



**PRINCESS MARGARET CANCER CENTRE
CLINICAL PRACTICE GUIDELINES**

LYMPHOMA

INDOLENT LYMPHOMAS

Site Group: Lymphoma – Indolent Lymphomas

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1. Introduction

Indolent lymphomas include a variety of clinical and pathological conditions that affect mainly older adults. This guideline relates to the management of these disorders currently at the Princess Margaret Cancer Centre.

2. Prevention

Prevention strategies are not currently available for indolent lymphomas.

3. Screening and Early Detection

Screening and early detection do not play a role in the diagnosis and management of indolent lymphomas. While a number of conditions that represent precursor lesions that have been shown to evolve to clinically evident lymphoma over time (eg follicular lymphoma in situ, monoclonal B cell lymphocytosis) have been described, the management of these entities is still evolving.

4. Diagnosis

The diagnosis of indolent lymphoma is dependent on histologic assessment of a surgically acquired incisional or excisional biopsy of an involved lymph node or other extra-nodal tissue, to ensure adequate evaluation based on morphology, immunohistochemistry and flow cytometry for accurate sub-typing. Increasingly, core biopsies obtained under image guidance (CT scan or ultrasound) are used to obtain diagnostic material; such biopsies may be supplemented by fine needle aspiration for flow cytometry and / or cytogenetic testing (by fluorescence in situ hybridization or FISH). Bone marrow aspiration and biopsy can be considered for completion of staging at diagnosis, and on rare occasion represent the primary biopsy site for final diagnosis.

5. Pathology

Patients are treated based on a diagnosis conforming to those described according to World Health Organization criteria, most often after primary evaluation or pathology review by an expert Hematopathologist at the University Health Network.

6. Management

6.1 Management Algorithms

Follicular lymphoma (FL)

Histologies:

Follicular grade 1

Follicular grade 2

Follicular grade 3A

[Follicular grade 3B is managed as diffuse large B cell lymphoma]

Pre-treatment evaluation and staging:

Staging Investigations:

Staging of indolent lymphomas is described according to the Ann Arbor staging classification system. Pre-treatment evaluation should include:

- Full history and physical examination including performance status
- CBC, albumin, LDH, beta 2 microglobulin, LFTs (bilirubin, ALT, AST, ALP), creatinine, immunoglobulin quantitation and serum protein electrophoresis (SPEP) (for lymphoplasmacytic and marginal zone lymphoma), HBsAg, HBsAb, HBcoreAb, HCV antibody, HIV test can be considered.
- Additional blood tests, e.g. direct/indirect antiglobulin tests, serum viscosity, and imaging tests, e.g., MRI, bone scan, ultrasound, as determined by symptoms or clinical circumstances
- CT Head and Neck, thorax, abdomen, pelvis
- FDG-PET scan should be performed on patients with limited stage indolent lymphoma by CT who are potential candidates for curative ISRT and for patients with advanced-stage disease who are candidates for immunochemotherapy.
- BM aspirate and biopsy for morphology, immunohistochemistry, flow cytometry; cytogenetics/FISH depending on histology can be considered. If not expected to alter clinical management, this procedure is not mandated.
- MUGA scan or 2D echocardiogram for patients for whom doxorubicin is considered, who are above the age of 60, are known to have cardiac disease or with risk factors for cardiac disease.
- Review of Pathology by UHN hematopathology
- Calculation of FLIPI score

Re-Staging Investigations:

- History and physical examination; including adverse events and performance status.
- Repeat of imaging tests previously demonstrating involvement by lymphoma (generally CT scan of neck, chest, abdomen, pelvis; MRI in selected cases.) FDG-PET/CT scanning may be considered if the results are expected to change management (e.g., direct biopsy in the case of inadequate response to therapy).
- CBC, bone marrow biopsy if involved and documentation of complete response to treatment is required/desirable.

Stage III/IV follicular lymphoma

i) Observation:

All patients who present without symptoms and who do not fulfill any requirements for therapy listed below within the first 3 months from diagnosis are candidates for a “watch and wait” approach. Such patients should undergo repeat imaging with CT scans to assess rate of progression of measureable disease; those who do not develop any of the adverse disease characteristics can be followed clinically at regular intervals, until an indication(s) for therapy develops. The GELF and other similar criteria can assist in the decision whether to start treatment for asymptomatic patients.

GELF Criteria:

- 1) Involvement of 3 nodal sites each with diameter of 3 cm
- 2) any nodal or extra-nodal mass 7 cm in diameter
- 3) B symptoms
- 4) splenomegaly
- 5) pleural effusion or ascites
- 6) cytopenias: wbc $<1.0 \times 10^9/L$ or plts $<100 \times 10^9/L$
- 7) leukemic phase of disease with $>5.0 \times 10^9/L$

ii) Systemic therapy

- Enrolment to clinical trial for first line therapies and/or maintenance therapies is strongly encouraged.
- Preferred frontline treatment: IV Bendamustine 90 mg/m² day 1 & 2 + IV rituximab 375mg/m² day 1 (cycle 1 only) / SC rituximab 1400mg (cycles 2-6) q28days x 6 cycles. For patients with CR/PR: maintenance SC rituximab 1400mg q3mos x 8 doses (2 years).

Alternative induction treatments:

- R-CVP, followed by R maintenance.
- R-CHOP, followed by R maintenance.
- Alkylator therapy: chlorambucil 0.1 mg/kg/day (for selected patients not appropriate for multi-

agent chemotherapy).

- Rituximab monotherapy (for unfit patients).
- Obinutuzumab + bendamustine (or CVP or CHOP) (not currently funded in Ontario).
- Lenalidomide and rituximab (not currently funded in Ontario).

Recent studies evaluating observation show that patients with prognostically favourable disease do not have worse outcomes, despite the availability of rituximab-based therapies. An evaluation of single agent rituximab has been performed in patients with asymptomatic follicular lymphoma, comparing rituximab followed by maintenance therapy, vs rituximab alone, vs observation; an improvement in progression-free survival and time to next lymphoma treatment was reported. Overall survival was similar between the 2 groups, without sustained improvement in quality of life, thus we do not routinely recommend this treatment approach to asymptomatic patients.

A large trial comparing lenalidomide with rituximab, to chemoimmunotherapy, has recently been reported. While this “chemotherapy-free” regimen resulted in similar response rates, progression-free and overall survival to bendamustine-rituximab and other standard regimens, it is not clear that the toxicity profile of lenalidomide-rituximab is sufficiently more favourable to recommend its adoption as standard of care.

ISRT for symptom control (total dose 4 Gy in 2 fractions) or local control (total dose 20 – 30 Gy in 5-15 fractions) for patients who present initially with bulky masses may be considered.

FDG-PET scan in the end of therapy was shown to be a very powerful prognostic tool, and is strongly encouraged.

Stage I/II follicular lymphoma

- Involved Site RT 24-30 Gy in 12-20 fractions.
- For cases treated with complete surgical excision, consider observation as an option.
- Early stage disease that is discontinuous or otherwise unsuitable for radiotherapy should be managed as advanced stage disease.

Relapsed/refractory (R/R) follicular lymphoma

General approach:

- Observation can be considered at relapse, with overall the same consideration as in first line.
- Repeat tissue biopsy is strongly encouraged at relapse to confirm relapse and rule in/out a transformation to aggressive lymphoma. Biopsy is not needed if observation is planned.
- For transformed disease, treatment strategy is detailed elsewhere.
- For symptomatic disease / other indication for treatment, the optimal treatment has not been determined. The choice between the various options will depend of patient fitness, previous treatments (agents that have been used, quality and duration of responses, toxicities), access to various regimens and lastly physician and patient preferences.
- Enrollment to a clinical trial in this setting is strongly encouraged, especially for early progressors (POD24).

Treatment options:

- Enrolment into clinical trials for R/R follicular lymphoma is strongly encouraged.
- Rituximab-based immunochemotherapy: R-CHOP, B-R, R-CVP. R-GDP is also an option, but only as induction prior to planned autologous stem cell transplant.
- For those who have achieved a relatively long remission duration, consider repeat therapy with immunochemotherapy, possibly with a different chemotherapy backbone.
- Obinutuzumab-based immunochemotherapy: B-O, O-CHOP, O-CVP. O-GDP is also an option, but only as induction prior to planned autologous stem cell transplant.
- For R/R fit patients progressed within 24 months (POD24), or during 12 months after their last rituximab administration, that are responsive to immunochemotherapy (at least PR), consolidation with high dose therapy ASCT is currently our preferred approach.
- Maintenance rituximab should be considered for patients that have not received maintenance with first line treatment. Maintenance obinutuzumab can be considered for selected patients who received rituximab maintenance for first line and obinutuzumab-based immunochemotherapy for second line.
- Low dose radiation regimen with 2x2 Gy can be considered for symptom control.
- Lenalidomide + rituximab is an effective regimen for R/R FL (AUGMENT study), but the benefit over immunochemotherapy in R/R FL is not known. This regimen is not currently CCO-funded.
- PI3K inhibitors and other novel agents that shown efficacy in R/R FL can be considered for selected patients according to availability, mainly in the setting of inability to access other treatments and clinical trials.
- Allogeneic stem cell transplant can be considered for selected R/R young and very fit FL patients, usually in the setting of failing to proceed to auto-SCT due to insufficient response, or in the setting of relapse after auto-SCT. Fewer patients are nowadays considered for allo-transplant due to the improved efficacy of frontline approaches and greater availability of effective novel therapies in clinical trial setting.

Marginal zone lymphoma (MZL)

Types:

Extra-nodal mucosa-associated lymphoid tissue (MALT) lymphoma

Nodal marginal zone lymphoma

Splenic marginal zone lymphoma

Stage III/IV MZL

Treatment: **Bendamustine + rituximab—6 cycles**
(or R-CVP – 6-8 cycles)

For patients with CR/PR: maintenance rituximab 375 mg/m² q3mos x 8 doses (2 years)

Alternative induction treatments (including rituximab):

Oral alkylator therapy: chlorambucil 0.1 mg/kg/day (for selected patients not appropriate for multi-agent chemotherapy)

Chlorambucil 6mg/m² daily x 6 weeks, then daily x 2 weeks, a 5 weeks x 3 cycles, (IESG 19) R-CVP x 8 cycles

ISRT for symptom control (total dose 4 Gy in 2 fractions) or local control (total dose 20 – 30 Gy fractionated in 5 – 15 F)

Additional considerations:

Patients with splenic marginal zone lymphoma and cytopenias or significant splenomegaly should undergo splenectomy as initial management if fit enough for surgery. For patients who are older and who are at high risk of complications from splenectomy, single agent rituximab may produce prolonged progression-free survival.

Patients with SMZL and other marginal zone lymphomas arising in the setting of chronic hepatitis C infection should be considered for initial treatment with HCV eradication therapy using antiviral therapy as directed by their hepatologist, as complete regression has been reporting following HCV eradication.

Stage I/II MZL

Extranodal marginal zone lymphomas of mucosa-associated lymphoid tissue (MALT) type represent ~7% of all non-Hodgkin's lymphomas in the western world and can arise at any extranodal site. At least one-third of them present as a primary gastric lymphoma, which in approximately two-thirds of cases is associated with a chronic *Helicobacter pylori* infection.

Stomach MALT

Helicobacter pylori eradication therapy must be given to all, independent of stage.

If the presence of active *H. pylori* infection is not demonstrated by histochemistry, it must be ruled out by serology, urea breath test and/or stool antigen test.

In addition to routine histology and immunohistochemistry, fluorescence in situ hybridization studies for detection of t(11;18) (p21;p21) may be useful for identifying patients who are unlikely to respond to antibiotic therapy.

In *H. pylori*-negative cases, a regression of the lymphoma after antibiotic treatment is unlikely and the immediate start of oncological treatments (see below) should be considered, but the administration of an anti-*H. pylori* regimen may be worthwhile since occasional lymphoma responses have been reported (possibly due to a false-negative test or to infection by other *Helicobacter* species). In these *H. pylori*-negative patients, an oncological treatment (usually radiotherapy as described below) should, however, be considered if no signs of lymphoma regression are seen at a repeat endoscopy assessment 2 to 3 months after antibiotics administration.

For persistent MALT lymphoma despite adequate *H. pylori* eradication therapy (allow at least 12 months from eradication therapy with endoscopy every 3 months):

Radiotherapy 30Gy in 20 fractions to stomach, perigastric nodes, celiac nodes.

Orbit MALT: Involved site RT 25 Gy in 10-15 fractions.

Other sites (MALTs): Involved site RT 24-30 Gy in 12-20 fractions.

For those with disease site and disease extent suitable for complete surgical excision and no residual lymphoma post-surgery, consider observation with no RT (typical sites where this approach is feasible include lung, skin, thyroid, breast).

Lymphoplasmacytic lymphoma / Waldenström's macroglobulinemia

Asymptomatic patients without evidence of bone marrow compromise may be observed and followed every 3-6 months. Indications for therapy generally include progressive anemia, organomegaly or symptoms of hyperviscosity. Asymptomatic increase in serum viscosity does not itself constitute an indication to initiate therapy.

Treatment: Bendamustine + rituximab—6 cycles
or R-CVP 6-8 cycles
For patients with CR/PR: maintenance rituximab 375 mg/m² q3mos x 8 doses (2 years)

Alternative induction treatments:

Single agent fludarabine 40mg/m² per day (30mg/m² if >75 yrs) for 5 days q28 days for up to 6 cycles or

fludarabine-containing combinations (eg. fludarabine + cyclophosphamide) q28days for up to 6 cycles or

Oral alkylator therapy: chlorambucil 0.1 mg/kg/day or 8mg/m² per day (6mg/m² per day if >75 yrs of age) for 10 days q28days for maximum of 12 cycles. (for selected patients not appropriate for multi-agent chemotherapy or oral purine analogue therapy).

Patients who present with symptoms and signs of hyperviscosity should be treated by plasma exchange to lower plasma viscosity prior to starting chemotherapy including rituximab.

The optimal therapy for Waldenström's macroglobulinemia is not known and treatment decisions should be based on fitness level and tolerability of treatment. Recent phase 3 data evaluating oral fludarabine versus oral chlorambucil shows a significant improvement in progression free survival with oral fludarabine therapy; overall survival benefit was not observed. The number of patients with LPL/WM enrolled in phase III trials including rituximab as part of therapy is relatively small; these studies suggest that R-CHOP and R-bendamustine have similar rates of disease control but bendamustine is associated with fewer side effects.

6.2 Surgery

Surgery does not play a role in the primary management of most patients with indolent lymphoma, beyond the need for an adequate excisional biopsy for accurate diagnosis.

6.3 Chemotherapy

The role of chemotherapy in primary management of indolent lymphoma is described in the treatment algorithms above.

6.4 Radiation Therapy

The role of radiation in primary management of indolent lymphoma is described in the treatment algorithms above.

6.5 Oncology Nursing

Refer to [general oncology nursing practices](#)

7 Supportive Care

7.1 Patient Education

Refer to [general patient education practices](#)

7.2 Psychosocial Care

Refer to [general psychosocial oncology care guidelines](#)

7.3 Symptom Management

VTE prophylaxis:

For patients with new venous thromboembolism (VTE) and active lymphoma:

- Treatment with either LMWH or DOACs are acceptable (preferred DOAC edoxaban 60mg PO OD)
- Continue until complete remission and resolution of thrombosis, or indefinitely

Refer to [general symptom management care guidelines](#)

7.4 Clinical Nutrition

Refer to [general clinical nutrition care guidelines](#)

7.5 Palliative Care

Refer to [general oncology palliative care guidelines](#)

8. Follow-up Care

Monitoring

Response assessment at 1 month post treatment:

- Document physical examination and CT scan of previously involved areas. Repeat CT imaging 2-3 months after IFRT for bulky disease is appropriate to document response. A repeat BM should be performed following systemic therapy if previously positive to document complete response to therapy or to investigate persistent cytopenias, but it is not necessary prior to initiation of maintenance therapy. Routine scanning for patients who are receiving maintenance therapy with rituximab may be performed on an annual basis for those in partial remission at the end of induction therapy, in order to ensure continued therapeutic benefit.

At each subsequent visit:

- Document history and physical examination, persistent toxicities and performance status; repeat CBC if blood counts have not returned to normal at prior visit or if previous involvement of blood or marrow with lymphoma. Consider repeat imaging studies for presence of new symptoms suggesting possible disease recurrence. Patients with previously demonstrated stable post-treatment masses need not be followed with CT scan if asymptomatic.
- Patients with follicular and other indolent lymphomas who have completed systemic therapy for advanced stage disease should be followed indefinitely, because risk of recurrence is ongoing. The use of CT imaging in follow-up of indolent lymphoma patients should be reserved for those who have symptoms or biochemical evidence of disease recurrence (eg unexplained rise in creatinine, ALP, bilirubin). Patients with lymphoplasmacytic lymphoma / Waldenstrom's should have IgM levels measured q6-12 months.
- Counselling re: physical and psychological health issues, including impact of treatment on quality of life, management of fatigue, fertility and contraception, cardiovascular fitness, risk of recurrence, and risk of second malignancy. Smoking cessation for smokers.

Oncology Clinic Follow-up Frequency:

First year	-	Visits every 3 months
2 - 3 years	-	Visits every 4 months
4 - 5 years	-	Visits every 6 months
> 5 years	-	annual follow up

In general, alternate follow up visits between attending medical oncologist/hematologist and radiation oncologist. Family physicians are encouraged to participate in the follow up as outlined, particularly for visits beyond 5 years from treatment. The majority of patients may be discharged to the care of their primary care practitioner by 10 years post-treatment.

Second malignancy screening

Routine primary care follow-up.

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