# Follicular Lymphoma

Drs. Kevin Imrie & Matthew Cheung
Updated August 2007*

**Updates:** Rituximab maintenance therapy

## Introduction

Follicular lymphoma is the second most frequent type of non-Hodgkin's lymphoma (NHL), accounting for 20-25% of all presentations [1]. The typical course of disease is characterized by initial responses to therapy but inevitable relapses, sometimes with histologic transformation to aggressive histology NHL [2]. Thus, the disease is considered incurable and current treatment paradigms are focused on palliation of symptoms and minimizing treatment toxicity. Median survival has remained stable in the range of 10 years for decades. However, more recent advances in therapies for frontline and relapsed disease may finally have an impact on the natural history of this lymphoma [3].

## Diagnosis

The diagnosis of follicular lymphoma (FL) is dependent on an adequate biopsy specimen (preferable open surgical biopsy) with immunohistochemistry. This lymphoma is composed of follicle center cells, usually a mixture of centrocytes (cleaved follicle center cells) and centroblasts (large non-cleaved follicle center cells). The pattern is at least partially follicular, but diffuse areas may be present. The tumor cells are usually surface immune globulin + and B-cell-associated antigen + (CD 19, 20, 79a). Lack of CD5 and CD43 is useful in distinguishing follicle center lymphoma from mantle cell lymphoma and the presence of CD10 can be useful in distinguishing it from marginal zone cell lymphomas [4]. Most cases express bcl-2, often, but not invariably associated with the translocation t(14;18) [5]. According to the WHO classification, this entity is classified as follicle center cell lymphoma, follicular grade I (small cleaved cell), grade II (mixed small and large cell) and grade III (large cell) [4]. Follicular large e cell lymphoma is discussed on **page 7**.

## Baseline Investigations

The following investigations are indicated for most patients with follicular lymphoma:

- Pathology review
- CBC, differential, blood film
- Serum electrolytes and creatinine
- Liver function tests
- Serum LDH
- Serum uric acid
- CT chest, abdomen and pelvis
- Unilateral bone marrow biopsy
- MUGA scan (see pg. 2)

Patients who will be managed with palliative intent may have more limited staging investigations with a focus on identification of disease that is likely to require symptomatic management. Bone marrow biopsy may not be necessary in patients who are not eligible for experimental treatments or curative radiotherapy.

### HIV Serology

As follicular lymphoma is not usually associated with HIV infection, testing should be limited to patients at risk of such an infection, especially if choice of treatment would be affected.



*Original treatment policy prepared by Dr. Louise Bordeleau; updated in 2005 & 2007 by Drs. Kevin Imrie & Matthew Cheung

### Cardiac Assessment

A cardiac assessment should be performed in all patients planned to receive an anthracycline-based chemotherapy (such as CHOP). MUGA scan or 2D-echocardiogram should be performed for those patients if known to have a history of:

- Age > 60 years
- Hypertension
- Congestive heart failure
- Peripheral vascular disease
- Cerebrovascular disease
- Angina
- Cardiac arrhythmia
- Myocardial infarction

### Gallium Scan or PET Scan

Gallium scans are not routinely recommended, but may be required for patients on experimental therapy. PET scanning will not routinely be performed for initial staging or response assessment.

## Staging & Prognosis

The Ann Arbor staging system continues to be in use in follicular lymphoma [6]. This system provides limited prognostic information, but is of use in determining therapeutic management. All patients should have an Ann Arbor stage assigned.

### Stage Definition

| | |
|---|---|
| **Stage I** | Involvement of a single lymph node region or a single extranodal site. |
| **Stage II** | Involvement of two or more lymph nodes on the same side of the diaphragm or localized involvement of an extra lymphatic organ or site and one or more lymph nodes on the same side of the diaphragm. |
| **Stage III** | Involvement of lymph node regions on both sides of the diaphragm that may also be accompanied by involvement of the spleen or by localized involvement of an extra lymphatic organ or site or both. |
| **Stage IV** | Diffused or disseminated involvement of one or more extra lymphatic organs or tissues, with or without associated lymph node involvement. |

The absence or presence of fever > 38.5 °C, drenching night sweats, and/or unexplained weight loss of 10 percent or more body weight in the six months preceding admission are to be denoted in all cases by the suffix A or B respectively.

### The Follicular Lymphoma International Prognostic Index

Previously, the predictive ability of the International Prognostic Index (IPI) for aggressive non-Hodgkin's lymphomas was extrapolated to the low-grade lymphomas [7, 8]. The IPI index is dependent on five prognostic factors: age, Ann Arbor stage, performance status, LDH and number of extranodal sites. Based on the IPI, ten-year overall survival rates for the risk groups are as follows: low, 73.6%; low-intermediate, 45.2%; high-intermediate, 53.5%; and high, 0% *($P < 0.001$)* [7].

More recently, an alternative index, the Follicular Lymphoma International Prognostic Index (FLIPI) was shown to be more discriminating than the IPI for patients with follicular lymphoma [9]. Five adverse prognostic factors were selected (mnemonic **NoLASH**):

- Number of **No**dal areas (> 4),
- **L**DH level (above normal),
- **A**ge (> 60 years),
- **S**tage (Ann Arbor III-IV), and
- **H**emoglobin level (< 120 g/L).

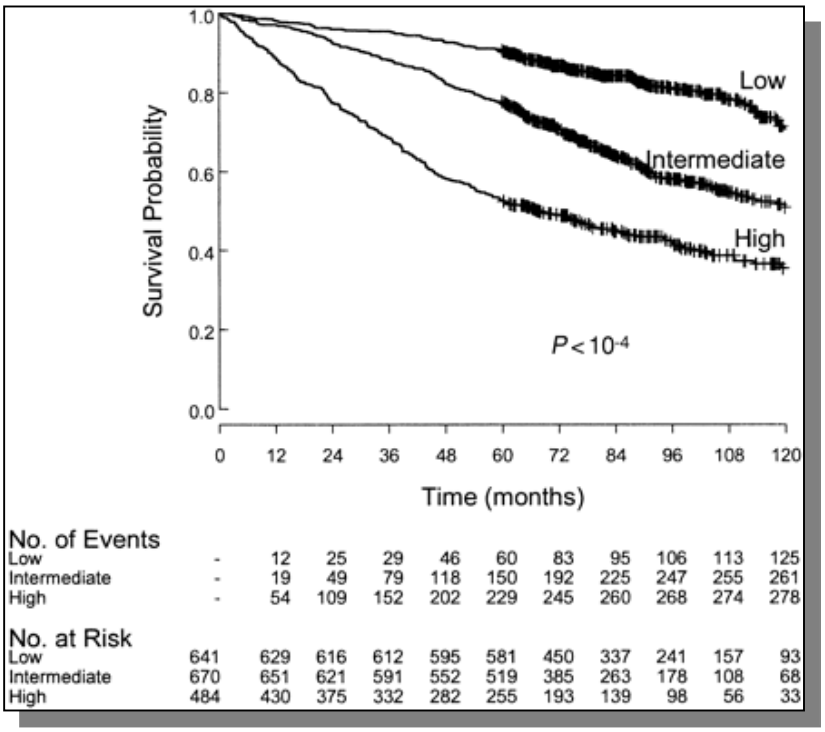
Of note, bulky disease was not incorporated into the prediction model because of a lack of consensus regarding its definition. Three risk groups were defined: low risk patients (0-1 adverse factor) were found to have a 10-year overall survival (OS) of 71%, intermediate risk patients (2 factors) an OS of 51%, and poor risk patients (≥ 3 adverse factors) an OS of 36%.

**Outcome and relative risk of death according to risk group as defined by the Follicular Lymphoma International Prognostic Index [9]**

| Risk Group | Number of factors* | Distribution of patients, % | 5-year OS, % (SE) | 10-year OS, % (SE) | RR | 95% CI |
|---|---|---|---|---|---|---|
| **Low** | 0-1 | 36 | 90.6 (1.2) | 70.7 (2.7) | 1.0 | NA |
| **Intermediate** | 2 | 37 | 77.6 (1.6) | 50.9 (2.7) | 2.3 | 1.9-2.8 |
| **High** | ≥ 3 | 27 | 52.5 (2.3) | 35.5 (2.8) | 4.3 | 3.5-5.3 |

N = 1795. OS indicates overall survival; SE, standard error; CI, confidence interval: RR, relative risk (of death), and NA, not applicable

*Factors adversely affecting survival in the FLIPI include age greater than 60 years; Ann Arbor stage III-IV; number of nodal sites greater than 4: serum LDH level greater than the upper limit of normal; and hemoglobin level less than 120 g/L.



The FLIPI was developed and tested prior to routine use of Rituximab containing regimens as initial therapy. Recently, the predictive value of the FLIPI was tested in patients treated with rituximab on the German prospective study of CHOP-R [10], as well as the CVP-Rituximab trial [11]. The FLIPI continues to predict shorter time-to-treatment-failure for patients with high-risk disease.

## Management of Follicular Stage I-II

Patients with localized disease at presentation (stage I-II) may be cured by radiotherapy. Ten-year relapse free survival (RFS) rates of 40-55% are reported [12]. A recent review of 460 patients treated at Princess Margaret Hospital confirmed excellent disease control with involved field radiation therapy alone. Disease-free survival was 56% at 5 years and 41% at 10 years. Of 460 patients treated, 450 achieved complete responses and only 5.5% relapsed in radiation fields (most relapses occurred in distant sites). Cumulative incidence of relapse at 10, 20, and 25 years was 48%, 56%, and 56% respectively [13], suggesting that the rate of very late relapse is quite low.

Long-term disease control within radiation fields can be achieved in a significant number of patients by using doses of radiation that usually range from **2,500 to 4,000 cGy** to involved sites or to extended fields, which cover adjacent nodal sites [14-17]. There is no evidence that adding chemotherapy or antibody therapy improves outcome [18, 19]. Most patients will be treated to a dose of **3600 cGy in 18 fractions**. For patients with involvement not encompassable by radiation therapy or patients for whom radiation therapy is contraindicated, we recommend treatment as described for the advanced stage.

## Management of Follicular Stage III-IV

The majority of patients with FL have advanced disease at presentation and remain incurable with present therapeutic approaches. Current management strategies include a "watch and wait" policy, the use of oral alkylating agents (such as chlorambucil or cyclophosphamide), newer purine analogues (fludarabine), and combination chemotherapy with or without the addition of agents such as rituximab and interferon alfa. The optimal treatment is controversial, as the vast majority of patients with advanced stages of follicular lymphoma are not cured with the current therapeutic options, despite the improved outcomes with chemotherapy and rituximab combinations.

**"Watch and Wait":** Multiple trials have demonstrated that initial therapy offers no advantage in patients with advanced, but asymptomatic disease [20, 21]. A recent study by the British National Lymphoma Investigation (BNLI) group detected no difference in overall or cause-specific mortality between patients who were treated with oral chlorambucil versus observation. Most patients managed on a "watch and wait" approach will require therapy within 2-4 years, but ~20% will be treatment free for up to 10 years [22, 23]. For patients over 70 years, 40% will not require treatment up to 10 years from diagnosis (BNLI). No randomized trials have compared "watch and wait" to combinations of chemotherapy and rituximab.

**Alkylator-based Chemotherapy:** Oral alkylating agents such as chlorambucil or cyclophosphamide produce response rates of 60-70% in untreated follicular lymphoma with median response durations of 2-3 years. The combination of cyclophosphamide, vincristine and prednisone (CVP) is an alternative to chlorambucil. This combination results in modestly higher response rates and duration than chlorambucil, but survival is similar [23, 24].

**Anthracycline-based Chemotherapy:** The addition of anthracyclines (i.e. doxorubicin) to CVP results in a more toxic regimen (CHOP) than chlorambucil or CVP, but without clear demonstration of improved long-term outcomes [24, 25].

**Fludarabine:** The use of fludarabine in follicular lymphoma is summarized in the CCO guideline 6-2 **(www.cancercare.on.ca)**. Intravenous and oral formulations are now available in Ontario. Fludarabine monotherapy has not been shown to significantly improve long-term outcomes, including time to progression or overall survival when compared with standard alkylator-based chemotherapy (i.e. CVP) [26]. Use of

fludarabine in combination with alkylator-based chemotherapy also has not resulted in improved outcomes, but does cause significant toxicity [27].

**Rituximab:** Rituximab is an anti-CD20 monoclonal antibody with established activity in follicular lymphoma. Initial studies demonstrated that one-half of patients with relapsed disease responded to rituximab monotherapy, with a median response duration of approximately 13 months [28].

**Combination with chemotherapy:** Because the anti-lymphoma effect of rituximab appeared to be higher in previously untreated patients and because of the limited toxicity associated with treatment, there has been considerable interest in combining rituximab with upfront chemotherapy. The addition of rituximab to chemotherapy has been studied in seven randomized trials [11, 29-34]. Six studies show significant improvement in progression-free survival and four show evidence of improved overall survival **(see CCO-PEBC EBS 6-8 at www.cancercare.on.ca)**. The improved outcomes have been reported with the combination of rituximab and several different chemotherapy regimens (MCP, FCM, CHOP, CHVP-Interferon, CVP). The results from six of the seven trials have recently been pooled and meta- analyzed by the Cochrane Haematological Malignancies Group and reported in abstract form [35]. Overall survival in these patients was significantly improved with the addition of rituximab to chemotherapy compared to chemotherapy alone (HR 0.61; 95% CI: 0.47-0.80). These trials enrolled patients who were rituximab-naïve, so the role of rituximab re-treatment at the time of relapse remains unclear. The CCO Hematology DSG recommends that rituximab be re-used in combination with appropriate chemotherapy in patients who have had at least a 12-month response to prior rituximab containing treatment [36]. Currently, this re-treatment is not funded in Ontario and would need to provided at patient cost and administered at a private infusion facility.

**Maintenance:** Rituximab has also been studied as maintenance treatment after initial therapy with chemotherapy, rituximab monotherapy, or combinations of chemotherapy with rituximab in five randomized trials [37-41]. All report an improvement in disease control and three report improved survival. The CCO Hematology DSG recommends the use of maintenance rituximab in patients who respond to induction therapy with (1) combination chemotherapy alone; (2) rituximab alone; or (3) combination chemotherapy and rituximab. Although many dosing strategies have been studied, one reasonable and convenient option is the use of rituximab 375 mg/m$^2$ every 3 months until relapse or 2 years.

**Interferon Alpha:** The evidence for interferon use in follicular lymphoma is summarized in CCO guideline 6-10 and a meta-analysis [42]. Interferon in combination with anthracycline-based chemotherapy is associated with a modest improvement in survival. The survival advantage was seen when interferon was combined with relatively intensive initial chemotherapy and at cumulative doses > 36 million units per month [42]. However, the use of interferon, particularly in this intensive manner, is associated with significant toxicity and inconvenience. The risks and benefits of adding interferon to initial chemotherapy should be discussed with patients considered for aggressive anthracycline-based chemotherapy. These trials were performed prior to the introduction of rituximab. Only one randomized trial has studied the combination of interferon and rituximab [28]. This trial included interferon in both arms and reported an improvement in event-free survival with the addition of rituximab.

**Radioimmunoconjugates:** Radioimmunoconjugates, monoclonal antibodies bound to radioisotopes, are an emerging class of agents with activity in lymphoma. These agents allow for the delivery of targeted radiation therapy via the binding of the monoclonal antibody to antigens on the surface of the malignant cells. Yttrium Y-90 ibritumomab tiuxetan (Zevalin) and iodine I-131 tositumomab (Bexxar) are both radiolabeled anti-CD20 antibodies currently approved for use in Canada, but neither is funded in Ontario at this time.

Initial studies of $^{90}$Y- ibritumomab have been predominantly in patients with refractory or relapsed follicular and other low-grade histologies **(see CCO-PEBC EBS 6-17 at www.cancercare.on.ca)**. A randomized controlled trial comparing $^{90}$Y-ibritumomab to rituximab monotherapy in this population demonstrated a higher overall response rate (80% versus 56%; p=0.002), but similar time-to-progression (11.2 versus 10.1 months; p=0.173) with the radioimmunoconjugate [43]. More importantly, $^{90}$Y-ibritumomab has demonstrated significant anti-lymphoma activity (high response rate in a single-arm, phase II trial) in patients with follicular lymphoma refractory to prior rituximab therapy. In a secondary analysis of this data, the response duration with $^{90}$Y- ibritumomab compared favourably with the duration observed after prior

rituximab therapy. $^{90}$Y-ibritumomab is thus positioned as an additional line of therapy in relapsed or refractory patients [44].

Less mature evidence is available on the role of $^{131}$I-tositumomab **(see CCO-PEBC EBS 6-17 at www.cancercare.on.ca)**. In a phase II trial of chemotherapy-refractory indolent or transformed lymphoma, 65% of patients responded to a single treatment with $^{131}$I- tositumomab and responses were more durable than those seen with their last course of treatment [45]. In another report of rituximab-refractory indolent lymphoma patients, 65% of patients responded with a median progression-free survival of 10.4 months. Among follicular grade 1 and 2 patients with low-bulk disease, overall response rate was 86% and progression-free survival was 48% at 3 years [46]. More recently, $^{131}$I- tositumomab has been administered as initial therapy in previously untreated patients [47]. Ninety-five percent of patients responded, including 75% complete responses. Median progression-free survival was 6.1 years. However, patients appeared to be highly selected with low-volume disease and younger-than-average individuals enrolled. Further comparative evidence is needed to define the role, and timing, of radioimmunoconjugates. These agents should be withheld in patients with platelets less than 100 x $10^9$/L, absolute neutrophil count less than 1.5 x $10^9$/L, prior myeloablative therapy with stem cell support, or bone marrow involvement greater than 25%.

**The Role of Dose Intense Therapy with Stem Cell Support**

The use of autologous stem cell transplantation (ASCT) in first remission has recently been studied in randomized phase III fashion. The German Low Grade Lymphoma Study Group performed a randomized study of ASCT versus maintenance interferon for young patients (age < 60) who attain initial partial or complete remission to anthracycline-based chemotherapy [48]. Progression–free survival was significantly prolonged in patients receiving ASCT *(64.7% vs. 33.3% after 5 years, p <0.0001)*. Early mortality was similarly low in both arms (<2.5%). In a study by the French GOELAMS of ASCT versus chemotherapy with interferon in patients < 60, ASCT was again associated with an extended event-free survival (median not reached versus 45 months) [49]. However, no survival benefit was detected due to an increased risk of subsequent MDS/AML and other secondary malignancies in patients receiving high-dose therapy. A recent third report from the GELA similarly compared a standard chemotherapy regimen plus interferon with chemotherapy followed by ASCT in patients ≤ 60 [50]. No differences in event-free or overall survival have been attained with ASCT in this report. Due to these concerns, ASCT in first remission should not yet be adopted as standard therapy.

A randomized trial comparing ASCT with or without purging to standard chemotherapy in younger patients responding to chemotherapy has been reported. This trial reported improved survival in the combined transplant arms compared to those treated with standard chemotherapy [51]. Interpretation of this trial is limited by incomplete accrual and limited sample size. Allogeneic transplantation can be considered in very select individuals with high-risk relapsed disease. The ideal candidate would be a younger patient with chemo-sensitive disease, preserved functional status, minimal comorbidities, and a matched sibling donor. In registry data comparing highly-selected allogeneic and autologous recipients, individuals who received allogeneic transplantation appeared to experience better long-term lymphoma control but at the cost of significantly higher transplant related mortality [52]. As a consequence, no overall survival benefit has been demonstrated with this approach.

**Synthesis of the Literature**

Many questions in the management of advanced stage follicular lymphoma remain unanswered, however, the following points can be drawn from the published literature:

- *There is no evidence that immediate treatment is superior to "watch and wait" for asymptomatic patients,*
- *No chemotherapy regimen tested (Chlorambucil, CVP, Fludarabine, CHOP) has proven superior to another in randomized trials,*
- *The addition of rituximab to any of the regimens tested (CVP, CHOP, CHVP-Interferon, MCP, FCM) improves progression-free survival and overall survival,*
- *Rituximab maintenance following first or subsequent lines of treatment improves disease control and overall survival,*

- *Retreatment with rituximab has not been studied, but is considered to be appropriate in patients who attain a response of 12-months or more to rituximab containing treatment,*
- *Interferon does modestly improve progression free and overall survival when added to intensive chemotherapy regimens at the cost of significant toxicity,*
- *Early promising phase II results suggest that radioimmunoconjugates are active agents in relapsed and refractory CD20+ indolent lymphoma; however, there is insufficient evidence that they are superior to other existing treatment options,*
- *For patients with follicular lymphoma in first remission, there is no consistent evidence that outcome is superior with ASCT than with no further therapy. For patients with relapsed disease, a single study suggests that ASCT is superior to chemotherapy alone.*

## Odette Cancer Centre Policy (Stage III-IV Follicular Lymphoma)

- Asymptomatic patients should be observed without treatment (ie. "watch and wait")
- Symptomatic patients should be considered for enrollment in a clinical trial
- If no trials are available, CVP-R will be used as first-line therapy for most patients
- Chlorambucil (with or without rituximab) will be offered to patients felt to unable to tolerate CVP and those who wish to avoid intravenous therapy
- CHOP-R will be reserved as initial therapy for patients with suspected transformation and those in need of rapid clinical response
- Patients who respond to therapy will be offered maintenance treatment with rituximab (1 dose of 375 mg/m$^2$ every 3 months for two years)

### Assessment of Response

Patients should be re-imaged with CT scans upon completion to assess response. Responses are classified according to the Cheson criteria [53] **(Appendix C)**. Treatment objectives are to achieve symptomatic control of the disease as well as to prevent potential complications. The achievement of complete remission is not a treatment goal. A revised set of response criteria have recently been published [54]. As these involve the use of PET scanning and this modality is not routinely available our site group will continue to utilize the 1999 criteria.

### Management of Incomplete Response

Unless symptomatic, patients with incomplete response should be observed carefully. Treatment (systemic or local) should be offered at the time of disease progression. Radiotherapy can be considered for disease that is bulky or critically located to prolong the disease-free interval (doses **2500-4000 cGy** to the involved field).

### Follow-Up

For advanced disease, recurrence is inevitable. The median time to progression is 31 months, with an overall median survival of 6 to 10 years [25, 55]. Patients should be followed every 3-4 months for the first 2 years and every 6-12 months thereafter. Assessment should consist of:

- History & physical exam
- CBC and differential
- Creatinine
- Serum LDH

Patients should not undergo routine CT scan monitoring as this is an inefficient means of identifying relapse. Imaging should be restricted to patients with suspected relapse.

## Follicular Grade III (Follicular Large Cell)

Grade III follicular lymphoma is a rare disease that represents ~ 3% of all NHL [4]. The condition is subdivided into 2 types: grade IIIa FL is characterized by a mixture of small centrocytes and centroblasts (> 15 per high power field) while grade IIIb contains sheets of large centroblasts. Weak evidence suggests that grade IIIb disease may behave similarly to diffuse large B-cell lymphoma, with treatment analogous to that used for

aggressive histology lymphomas (CHOP with rituximab) [56]. Patients with grade III follicular lymphoma and a clinically aggressive presentation will be treated with CHOP-R. Those with more indolent presentations, particularly those with grade IIIa disease will be treated similarly to other follicular lymphomas.

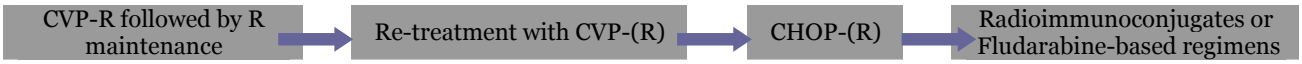
## Management of Relapse Disease

Relapse with follicular low-grade non-Hodgkin's lymphoma is inevitable in patients with advanced disease and common in patients with localized disease. Although patients often respond again to the same or a similar induction regimen, the quality of their response becomes worse and the duration shorter. Favorable survival after relapse has been associated with age younger than 60 years, complete remission rather than partial remission, and duration of response longer than 1 year [57]. Relapse with both indolent or aggressive histology (histologic conversion) may occur. Biopsy should be performed if the clinical pattern of relapse suggests that the disease is behaving in a more aggressive manner, has rapid growth or discordant growth between various disease sites.

## Relapse with Indolent Lymphoma

Patients who experience a relapse with indolent lymphoma can often have their disease controlled with palliative radiation or systemic therapy. Experimental therapy should be considered at this time. Otherwise, we recommend re-treatment with the same regimen if the remission duration is > 1 year. If remission duration is < 1 year, an alternate regimen should be considered. Patients who have not previously received rituximab therapy can have this treatment added to their regimen. Autologous stem cell transplantation has been considered in this population. A randomized controlled trial suggested improved progression-free and overall survival with ASCT compared to chemotherapy alone (CUP), although further studies are required to validate the results of this small trial.

**The therapy of relapsed follicular low-grade lymphoma should be individualized. A possible sequence appropriate for many patients could consist of the following:**




Autologous and/or allogeneic transplantation should be considered for high-risk first progression (3+ FLIPI risk factors or relapse within one year), and beyond.

**Note:** Criteria for funding of rituximab varies by jurisdiction. At the time of writing of this document, re-use of rituximab in combination with chemotherapy is not funded in Ontario. Practitioners should check criteria with local funding agencies.

### Radiotherapy

### Palliative

**Good performance status patients, limited disease:** Doses **2500-4000 cGy** to involved sites or extended fields as judged appropriate

**Poor performance status patients, short anticipated survival, multiple sites, involved fields**: Doses 4 Gy – single fraction and 4 Gy – 2 Gy fraction – 48 hours between are reported to have 61% CR and 31% PR with most patients having response at 2-6 weeks with median time to local progression for CR patients of 42 months and PR patients 10 months [58].

### Relapse with Histologic Conversion

Approximately 25% of patients will undergo histologic conversion within 10 years from initial diagnosis [59]. Patients with histologic conversions should be treated with the regimens described in the aggressive, recurrent adult NHL section (CHOP-R x 6 cycles) or considered for experimental protocols. A subset of patients with histologic transformation enjoys relatively long-term survival. Patients with limited disease and no previous exposure to chemotherapy have the most favorable prognosis [60]. The addition of radiotherapy can also be considered in patients with residual localized low-grade NHL.

## References


1. *A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project.* Blood, 1997. **89**(11): p. 3909-18.
2. Horning, S.J., *Natural history of and therapy for the indolent non-Hodgkin's lymphomas.* Semin Oncol, 1993. **20**(5 Suppl 5): p. 75-88.
3. Fisher, R.I., et al., *New treatment options have changed the natural history of follicular lymphoma [Abstract #583].* Blood, 2004. **104**(11): p. 168a.
4. Harris, N.L., et al., *A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group.* Blood, 1994. **84**(5): p. 1361-92.
5. Winter, J.N., R.D. Gascoyne, and K. Van Besien, *Low-grade lymphoma.* Hematology (Am Soc Hematol Educ Program), 2004: p. 203-20.
6. Greene, F.L., et al., *AJCC cancer staging manual.* 6th ed. 2002, New York: Springer-Verlag. xiv, 421 p.
7. Lopez-Guillermo, A., et al., *Applicability of the International Index for aggressive lymphomas to patients with low-grade lymphoma.* J Clin Oncol, 1994. **12**(7): p. 1343-8.
8. Decaudin, D., et al., *Low-grade stage III-IV follicular lymphoma: multivariate analysis of prognostic factors in 484 patients--a study of the groupe d'Etude des lymphomes de l'Adulte.* J Clin Oncol, 1999. **17**(8): p. 2499-505.
9. Solal-Celigny, P., et al., *Follicular lymphoma international prognostic index.* Blood, 2004. **104**(5): p. 1258-65.
10. Buske, C., et al., *The Follicular Lymphoma International Prognostic Index (FLIPI) separates high-risk from intermediate- or low-risk patients with advanced-stage follicular lymphoma treated front-line with rituximab and the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) with respect to treatment outcome.* Blood, 2006. **108**(5): p. 1504-8.
11. Marcus, R., et al., *CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma.* Blood, 2005. **105**(4): p. 1417-23.
12. Pendlebury, S., et al., *Radiotherapy results in early stage low grade nodal non-Hodgkin's lymphoma.* Radiother Oncol, 1995. **36**(3): p. 167-71.
13. Peterson, P.M., et al., *Long-term outcome in stage I and II follicular lymphoma following treatment with involved field radiation therapy alone [Abstract# 6521].* Proc Am Soc Clin Oncol, 2004. **23**: p. 561.
14. Denham, J.W., et al., *The follicular non-Hodgkin's lymphomas--I. The possibility of cure.* Eur J Cancer, 1996. **32A**(3): p. 470-9.
15. Mac Manus, M.P. and R.T. Hoppe, *Is radiotherapy curative for stage I and II low-grade follicular lymphoma? Results of a long-term follow-up study of patients treated at Stanford University.* J Clin Oncol, 1996. **14**(4): p. 1282-90.
16. Lawrence, T.S., et al., *Retrospective analysis of stage I and II indolent lymphomas at the National Cancer Institute.* Int J Radiat Oncol Biol Phys, 1988. **14**(3): p. 417-24.
17. Vaughan Hudson, B., et al., *Clinical stage 1 non-Hodgkin's lymphoma: long-term follow-up of patients treated by the British National Lymphoma Investigation with radiotherapy alone as initial therapy.* Br J Cancer, 1994. **69**(6): p. 1088-93.
18. Kelsey, S.M., et al., *A British National Lymphoma Investigation randomised trial of single agent chlorambucil plus radiotherapy versus radiotherapy alone in low grade, localised non-Hodgkins lymphoma.* Med Oncol, 1994. **11**(1): p. 19-25.
19. Seymour, J.F., et al., *High rate of prolonged remissions following combined modality therapy for patients with localized low-grade lymphoma.* Ann Oncol, 1996. **7**(2): p. 157-63.

20. Brice, P., et al., *Comparison in low-tumor-burden follicular lymphomas between an initial no-treatment policy, prednimustine, or interferon alfa: a randomized study from the Groupe d'Etude des Lymphomes Folliculaires. Groupe d'Etude des Lymphomes de l'Adulte.* J Clin Oncol, 1997. **15**(3): p. 1110-7.
21. Ardeshna, K.M., et al., *Long-term effect of a watch and wait policy versus immediate systemic treatment for asymptomatic advanced-stage non-Hodgkin lymphoma: a randomised controlled trial.* Lancet, 2003. **362**(9383): p. 516-22.
22. Rosenberg, S.A., *Karnofsky memorial lecture. The low-grade non-Hodgkin's lymphomas: challenges and opportunities.* J Clin Oncol, 1985. **3**(3): p. 299-310.
23. Hoppe, R.T., et al., *The treatment of advanced stage favorable histology non-Hodgkin's lymphoma: a preliminary report of a randomized trial comparing single agent chemotherapy, combination chemotherapy, and whole body irradiation.* Blood, 1981. **58**(3): p. 592-8.
24. Ezdinli, E.Z., et al., *Moderate versus aggressive chemotherapy of nodular lymphocytic poorly differentiated lymphoma.* J Clin Oncol, 1985. **3**(6): p. 769-75.
25. Dana, B.W., et al., *Long-term follow-up of patients with low-grade malignant lymphomas treated with doxorubicin-based chemotherapy or chemoimmunotherapy.* J Clin Oncol, 1993. **11**(4): p. 644-51.
26. Hagenbeek, A., et al., *Fludarabine versus conventional CVP chemotherapy in newly diagnosed patients with stages III and IV low grade malignant non-Hodgkin's lymphoma. Preliminary results from a prospective, randomized phase II clinical trial in 381 patients [Abstract #1294].* Blood, 1998: p. 315a.
27. Hochster, H.S., et al., *Results of E1496: A phase III trial of CVP with or without maintenance rituximab in advanced indolent lymphoma (NHL) [Abstract# 6502].* Proc Am Soc Clin Oncol, 2004. **23**: p. 556.
28. McLaughlin, P., et al., *Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program.* J Clin Oncol, 1998. **16**(8): p. 2825-33.
29. Hiddemann, W., et al., *Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group.* Blood, 2005. **106**(12): p. 3725-32.
30. Salles, G.A., et al., *Rituximab added to alpha-INF+CHVP improves the outcome of follicular lymphoma patients with a high tumour burden: First analysis of the GELA-GOELAMS FL-2000 randomized trial in 359 patients [Abstract# 160].* Blood, 2004. **104**(11): p. 49a.
31. Herold, M., et al., *Results of a prospective randomized open label phase III study comparing rituximab plus mitoxantrone, chlorambucile, prednisolone chemotherapy (R-MCP) versus MCP alone in untreated advanced indolent non-Hodgkin's lymphoma (NHL) and mantle-cell-lymphoma [Abstract #584].* Blood, 2004. **104**(11): p. 169a.
32. Forstpointner, R., et al., *The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared with FCM alone in patients with relapsed and refractory follicular and mantle cell lymphomas: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group.* Blood, 2004. **104**(10): p. 3064-71.
33. Rivas-Vera, S., et al., *Is First Line Single Agent Rituximab the Best Treatment for Indolent Non-Hodgkin's Lymphoma? Update of a Multicentric Study Comparing Rituximab vs CNOP vs Rituximab Plus CNOP.* ASH Annual Meeting Abstracts, 2005. **106**(11): p. 2431-.
34. Dreyling, M.H., et al., *Combined immuno-chemotherapy (R-FCM) results in superior remission rates and overall survival in recurrent follicular and mantle cell lymphoma: Follow-up of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG).* J Clin Oncol (Meeting Abstracts), 2005. **23**(16_suppl): p. 6528-.
35. Schulz, H., et al., *Does Combined Immunochemotherapy with the Monoclonal Antibody Rituximab Improve Overall Survival in the Treatment of Patients with Indolent Non-Hodgkin Lymphoma? Preliminary Results of a Comprehensive Meta-Analysis.* ASH Annual Meeting Abstracts, 2005. **106**(11): p. 351-.
36. Cheung, M.C., et al., *Rituximab in lymphoma: a systematic review and consensus practice guideline from Cancer Care Ontario.* Cancer Treat Rev, 2007. **33**(2): p. 161-76.

37. Van Oers, M.H.J., et al., *Chimeric Anti-CD20 Monoclonal Antibody (Rituximab; Mabtheraa) in Remission Induction and Maintenance Treatment of Relapsed /Resistant Follicular Non-Hodgkin's Lymphoma : A Phase III Randomized Intergroup Clinical Trial.* ASH Annual Meeting Abstracts, 2004. **104**(11): p. 586-.
38. Ghielmini, M., et al., *Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly x 4 schedule.* Blood, 2004. **103**(12): p. 4416-23.
39. Hainsworth, J.D., et al., *Maximizing therapeutic benefit of rituximab: maintenance therapy versus re-treatment at progression in patients with indolent non-Hodgkin's lymphoma--a randomized phase II trial of the Minnie Pearl Cancer Research Network.* J Clin Oncol, 2005. **23**(6): p. 1088-95.
40. Hochster, H.S., et al., *Maintenance Rituximab after CVP Results in Superior Clinical Outcome in Advanced Follicular Lymphoma (FL): Results of the E1496 Phase III Trial from the Eastern Cooperative Oncology Group and the Cancer and Leukemia Group B.* ASH Annual Meeting Abstracts, 2005. **106**(11): p. 349-.
41. Forstpointner, R., et al., *Maintenance therapy with rituximab leads to a significant prolongation of response duration after salvage therapy with a combination of rituximab, fludarabine, cyclophosphamide, and mitoxantrone (R-FCM) in patients with recurring and refractory follicular and mantle cell lymphomas: Results of a prospective randomized study of the German Low Grade Lymphoma Study Group (GLSG).* Blood, 2006. **108**(13): p. 4003-8.
42. Rohatiner, A.Z., et al., *Meta-analysis to evaluate the role of interferon in follicular lymphoma.* J Clin Oncol, 2005. **23**(10): p. 2215-23.
43. Witzig, T., et al., *Randomized controlled trial of yttrium-90-labeled ibritumonab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapse or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma.* J Clin Oncol, 2002. **20**(10): p. 2453-63.
44. Witzig, T., et al., *Treatment with ibritumomab tiuxetan radioimmunotherapy in patients with rituximab-refractory follicular non-Hodgkin's lymphoma.* J Clin Oncol, 2002. **20**(15): p. 3262-9.
45. Kaminski, M., et al., *Pivotal study of iodine I 131 tositumomab for chemotherapy-refractory low-grade or transformed low-grade B-cell non-Hodgkin's lymphomas.* J Clin Oncol, 2001. **19**(19): p. 3918-28.
46. Horning, S.J., et al., *Efficacy and safety of tositumomab and iodine-131 tositumomab (Bexxar) in B-cell lymphoma, progressive after rituximab.* J Clin Oncol, 2005. **23**(4): p. 712-9.
47. Kaminski, M.S., et al., *131I-tositumomab therapy as initial treatment for follicular lymphoma.* N Engl J Med, 2005. **352**(5): p. 441-9.
48. Lenz, G., et al., *Myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission prolongs progression-free survival in follicular lymphoma: results of a prospective, randomized trial of the German Low-Grade Lymphoma Study Group.* Blood, 2004. **104**(9): p. 2667-74.
49. Deconinck, E., et al., *High dose therapy followed by autologous purged stem cell transplantation and doxorubicin based chemotherapy in patients with advanced follicular lymphoma: a randomized multicenter study by the GOELAMS.* Blood, 2005.
50. Sebban, C., et al., *Standard chemotherapy with interferon compared with CHOP followed by high-dose therapy with autologous stem cell transplantation in untreated patients with advanced follicular lymphoma: the GELF-94 randomized study from the Groupe d'Etude des Lymphomes de l'Adulte (GELA).* Blood, 2006. **108**(8): p. 2540-4.
51. Schouten, H.C., et al., *The CUP trial: a randomized study analyzing the efficacy of high dose therapy and purging in low-grade non-Hodgkin's lymphoma (NHL).* Ann Oncol, 2000. **11 Suppl 1**: p. 91-4.
52. Peniket, A.J., et al., *An EBMT registry matched study of allogeneic stem cell transplants for lymphoma: allogeneic transplantation is associated with a lower relapse rate but a higher procedure-related mortality rate than autologous transplantation.* Bone Marrow Transplant, 2003. **31**(8): p. 667-78.
53. Cheson, B.D., et al., *Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group.* J Clin Oncol, 1999. **17**(4): p. 1244.
54. Cheson, B.D., et al., *Revised response criteria for malignant lymphoma.* J Clin Oncol, 2007. **25**(5): p. 579-86.
55. Johnson, P.W., et al., *Patterns of survival in patients with recurrent follicular lymphoma: a 20-year study from a single center.* J Clin Oncol, 1995. **13**(1): p. 140-7.

56. Bartlett, N.L., et al., *Follicular large-cell lymphoma: intermediate or low grade?* J Clin Oncol, 1994. **12**(7): p. 1349-57.
57. Weisdorf, D.J., et al., *Survival after relapse of low-grade non-Hodgkin's lymphoma: implications for marrow transplantation.* J Clin Oncol, 1992. **10**(6): p. 942-7.
58. Haas, R.L., et al., *High response rates and lasting remissions after low-dose involved field radiotherapy in indolent lymphomas.* J Clin Oncol, 2003. **21**(13): p. 2474-80.
59. Montoto, S., et al., *Risk and clinical implications of transformation of follicular lymphoma to diffuse large B-cell lymphoma.* J Clin Oncol, 2007. **25**(17): p. 2426-33.
60. Yuen, A.R., et al., *Long-term survival after histologic transformation of low-grade follicular lymphoma.* J Clin Oncol, 1995. **13**(7): p. 1726-33.