FOLLICULAR LYMPHOMA

Executive Summary

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 Western countries. The incidence of FL, as with other non-Hodgkin lymphoma, is rising, although varies between geographical regions and ethnic groups – being lower in Asian and sub-Saharan African countries than in western regions – likely as a combination of both genetic and environmental factors. [1][2]

The initial symptoms of follicular lymphoma 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 old and there is a slight preponderance in women. The progression of FL varies, depending upon the speed of the tumor’s growth and the involvement of other organs. Sometimes people with FL will have no symptoms for many years and do not need treatment. Some cases of FL either behave like or transform into a more aggressive form of NHL, such as DLBCL. Approximately 45% (3% of FL patients per year) eventually transform (progress) to an aggressive disease that resembles diffuse large B-cell lymphoma (DLBCL). Transformation severely worsens outcomes and 10-year survival drops from 75% to 36% for patients with transformed FL. [3]

The prognosis of FL has improved substantially over the past 2 decades but a cure for FL has remained elusive. Treatment therefore depends upon a person’s symptoms, tumour grade, age and general health. [4] The majority of people with FL have widespread disease when first diagnosed. Bone marrow involvement is common and is present in more than 50% of patients. The vast majority of patients present with advanced (stage III-IV Ann Arbor stage 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 (OS), treatment should be started on the basis of symptoms associated with tumour burden (GELF criteria) 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. Chemotherapy in this circumstance has often been a combination of cyclophosphamide, vincristine and prednisone (CVP). CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) is sometimes used, particularly in patients with large tumor burden or high grade disease. All grade 1-3a FL are treated according to the paradigms of FL and other indolent lymphomas, with R-CVP or B-R, whereas grade 3b FL is treated as an aggressive B cell NHL and may be cured with R-CHOP. For patients with grade 1-3a disease, CHOP gives no advantage over CVP, and has the added toxicity of an anthracycline. More recently bendamustine-rituximab (B-R) has been shown to be as good or superior to R-CVP. While rituximab is more costly than the drugs comprising CVP and is more difficult to administer, the availability of rituximab has been partly responsible for
improved median OS in patients with FL. [6] Consequently, we recommend that rituximab be added to the Essential Medicines List.

Public Health Relevance

Epidemiologic data pertaining to low-grade follicular lymphomas is limited. However, the incidence of general follicular lymphomas is known to account for about one-third of non-Hodgkin lymphomas (NHLs) (24). Epidemiological information for NHLs serves as an approximation for lesser-known information concerning follicular lymphomas.

GLOBOCAN estimates global incidence of total NHLs in 2012 to be 385,741 (ASR of 5.0 per 100,000) (25). The incidence of NHLs in more developed regions (190,403 with an ASR of 8.6 per 100,000) was more than twice the incidence found in less developed regions (190,811 with an ASR of 3.6 per 100,000). According to GLOBOCAN, NHLs seem to affect North America, the United Kingdom, and South Africa more than other regions. The 2012 prevalence of NHLs in men was 463,300 versus a prevalence of 162,200 in women. 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

Diagnostics:

An accurate diagnosis of lymphoma is paramount.

Excisional lymph-node or tissue biopsies are needed for definitive histopathological diagnosis. While FL has characteristic morphological features, immunohistochemical stains are needed for diagnosis. This requires a histological specimen (H and E stain), immunostaining for B cell markers CD79a and CD20, the T cell marker CD3 and the proliferative marker Ki67. (With Ki67 a cut-off of less than 30% is consistent with low-grade lymphoma.) Immunohistochemical detection of CD20 antigen on malignant B-lymphocytes is required where treatment with R-CHOP is possible. Further immunostaining with CD5, CD23, CD10 cyclin D1 and CD21 allows differentiation of low-grade lymphoma’s 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 number of centroblasts per high powered field (grade 1 0-5, grade 2 6-15, grade 3 >15 (with grade 3a having centrocytes also present but grade 3b having sheets of centroblasts). This is important because all grade 1-3a FL are treated according to the paradigms of FL and other indolent lymphomas, whereas grade 3b FL is treated as an aggressive B cell NHL and may be cured with RCHOP.

Testing:

Staging of FL is done in accordance with the Ann Arbor staging system. Contrast CT is the basic imaging technique required for staging. $^{18}$F-FDG-PET is not required for staging, 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 pre-treatment cardiac function with echocardiography or nuclear imaging is controversial and is likely not required.

**Administration and Care of Patients:**
Administration requires intravenous infusion capacity, and requires that the patient have regular access to clinical care. In developed countries, administration of chemotherapy is usually performed in out-patient facilities, though in other settings, patients may be treated as in-patients. Anti-emetics should be given to all patients being administered 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 and this 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, including adrenaline, steroids and antihistamines, readily available. Premedication with tylenol 650mg PO, hydrocortisone 100mg IV, and diphenhydramine 25-50mg IV 30-60 minutes prior to rituximab (at least prior to the first rituximab) is recommended and can be scaled back if there was no reaction to the first dose).

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

**Overview of Regimens**
The following tables include basic information on administration and dosing for rituximab, CHOP and R- CHOP, and exclude ancillary medications pertaining to the management of side effects. Where rituximab is administered as monotherapy for asymptomatic advanced disease it is given weekly for 4 weeks. For both CHOP and R-CHOP 6 cycles of therapy is recommended.

**Local Disease (Stage I or contiguous Stage II)**
- Involved Field radiotherapy (RT) 30-36 Gy

**Advanced Asymptomatic Disease:**

**Essential Regimen**
- Observation (‘watch-and-wait’)

**Advanced Regimen**
- Observation (‘watch-and-wait’)
- Or Advanced disease with low tumor burden (if rituximab available)
- Rituximab monotherapy, weekly for 4 weeks
- Rituximab: 375mg/m² IV, day 1
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Standard regimen – Bendamustine-Rituximab

*B-R administered every 4 wks x 4 cycles

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bendamustine</td>
<td>90 mg/m2</td>
<td>IV</td>
<td>1,2</td>
</tr>
<tr>
<td>Rituximab*</td>
<td>375 mg/m2</td>
<td>IV</td>
<td>1</td>
</tr>
</tbody>
</table>

Standard Regimen for advanced symptomatic disease, grades 1-3a

R-CVP: q 3 wks, 6 cycles

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab*</td>
<td>375 mg/m2</td>
<td>IV</td>
<td>1</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>750 mg/m2</td>
<td>IV</td>
<td>1</td>
</tr>
<tr>
<td>Vincristine**</td>
<td>1.4 mg/m2</td>
<td>IV</td>
<td>1</td>
</tr>
<tr>
<td>Prednisone</td>
<td>100 mg/day</td>
<td>orally</td>
<td>1-5</td>
</tr>
</tbody>
</table>

Essential regimen for advanced symptomatic disease, high-grade disease 3b (should be treated similar to Diffuse Large B-cell lymphoma)

R-CHOP: q 3 wks, 6 cycles

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab*</td>
<td>375 mg/m2</td>
<td>IV</td>
<td>1</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>750 mg/m2</td>
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</tr>
<tr>
<td>Doxorubicin</td>
<td>50 mg/m2</td>
<td>IV</td>
<td>1</td>
</tr>
<tr>
<td>Vincristine**</td>
<td>1.4 mg/m2</td>
<td>IV</td>
<td>1</td>
</tr>
<tr>
<td>Prednisone</td>
<td>100 mg daily</td>
<td>orally</td>
<td>1-5</td>
</tr>
</tbody>
</table>

*If rituximab is not available or affordable, regimens should be given as listed without rituximab

**Vincristine dose always capped at 2 mg total dose

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 more than half will enjoy durable long-term remission. In a large study of a population database of 6568 patients with stage I or II disease diagnosed between 1973-2004, patients who received a RT enjoyed higher 5-year (90 v 81%), 10 year (79 v 66%) and 20-year (63 v 51%) disease-specific survival rates and 5-year (81 v 71%), 10-year (61 v 48%) and 20 year (35 v 23%) overall survival rates when compared with other therapeutic approaches. [7] As a result, involved field radiotherapy is the standard of care for most patients with limited stage FL, with systemic
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treatment like that given to patients with advanced stage disease considered only for patients with high tumour burden or for those who do not respond to initial radiotherapy. In selected patients with stable, low-bulk Stage I/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 undergoing immediate treatment. [8]

**Advanced Stage FL**
The majority of patients have advanced disease at diagnosis but most are asymptomatic. As cure of FL is generally not possible, the main reasons to commence treatment are to improve symptoms and/or improve survival. Selection of patients for treatment, as opposed to observation (‘watch-and-wait’) are 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 Group D’Etude des Lymphomes Folliculaires (GELF) criteria. [9]

**GELF Criteria**
- Normal lactate dehydrogenase (LDH)
- Largest nodal or extranodal mass <7cm
- No more than 3 nodal sites with a diameter >3cm
- Less than 5 x 10^9/L circulating tumour cells
- Hemoglobin >10g/dL, absolute neutrophil count >1.5 x 10^9/L, platelets >100 x 10^9/L
- No significant serous effusions
- No risk of organ compression or compromise
- Spleen <16cm by CT scan.

This approach is supported by a number of RCTs that compared observation with (watch and wait) versus immediate treatment which show that immediate treatment does not yield longer survival. A study by Ardesna et al demonstrated clearly that when compared with oral chlorambucil – an alkylating agent – patients in the watch-and-wait cohort had at least as long a survival as the treated group. [10] More recently, Ardesna and colleagues have investigated the use of rituximab monotherapy in low tumour burden FL patients. [11] This RCT showed that the immediate use of rituximab significantly prolonged time to initiation of new therapy compared with watchful waiting and improved mental adjustment to illness and coping but had no impact on quality of life and no impact on overall survival. As a consequence, while rituximab therapy for patients with newly diagnosed disease without GELF criteria may be an option for patients in resource-rich environments where it is subsidized for this use, for most patients a watch-and-wait strategy remains the most common approach to asymptomatic advanced FL.

There is no controversy, however, regarding the need for treatment in patients who have symptomatic advanced FL. While such patients have traditionally been treated with combination chemotherapy, CHOP or CVP, in recent years the benefit of adding rituximab to combination chemotherapy has been clearly established in RCTs – all of which demonstrate improvements in response rates, time to progression and overall survival. [12][13][14] Indeed a systematic review and meta-analysis of all relevant trials from 1990-2005 comparing rituximab to 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 a 65% reduction in the risk of death due to lymphoma. [15] In regards to which chemotherapy regimen is best - the FOLL05 trial conducted by the Fondazione Italiana Linfomi (FIL) compared R-CVP, R-CHOP and R-FM in 534 patients with stage II-IV FL. [16] This found R-CVP was associated with an inferior time-to-treatment failure (TTF) 47% compared with R-FM (60%) and R-CHOP (57%). R-CHOP had an anti-lymphoma activity similar to R-FM but had a better toxicity profile and was associated with less risk of second malignancy. Most consider R-CVP standard of care for patients with grades 1-3a disease, and R-CHOP for patients with grade 3b disease. In recent years evidence has begun to emerge that bendamustine plus rituximab (B+R) may offer better results that R-CHOP in patients with advanced FL, mantle cell and other indolent lymphoma – with higher CR rates (40 v 30% p 0.03), longer PFS (55 months v 35 months p < 0.01) and a lower toxicity profile. [17]

Recent trials have investigated the role of rituximab maintenance after first-line therapy and in patients with relapsed or refractory FL in an effort to increase progression-free survival (PFS), 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. This study found a longer PFS at 36 months in the rituximab maintenance group (74.9% v 57.6%) but no difference in overall survival. Patients who received maintenance therapy were also more likely to be in remission at the end of the maintenance therapy but had more grade 2-4 infections. [18]

The vast majority of patients with FL will, however, ultimately relapse. In these situations, salvage immunochemotherapy will often offer disease control. In resource-rich countries autologous stem cell transplantation (ASCT) 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. [20]

Harms and Toxicity Considerations

Common
Bendamustine causes severe (grade 3-4) lymphocytopenia in most patients, neutropenia and thrombocytopenia are also common. [17] Patients may experience dermatologic effects including rash and pruritus, though the reaction is typically mild. [21]

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 (≤5%) [12,16,17]. 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 as compared to CHOP regimens, but generally adverse effects are more mild. Peripheral neuropathy from vincristine and gastrointestinal toxicity are the most common adverse effects CVP regimens, patients do not experience alopecia.[22]

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 medicines are available both as premedications and to treat allergic reactions as required.

**Serious**

Doxorubicin is associated with a risk of congestive heart failure. This risk is dose-dependent and at the doses delivered with 6 cycles of CHOP or R-CHOP (300 mg/m²), the risk is small and far out-weighed by 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 multiformal leukoencephalopathy. [23]

The risk of long-term bone marrow damage or secondary malignancies is small (less than 1%) but significant. This risk is similar across the treatment regimens above.[16,17]

**Systematic Reviews**


**Background:** Addition of the anti-CD20 monoclonal antibody rituximab to chemotherapy (R-chemo) has been shown to improve response rates and progression-free survival in patients with indolent or mantle cell lymphoma. However, the impact of R-chemo on overall survival is unclear. We performed a comprehensive systematic review and meta-analysis to examine the efficacy of combined immunochemotherapy using R-chemo compared with the identical chemotherapy alone with respect to overall survival in patients with advanced indolent lymphoma or mantle cell lymphoma.

**Methods:** Medical databases and conference proceedings were searched for randomized controlled trials published from January 1990 through December 2005 that compared R-chemo with chemotherapy alone in patients with newly diagnosed or relapsed indolent lymphoma or mantle cell lymphoma. We included full-text and abstract publications. Endpoints were overall survival, disease control, overall response, and toxicity. A fixed-effects model was assumed in all meta-analyses. For binary data, the relative risk was used as an indicator of treatment effect, and the Mantel-Haenszel method was used to pool relative risks. Statistical tests for heterogeneity were one-sided; statistical tests for effect estimates were two-sided. **Results:** Seven randomized controlled trials involving 1943 patients with follicular lymphoma, mantle cell lymphoma, or other indolent lymphomas were included in the meta-analysis. Five studies were published as full-text articles, and two were in abstract form. Patients treated with R-chemo had better overall survival (hazard ratio [HR] for mortality = 0.65; 95% confidence interval [CI] = 0.54 to 0.78), overall response (relative risk of tumor response = 1.21; 95% CI = 1.16 to 1.27), and disease control (HR of disease event = 0.62; 95% CI = 0.55 to 0.71) than patients treated with chemotherapy alone. R-chemo improved overall survival in patients with follicular lymphoma (HR for mortality = 0.63; 95% CI = 0.51 to 0.79) and inpatients with mantle cell lymphoma (HR for mortality = 0.60; 95% CI = 0.37 to 0.98). However, in the latter case, there was heterogeneity among the trials (P = .07), making the survival benefit less reliable. **Conclusion:**
In patients with indolent or mantle cell lymphoma, R-chemo is superior to chemotherapy alone with respect to overall survival.

Recommendations

The reviewers recommend the incorporation of follicular lymphoma treatment options into the WHO Model List of Essential Medicines, and recommend specifically that rituximab and bendamustine be added to the core Essential Medicines List.

Additions proposed for Section 8.2 of the EML

Rituximab
Bendamustine
References


[22] Freedman AS, Friedberg JW. Initial treatment of advanced stage (III/IV) follicular lymphoma. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA, 2014.

