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 occasions represent the primary biopsy site for final diagnosis.

5. Pathology

Patients are treated based on a diagnosis conforming to those described according to the 5th edition of the World Health Organization Classification of Haematolymphoid Tumours (WHO-HEAM5) and/or the International Consensus Classification (ICC), 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)

Histology:

In the WHO-HEAM5 classification, grading is no longer mandatory and classic FL (cFL) encompasses previously recognized FL grade 1, 2 and 3A. FL grade 3B has been renamed follicular large B-cell lymphoma (FLBL) and is managed as diffuse large B cell lymphoma. A new subtype was introduced, FL with uncommon features (uFL).

In opposition to the WHO-HEAM5, the ICC maintains cytological grades.

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. It is recommended to confirm limited stage disease in all pts.

- MUGA scan or 2D echocardiogram for patients for whom doxorubicin is considered and 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 at the end of treatment is recommended as it has prognostic significance and may occasionally 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.

<u>Stage III/IV follicular lymphoma</u>

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 the 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. The GELF and other similar criteria can assist in the decision of 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 $<1.0x10^9$/L or platelets $<100x10^9$/L
7) leukemic phase of disease with $>5.0x10^9$/L

ii) **Systemic therapy**

- Enrolment to clinical trials for first-line therapies and/or maintenance therapies is strongly encouraged.
- Preferred frontline treatment:
- **IV Bendamustine 90 mg/m^2 day 1 & 2 + IV rituximab 375mg/m^2 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). The benefits and risks of rituximab maintenance should be evaluated on an individual basis.**

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 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.

<u>Stage I/II follicular lymphoma</u>

- Involved Site RT 24-30 Gy in 12-20 fractions.

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

- Limited-stage disease that is discontiguous 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 considerations 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 on 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:

- 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 (for those whose progression is within 6 months of Rituximab treatment, which could include its use for maintenance): 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.
- Tisa-cel and Axi-cel recently received conditional positive recommendations at CADTH for patients with relapsed/refractory follicular lymphoma after 2 lines of therapy, thus may become a standard of care option in the near future. BITEs such as mosunetuzumab also offer a promising treatment option, but are not currently available in Canada for this indication.
- 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 the 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:

IV Bendamustine 90 mg/m^2 day 1 & 2 + IV rituximab 375mg/m^2 day 1 (cycle 1 only) / SC rituximab 1400mg (cycles 2-6) q28days x 6 cycles.
(*or* R-CVP – 6-8 cycles)

For patients with CR/PR: maintenance SC rituximab 1400mg q3mos x 8 doses (2 years).

The benefits and risks of rituximab maintenance should be evaluated on an individual basis.
Rituximab maintenance is recommended based on results from the MZL analysis of the phase 3 StiL NHL7-2008 MAINTAIN trial (104 randomized patients), which showed a superior PFS for rituximab maintenance over observation (median PFS not reached vs. 92.2 months, HR 0.35, 95% CI 0.17–0.76; $p = 0.008$)

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/m^2 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 in 5-15 fractions)

Additional considerations:

Patients with splenic marginal zone lymphoma and cytopenias or significant splenomegaly should be considered for 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 reported 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. If disease burden is too extensive for radiotherapy (for eg multifocal lung MALT), treatment as per advanced stage disease with BR is recommended. The role of maintenance rituximab in advanced MALT lymphoma has not been well defined, as such patients, were not included in the phase 3 StiL NHL7-2008 MAINTAIN trial.

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 (LPL/WM)

Investigations:

- Baseline testing to include: β2microglobulin, LDH, total immunoglobulins, SPEP, serum IFE, cryoglobulins (if positive, may render M-protein falsely low), serum viscosity, nerve conduction studies. Consider Mitogen anti-myelin associated glycoproteins & neurologic disease panel (if evidence of neuropathy), consider yearly ophthalmologic exam (if total IgM ≥40g/L)
- If anemic, perform a hemolytic workup (DAT, retics, bilirubin, haptoglobin, cold agglutinins), serum ferritin, serum iron, TIBC, iron saturation, and/or soluble transferrin receptor (hepcidin dysregulation common in WM)
- If concerns regarding bleeding, perform bleeding assessment tool, INR, PTT, with consideration for further specialized testing such as von Willebrand testing, based on clinical assessment
- Tissue or bone marrow based diagnostic testing with MYD88 (WM NGS panel including CXCR4 is available as research test) and congo red for concurrent amyloid

Frontline therapy:

- Clinical trials should be considered
- Preferred: bendamustine 90mg/m^2 days 1+2 and rituximab 375mg/m^2 day 1 x 6 cycles (can dose reduce to 70mg/m^2 if less fit)
- Alternatives include:
    - BTK inhibitor if less fit or Bing Neel Syndrome (zanubrutinib preferred) – BTKis are not preferred if known to have CXCR4 mutation or wild-type MYD88
    - DRC (DEX 20mg, rituximab 375mg/m^2 day 1, cyclo 100mg/m^2 PO BID days 1-4) every 21 days x 6 cycles – may be considered if autoimmune cytopenias
    - BDR (bortezomib 1.5mg/m^2 SC, DEX 40mg weekly, rituximab 375mg/m^2 SC monthly x 6 cycles) – may be preferred with renal dysfunction
- Monotherapy rituximab (375mg/m^2 SC weekly x 4) can be considered for isolated neuropathy
- Plasmapheresis for hyperviscosity signs or symptoms (asymptomatic serum viscosity levels do NOT warrant plasmapheresis)
- If starting rituximab-based therapy, risk of IgM flare highest if IgM >50g/L or with monotherapy. Mitigation strategies include choice of:
    - Omit first dose of rituximab
    - Plasmapheresis prior to start (rarely needed)
    - Proceed with therapy but follow IgM levels and viscosity weekly and pherese as needed if symptomatic flare occurs
- Maintenance rituximab after initial BR is NOT routinely recommended (can consider if not in PR after BR completion)

Second-line therapy:

- Clinical trials should be considered
- Any of above depending on frontline therapy and duration of remission
- Other options include: fludarabine or cladribine-based regimens, R-CVP or R-CHOP

Special situations:

- Bing Neel – choose regimens that cross BBB – BTK inhibitors are preferred but others include high dose MTX, IT MTX if CSF positive, fludarabine, craniospinal irradiation (infrequently used now with BTKi use)
- Amyloidosis – Dara-CyBorD (followed by ASCT if not in VGPR or better); BR may be preferred if CD38negative in BM
- Isolated anemia – perform iron studies and consider trial of parenteral iron
- Peripheral neuropathy – single agent rituximab, plasmapheresis, BTK inhibitor – outcomes inconsistent

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

- Treatment with either low-molecular weight heparin (LMWH) or direct oral anticoagulants (DOACs) are acceptable

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. 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 (e.g., unexplained rise in creatinine, ALP, bilirubin). Patients with lymphoplasmacytic lymphoma / Waldenström'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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