LYMPHOMA

INDOLENT LYMPHOMAS
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 have been described that have been shown to evolve to clinically evident lymphoma over time (eg follicular lymphoma in situ, monoclonal B cell lymphocytosis), 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 are currently standard 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, LFTs (bilirubin, ALT, AST, ALP), creatinine, immunoglobulin quantitation (lymphoplasmacytic and marginal zone lymphoma)
- CT Head and Neck, thorax, abdomen, pelvis
- FDG-PET scan for patients with limited stage indolent lymphoma by CT who are potential candidates for curative IFRT
- MUGA scan or 2D echocardiogram (patients for whom doxorubicin is considered appropriate, age >60 or those with risk factors for cardiac disease)
- Additional blood tests and imaging tests, e.g. MRI, bone scan, ultrasound, as determined by symptoms or clinical circumstances
- BM aspirate and biopsy for morphology, immunohistochemistry, flow cytometry
- HBsAg, HBsAb, HBcoreAb; HCV antibody
- HIV test if risk factors present
- Review of Pathology at PMH-UHN

**Re-Staging Investigations:**

(Applicable for patients receiving combined modality therapy, to document response after receiving chemotherapy, prior to radiation therapy)

- 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)
• CBC, LDH; bone marrow biopsy if involved and documentation of complete response to treatment is required/desirable
• A complete or partial response is required to proceed to planned radiation therapy (by CT scan +/- functional imaging). A less than partial response may require alternate treatment strategy.

**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 measurable 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:

<table>
<thead>
<tr>
<th>BNLI Criteria –</th>
<th>GELF Criteria –</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) hematopoietic impairment (Hgb &lt;100g/L, WBC &lt;3.0x10^9/L, Plts&lt;100 g/L)</td>
<td>1) Involvement of 3 nodal sites each with diameter of 3 cm</td>
</tr>
<tr>
<td>2) pruritis or B-symptoms</td>
<td>2) any nodal or extra-nodal mass 7 cm in diameter</td>
</tr>
<tr>
<td>3) rapidly progressing lymphoma within the last 3 months</td>
<td>3) B symptoms</td>
</tr>
<tr>
<td>4) life endangering organ involvement</td>
<td>4) splenomegaly</td>
</tr>
<tr>
<td>5) localized bone lesions</td>
<td>5) pleural effusion or ascites</td>
</tr>
<tr>
<td>6) renal infiltration</td>
<td>6) cytopenias: wbc &lt;1.0x10^9/L or plt&lt;100x10^9/L</td>
</tr>
<tr>
<td>7) macroscopic liver involvement</td>
<td>7) leukemic phase of disease with &gt;5.0x10^9/L</td>
</tr>
</tbody>
</table>

**ii) Systemic therapy for symptomatic disease**

Treatment: Bendamustine 90 mg/m2 day 1 & 2 + rituximab day 1 q28days x 6 cycles
For patients with CR/PR: maintenance rituximab 375 mg/m2 q3mos x 8 doses (2 years)

Alternative induction treatments:
R-CHOP (younger pts, bulky disease) – 6 cycles
R-CVP – 8 cycles
Oral alkylator therapy: chlorambucil 0.1 mg/kg/day (for selected patients not appropriate for multi-agent chemotherapy)

Recent studies evaluating observation as initial treatment strategy show that patients with prognostically favourable disease do not have worse outcomes, despite the availability of rituximab-based therapies. A preliminary evaluation of single agent rituximab in patients with asymptomatic follicular lymphoma, comparing rituximab followed by maintenance therapy, vs rituximab alone, vs observation; reported an improvement in progression-free survival and time to next lymphoma treatment. Longer follow-up and information from this trial on other endpoints including quality of life and survival are needed before treatment of asymptomatic patients can be recommended.

IFRT for symptom control (total dose 4 Gy in 2 fractions) or local control (total dose 20 – 30 Gy in 5-15 fractions)

**Stage I/II follicular lymphoma**

Treatment: Involved Field RT 30 Gy in 20 fractions

For stage I & IIB, IIA extensive, bulk > 5cm, consider combined modality therapy (6 cycles CVP + rituximab) or chemotherapy alone.

For cases treated with complete surgical excision, consider observation as an option.

**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: 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):
Bendamustine—6 cycles
Fludarabine-containing combinations (eg. Fludarabine + cyclophosphamide) – 6 cycles
Oral alkylator therapy: chlorambucil 0.1 mg/kg/day (for selected patients not appropriate for multi-agent chemotherapy or fludarabine)
IF RT 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.

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

Stage I/II MZL

Stomach
Helicobacter pylori eradication therapy.

For persistent MALT lymphoma despite adequate H. pylori eradication therapy (allow at least 12 months from eradication therapy):
RT to stomach, perigastric nodes, celiac nodes to 30 Gy in 20 fractions.

Treatment: Orbit: Involved field RT to 25 Gy in 10-15 fractions.
Other sites: Involved-field RT to 30 Gy in 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 / Waldenstrom’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/m\(^2\) q3mos x 8 doses (2 years)

**Alternative induction treatments:**

Single agent fludarabine 40mg/m\(^2\) per day (30mg/m\(^2\) 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/m\(^2\) per day (6mg/m\(^2\) 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 Waldenstrom'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 RCHOP 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.

**6.4.1 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

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

Response assessment one 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 with aggressive histology lymphoma. 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.

• Counseling re: physical and psychological health issues, including impact of treatment on quality of life, reproduction, 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/haematologist and radiation oncologist. Family physicians are encouraged to participate in the follow up as outlined, particularly for visits beyond 5 years from treatment.
9. References:


Last Revision Date – September 2013


