012 prevalence of NHLs in men and women was 463 300 and 162 200 respectively. Global mortality rate due to all NHLs in 2012 was estimated to be 199 670 (ASR of 2.5 per 100 000).

### **Requirements for diagnosis, treatment, and monitoring**

#### *Diagnosics*

An accurate diagnosis of lymphoma is paramount. Excisional lymph node or tissue biopsies are needed for definitive histopathological diagnosis. Although FL has characteristic morphological features, diagnosis requires immunohistochemical stains. This requires a histological specimen (haematoxylin and eosin stain), immunostaining for B-cell markers CD79a and CD20, the T-cell marker CD3 and the proliferative marker Ki67. Immunohistochemical detection of CD20 antigen on malignant B-lymphocytes is required where treatment with R-CHOP is possible. Further immunostaining for CD5, CD23, CD10, cyclin D1 and CD21 allows differentiation of low-grade lymphomas into FL, mantle-cell NHL, marginal-zone lymphoma and small-cell lymphocytic lymphoma.

Grading of FL can be helpful in determining prognosis and optimal therapy. Grading is based on the number of centroblasts per high-powered field (grade 1, 0–5; grade 2, 6–15; grade 3, >15; in grade 3a, centrocytes are also present but in grade 3b there are sheets of centroblasts. This is important because all cases of grade 1–3a FL are treated according to

the paradigms for FL and other indolent lymphomas, whereas grade 3b FL is treated as an aggressive B-cell NHL.

### *Testing*

Staging of FL is done in accordance with the Ann Arbor staging system. Contrast computerized tomography is the basic imaging technique required for staging; <sup>18</sup>F-FDG (fludeoxyglucose) positron emission tomography is not required, except for excluding distant involvement in apparent stage I or II FL, and is not routinely recommended. If the patient is considered to have stage I or II disease and local radiation is considered, a bone marrow biopsy is required to rule out stage IV disease.

Full blood count, biochemistry and lactate dehydrogenase (LDH) are required to assess tumour load, bone marrow function, and critical organ function, including renal and hepatic function. The role of pretreatment cardiac function assessment with echocardiography or nuclear imaging is controversial and probably unnecessary.

### *Administration and care of patients*

Administration requires intravenous infusion capacity, and the patient must have regular access to clinical care. In developed countries, administration of chemotherapy is usually performed in outpatient facilities, although patients may be treated as inpatients in other settings. Antiemetics should be given to all patients being treated with CVP, R-CVP, CHOP, R-CHOP and B-R. Intravenous hydration is required for the cyclophosphamide-containing regimens. Care should be taken to avoid extravasation of both doxorubicin and vincristine, which may cause severe soft tissue injury and necrosis. Rituximab can cause allergic reactions and anaphylaxis and must be given slowly, with close monitoring and supportive medicines readily available, including adrenaline, steroids and antihistamines. Premedication with paracetamol 650 mg orally, hydrocortisone 100 mg IV, and diphenhydramine 25–50 mg IV 30–60 minutes before rituximab (at least before the first rituximab dose) is recommended and can be scaled back if there is no reaction to the first dose. If the patient has evidence of hepatitis B or C infection, this should be monitored since administration of rituximab can reactivate either of these infections. Given the severe consequences associated with reactivated infection, screening and prophylaxis against hepatitis B is recommended.

Monitoring requires that clinicians have access to laboratory facilities, as well as the ability to recognize and address potential adverse events related to the effects of FL and to the treatment, including bone marrow suppression, infection, allergic reactions to rituximab, and gastrointestinal toxicity. Social and financial well-being can be affected by the side-effects of treatment and should also be monitored and addressed.

### **Overview of regimens**

The following includes basic information on administration and dosing for rituximab, B-R, R-CVP and R-CHOP; no details are given of ancillary medications pertaining to the management of adverse events. Where rituximab is administered as monotherapy for

asymptomatic advanced disease, it is given weekly for 4 weeks. For both CHOP and R-CHOP, six cycles of therapy are recommended.

- **Local disease (stage I or contiguous stage II)**
  - involved-field radiotherapy (RT) 30–36 Gy
- **Advanced asymptomatic disease**
  - observation (“watch-and-wait”)
  - or, for advanced disease with low tumour burden:*
    - rituximab 375 mg/m<sup>2</sup> IV on day 1 (if available/affordable)
    - or*
    - bendamustine 90 mg/m<sup>2</sup> IV on days 1 and 2
    - rituximab 375 mg/m<sup>2</sup> IV on day 1 (if available/affordable)

The Expert Committee noted, however, that in elderly, frail or pretreated patients, the dosage of bendamustine should be reduced to 70–80mg/m<sup>2</sup> in order to avoid haemotoxicity.

*Standard regimen for advanced symptomatic disease, grades 1–3a*

- **R-CVP (every 3 weeks x 6 cycles)**
  - rituximab 375mg/m<sup>2</sup> IV on day 1 (if available/affordable)
  - cyclophosphamide 750 mg/m<sup>2</sup> IV on day 1
  - vincristine 1.4 mg/m<sup>2</sup> IV on day 1 (capped at 2 mg total dose)
  - prednisone 100 mg/day orally on days 1–5

*Standard regimen for advanced symptomatic disease, high-grade disease 3b (should be treated similarly to diffuse large B-cell lymphoma)*

- **R-CHOP (every 3 weeks x 6 cycles)**
  - rituximab 375mg/m<sup>2</sup> IV on day 1 (if available/affordable)
  - cyclophosphamide 750 mg/m<sup>2</sup> IV on day 1
  - doxorubicin 50 mg/m<sup>2</sup> IV on day 1
  - vincristine 1.4 mg/m<sup>2</sup> IV on day1 (capped at 2 mg total dose)
  - prednisone 100 mg/day orally on days 1–5

## **Review of benefits and harms**

### *Benefits*

#### **Limited-stage FL**

Approximately 10–20% of patients with FL present with limited (stage I and contiguous stage II) disease. In these patients, involved-field or extended-field radiotherapy (RT) with 30–36 Gy without additional chemotherapy is highly effective and will achieve durable long-term remission in more than 50% of cases. In a large study of 6568 patients with stage I or II disease diagnosed between 1973 and 2004, patients who received RT had better 5-year (90% vs 81%), 10-year (79% vs 66%) and 20-year (63% vs 51%) disease-specific survival rates and 5-year (81% vs 71%), 10-year (61% vs 48%) and 20-year (35% vs 23%) overall survival rates compared with those treated with other therapeutic approaches (9). Involved-field

radiotherapy is therefore the standard of care for most patients with limited-stage FL, with systemic treatment (as given to patients with advanced-stage disease) considered only for patients with a high tumour burden and those who do not respond to initial radiotherapy.

In selected patients with stable, low-bulk stage I and II disease, deferred therapy may also be an acceptable approach to initial management. In a retrospective analysis from Stanford University, more than half of patients remained untreated at a median of 6 or more years, and survival was comparable to that observed in patients given immediate treatment (10). The Committee noted that other data suggest that there is no difference in overall survival between radiotherapy and observation and considered that observation should also be considered as a standard treatment for limited-stage disease.

### **Advanced-stage FL**

The majority of patients have advanced disease at diagnosis but most are asymptomatic. Since cure of FL is generally not possible, the main reason for starting treatment is to improve symptoms and/or avoid complications. Selection of patients for treatment, as opposed to observation, is therefore often made on the basis of certain features of active disease, including progressive enlargement of lymph nodes, B symptoms (fever, weight loss or night sweats) or bone marrow failure and/or on the basis of an assessment of tumour burden. The tumour burden in FL can be defined in different ways but is often defined using the GELF criteria or FLIPI (11).

This approach is supported by a number of randomized controlled trials (RCTs) comparing observation with “watch and wait” versus immediate treatment, which showed that immediate treatment does not yield longer survival. A study by Ardeschna et al. demonstrated clearly that, when compared with patients treated with oral chlorambucil – an alkylating agent – survival among patients in the “watch and wait” cohort was at least as long (12). More recently, Ardeschna and colleagues investigated the use of rituximab monotherapy in FL patients with low tumour burden (13). This RCT showed that, compared with watchful waiting, the immediate use of rituximab significantly prolonged time to initiation of new therapy and improved mental adjustment to illness and coping; however, it had no impact on quality of life or overall survival. Thus, while rituximab therapy for patients with newly diagnosed disease without GELF criteria may be an option in resource-rich environments where this approach is subsidized, a “watch and wait” strategy remains the most common approach for most patients with advanced asymptomatic FL.

There is no debate about the need for treatment in patients with symptomatic advanced FL. Such patients have traditionally been treated with combination chemotherapy (CHOP or CVP), but the benefit of adding rituximab to this treatment has been clearly established in recent RCTs, all of which demonstrated improvements in response rates, time to progression and overall survival (14-16). A systematic review and meta-analysis of all relevant trials from 1990–2005 that compared rituximab with non-rituximab-containing regimens in patients with newly diagnosed or relapsed indolent lymphoma established that R-chemotherapy was associated with superior response rates and duration of response and

with a 65% reduction in the risk of death due to lymphoma (17). In an effort to establish which chemotherapy regimen is best, the Fondazione Italiana Linfomi conducted the FOLL05 trial, comparing R-CVP, R-CHOP and R-FM (fludarabine and mitoxantrone) in 534 patients with stage II–IV FL (18). Results showed that R-CVP was associated with an inferior time-to-treatment failure (TTF) (47%) compared with R-FM (60%) and R-CHOP (57%). The anti-lymphoma activity of R-CHOP was similar to that of R-FM, but R-CHOP had a better toxicity profile and was associated with less risk of second malignancy. Generally, R-CVP is considered to be the standard of care for patients with grade 1–3a disease and R-CHOP for patients with grade 3b disease.

Data on the effectiveness and safety of rituximab confirm an overall survival advantage, irrespective of choice of chemotherapy regimen. In absolute terms, this corresponds to 28 patients who would need to be treated with R-chemotherapy to prevent one additional death in two years (95% CI: 21–50).

In recent years evidence has begun to emerge that bendamustine plus rituximab (B-R) may offer better results than R-CHOP in patients with advanced FL, mantle-cell and other indolent lymphomas. Complete response (CR) rates were higher with B-R (40% vs 30%,  $P=0.021$ ), progression-free survival longer (55 months vs 35 months,  $P < 0.01$ ) and the toxicity profile better (grade 3–4 neutropenia 2.25 times less frequent with B-R than with R-CHOP) (19). The comparable effectiveness of B-R to that of R-CHOP on surrogate outcomes (i.e. overall response) was confirmed in a second large, multi-centre RCT, again with a favourable safety profile (20). Median overall survival data were not yet mature because patients were still being followed up. Although the B-R regimen was associated with a significantly higher incidence of drug hypersensitivity, vomiting and nausea than the R-CVP regimen, it offered a different toxicity profile. In a disease that affects mostly elderly individuals, the toxic effects of CHOP and CVP regimens are a particular concern because existing comorbidities or impaired organ function can compromise the ability to tolerate cytotoxic chemotherapy. Even considering that results for the R-CHOP regimen were inferior compared with those noted in other studies, the effectiveness of bendamustine was clinically highly relevant, confirming the favourable and unique safety profile of bendamustine, and the equivalent efficacy to CHOP and CVP chemotherapies.

Recent trials have investigated the role of rituximab maintenance after first-line therapy, and in patients with relapsed or refractory FL, in increasing progression-free survival, time to treatment failure and overall survival. The PRIMA trial compared 2 years of maintenance rituximab every 8 weeks with observation in patients with previously untreated FL who had received immunochemotherapy induction. Progression-free survival at 36 months was longer in the rituximab maintenance group (74.9% vs 57.6%), but there was no difference in overall survival. Patients who received maintenance therapy were also more likely to be in remission at the end of maintenance therapy but had more grade 2–4 infections (21). The lowered risk of disease progression after responding to induction is likely to be preferred by patients with FL, but this preference should be balanced with the constraints and costs associated with several years of rituximab maintenance.

An RCT that aims to assess the addition of rituximab maintenance after B-R induction (i.e. StiL NHL (MAINTAIN) ClinicalTrials.gov Identifier: NCT00877214) is in process and no data are yet available.

The addition of bendamustine to rituximab has been explored only in single-arm trials. Results have confirmed the promising clinical activity of bendamustine, with acceptable toxicity, in patients with indolent B-cell, rituximab-refractory lymphoma.

The Committee noted the outcomes of the recently published RESORT trial in which patients with low-burden FL were randomized either to maintenance rituximab or to rituximab only at relapse. With a median follow-up of 4–5 years, there was no difference in median time to treatment failure between the two treatment arms (22).

The vast majority of patients with FL will ultimately relapse. In these situations, salvage immunochemotherapy will often offer disease control. In resource-rich countries, autologous stem cell transplantation may be used to consolidate remission in patients with relapsed FL, achieving long-lasting remissions and a plateau in long-term survival curves in patients with all grades of FL (23).

#### *Harms and toxicity considerations*

##### **Common**

Patients receiving CHOP and R-CHOP will experience alopecia and blood count suppression, particularly neutropenia, which increases the risk of infection. In spite of this, the incidence of serious infection in these patients is low ( $\leq 5\%$ ) (14, 18, 19). Vincristine may cause peripheral and autonomic neuropathy, particularly in older patients, but this is usually mild and reversible.

The CVP and R-CVP regimens have a similar toxicity profile to CHOP regimens, but adverse effects are generally milder. Peripheral neuropathy from vincristine and gastrointestinal toxicity are the most common adverse effects of CVP regimens; patients do not experience alopecia (24).

Because rituximab can cause significant systemic allergic reactions during administration, special precautions must be taken, particularly during the first infusion. It is important that rituximab is administered slowly and that appropriate medicines are available both for premedication and to treat allergic reactions as necessary.

Bendamustine causes severe (grade 3–4) lymphocytopenia in most patients; neutropenia and thrombocytopenia are also common (19). Patients may experience dermatological effects, including rash and pruritus, although these are typically mild (25).

##### **Serious**

Doxorubicin is associated with a risk of congestive heart failure. The risk is dose-dependent and, at the doses delivered with 6 cycles of CHOP or R-CHOP (300 mg/m<sup>2</sup>), small and is considered to be outweighed by the potential benefits of treatment.

Rituximab may also cause neutropenia and, infrequently, viral infection or reactivation of latent viral infection, including viral hepatitis and JC virus, resulting in progressive multifocal leukoencephalopathy (26).

The risk of long-term bone marrow damage or secondary malignancies is small (less than 1%) but significant and is similar across the treatment regimens detailed above (18, 19).

### **Recommendations**

The Expert Committee acknowledged that systemic treatment of FL is considered only for patients with high tumour burden, for those who do not respond to initial radiotherapy, and for patients with symptomatic-stage FL. The Committee also acknowledged that diagnosis, staging, grading, treatment and monitoring of FL require access to clinical care with laboratory, imaging and intravenous infusion capacity and considered that there is a public health need to add to existing CHOP or CVP regimens for patients with advancing FL. Therefore, and on the basis of the available evidence, the Committee made the following recommendations in relation to treatment for advanced symptomatic follicular lymphoma with the goal of achieving remission:

- that rituximab and bendamustine be added to the complementary list;
- that cyclophosphamide, doxorubicin, vincristine and prednisone, currently on the complementary list, should be specifically endorsed for this indication.

The Committee noted that maintenance therapy with rituximab has not been shown to be associated with a relevant clinical benefit over rituximab treatment at relapse. The Committee therefore did not recommend inclusion of rituximab on the EML for use in maintenance treatment of FL.

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