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1. Introduction

Aggressive lymphomas include a variety of clinical and pathological conditions that may affect adults at any age. 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 aggressive lymphomas. While it is recognized that persons with Human Immunodeficiency Virus infection, chronic HTLV-1 infection, and iatrogenic immunosuppression because of organ transplantation or chronic inflammatory diseases are at higher risk for developing lymphoma, there are no current prevention strategies that can be endorsed in these patient populations.

3. Screening and Early Detection

Screening and early detection do not play a role in the diagnosis and management of aggressive lymphomas.

4. Diagnosis

The diagnosis of aggressive 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

Aggressive histology lymphomas

Histologies:

B cell: Diffuse large B-cell lymphoma (include transformed follicular and transformed MALT) and variants (T cell rich B cell lymphoma, etc)
   Primary mediastinal lymphoma
   Follicular Grade 3B lymphoma

T cell: Anaplastic large cell lymphoma, ALK positive
   Peripheral T cell lymphoma and variants (angioimmunoblastic T cell, ALCL
   ALK negative, etc)

Others (see below):
   Mantle cell lymphoma
   Extranodal NK
   Burkitt lymphoma

Pretreatment evaluation and staging:

a) Staging Investigations:

Staging of aggressive 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
- 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, who are age ≥60, or those with a history of or 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; cytogenetics/FISH depending on histology
- Lumbar puncture for protein, glucose, cell count and cytology/flow cytometry – for those considered at risk for CNS involvement
- HBsAg, HBsAb, HBcoreAb; HCV antibody
b) **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.

**Diffuse Large B cell lymphoma: Stage I/II**

Risk-adapted therapy, treatment recommendation based on the presence or absence of the following prognostic factors:

**Prognostic factors:**

IPI factors:  
- age > 60
- abnormal LDH
- stage II

Tumor size:  
- bulk > 5 cm

Extranodal:  
- testis
- bone
- epidural

**Treatment:**

No risk factors:  
**R-CHOP x 4 cycles**  
IF RT 35 Gy in 20 fractions

≥ 1 factor(s):  
**R-CHOP x 6 cycles**  
IF RT 30 Gy in 20 F (35 Gy if initial bulk > 5 cm)
Optional: For patients achieving CR after 4 or 6 cycles of R-CHOP, observation with no RT should be discussed as a reasonable alternative, particularly if the following features are present:

a) non-bulky (< 5 cm) presentation
b) prior surgical excision of all gross disease (e.g. tonsil, splenectomy)
c) multiple nodal regions involved (> 3), particularly if non-contiguous

Additional considerations:

Chemotherapy sanctuary sites (e.g. testes), or clinically critical sites (e.g. airway or spinal cord compression at presentation) should still receive IF RT to achieve optimal local control.

Stage I-II testis and epidural presentations should receive CNS prophylaxis: 2-3 cycles of high-dose methotrexate with or without IT chemotherapy if tolerable on basis of age, GFR.

Patients with primary mediastinal large B cell lymphoma and localized gastric DLBCL should receive involved field radiation following CR or PR following R-CHOP, even for presentations that do not meet conventional criteria for bulky disease, based on phase II and cohort data suggesting optimal treatment outcomes with combined modality therapy.

Diffuse Large B cell lymphoma: Stage III/IV

Treatment:

R-CHOP x 6 cycle (age > 60) or 6-8 cycles for those age ≤ 60
CT scan after cycle 3 or 4 and after cycle 6; FDG-PET at end of chemotherapy for residual imaging abnormalities > 2 cm.

If residual mass post completion of systemic chemotherapy is FDG-avid, consider biopsy and salvage chemotherapy and stem cell transplant if biopsy is positive. For those not eligible for stem cell transplant, and for those where combined modality treatment was a consideration due to bulk of disease at diagnosis, if the residual mass is localized, radiation may be considered (35 – 40 Gy in 20 fractions).

Radiation is not considered standard for patients with advanced DLBCL and is currently being investigated in prospective clinical trials. However, in certain clinical circumstances, involved field radiation may be appropriate, to reduce the risk of local recurrence or decrease future morbidity. Such circumstances include but are not limited to patients presenting with bulky masses (> 10 cm), extradural tumour with spinal...
cord/nerve root compression, impending or actual organ compromise (orbit, airway, long bone or weight-bearing bone fracture, etc).

**Additional considerations:**

CNS prophylaxis: Some patients with DLBCL are at higher risk of CNS recurrence, but there is no consensus on reliable factors that predict risk of CNS relapse, and intrathecal chemotherapy with methotrexate and cytarabine has not been shown to be efficacious. Patients subsets that may warrant consideration of this therapy include high risk IPI scores at presentation; encroachment on or invasion of dura; testicular involvement, multiple extranodal sites or those with lymphoma intermediate between DLBCL and Burkitt lymphoma (dual translocation or “double hit”). Evaluation of CSF with cytology supplemented by flow cytometry at diagnosis is recommended to detect CSF involvement.

Dose-intensity and the use of granulocyte colony-stimulating factor (G-CSF): Evidence currently does not indicate an improvement in overall survival with the use of primary prophylaxis with G-CSF. Such therapy is recommended for patients experiencing febrile neutropenia who have otherwise tolerated full dose R-CHOP, and as primary prophylaxis for patients age >65, with bone marrow compromise from lymphoma, patients with significant comorbidities, patients with poor performance status (ECOG ≥3) and immunocompromised patients (HIV+, organ transplant recipients).

Six cycles of R-CHOP results in similar PFS and overall survival to 8 cycles with less toxicity; there does not seem to be any advantage to an additional 2 cycles of therapy for those who have achieved PR by CT scan after 6 cycles. Such patients may be candidates for biopsy to exclude residual disease or IFRT if presenting with bulky disease initially. There is no advantage in terms of PFS or OS with the use of a 14 day schedule for R-CHOP supported by G-CSF compared to a 21-day schedule.

Patients who are HIV positive and are fit to receive combination chemotherapy should receive 6 cycles of CHOP with antiretroviral therapy and anti-infectious prophylaxis as appropriate for their CD4 counts during treatment. Those with stage I and II DLBCL should receive IFRT following completion of chemotherapy.

**Mantle cell lymphoma:**

Initial period of observation: asymptomatic, no marrow compromise, no impending organ compromise (see watch and wait criteria for indolent lymphomas)

**Limited stage (I,II)**

Treatment: **CHOP + rituximab x 4 - 6 cycles + involved field RT**
Advanced stage (III, IV) - Age < 65 years, no comorbidities precluding intensive therapy: plan for autologous stem cell transplantation (ASCT)

Treatment: R-CHOP alternating with R-DHAP (dexamethasone, cytarabine, cisplatin) for 6 cycles
CR, PR (after cycle 4) → stem cell mobilization → cycles 5 + 6 → autologous stem cell transplantation

Intensive therapy:
Total Body Radiation (TBI)*: 1000 cGy/6 fractions/od/bid days -7, -6, -5, 0
Cytarabine 1.5 g/m² q12h 4 doses days -4, -3
Melphalan 140 mg/m², i.v., day -2
Transplant day 0

*TBI will be included in the conditioning regimen, for patients age ≤ 60 and for those over 60 without comorbidities and with normal lung function

Post-transplant consolidation with Rituximab 375 mg/m² weekly x 4 weeks, commencing 3 and 9 months following completion of chemoimmunotherapy

Age > 65, or not considered eligible for ASCT

Treatment: bendamustine + rituximab x q4wks 6 cycles

Alternative chemotherapy regimens:
CHOP + rituximab q3weeks x 6 cycles
CVP + rituximab q3weeks x 6-8 cycles

Elderly patients with significant co-morbidities or who wish to avoid the toxicity of combination chemotherapy should be treated with chlorambucil 0.1 mg/kg/d for 4-6 months as tolerated

i) Maintenance/consolidation therapy: should be considered for patients with CR or PR after primary therapy (or second-line treatment, if rituximab naïve), using Rituximab every 3 months for 8 doses.

Additional considerations: Recommendation for the use of bendamustine as front line therapy is based on a subset of MCL patients in the larger indolent lymphoma cohort of the trial by Rummel et al; this subset analysis did show a large improvement in PFS compared to RCHOP, with significantly less toxicity. However the PFS from RCHOP in that trial appears much less that reported in other trials (eg Kluin-Nelemans et al), and to date there are no data suggesting overall survival with bendamustine as initial therapy. Use of bendamustine-rituximab as induction therapy prior to ASCT is not recommended outside of a clinical trial.
Peripheral T cell lymphoma and variants (including Anaplastic Large Cell lymphoma):

The prognosis for PTCL and its variants (including CD30+ ALK negative ALCL) is generally inferior to that for DLBCL, and the optimal therapies have not been defined in prospective trials. Chemotherapy and radiation treatment recommendations are derived by extrapolation from results in aggressive B cell lymphomas or from retrospective analyses of large case series of PTCL. In contrast, the outcome of ALCL that expresses anaplastic lymphoma kinase (ALK) detected by immunohistochemistry or with a t(2;5) by FISH may have a better prognosis when treated with standard CHOP +/- etoposide. Prospective evaluation of treatment interval (CHOP-14 vs CHOP-21) has not been performed. Cohort studies have reported encouraging outcomes from the addition of autologous stem cell transplantation in first remission, but this therapy has not been compared prospectively to standard dose chemotherapy.

Stage I/II

Treatment: **CHOP x 6 cycles + IFRT 35 Gy in 20 fractions**

Stage I cutaneous ALCL, ALK positive: RT alone (35 Gy) is appropriate

Stage III/IV

Treatment: **CHOP x 6-8 cycles**  
**CHOEP x 6-8 cycles (ALK +ve ALCL)**

Extranodal NK lymphoma, nasal type:

Stage IE/IIE

Treatment: 1) *Concurrent weekly cisplatin 30 mg/m$^2$ with IFRT 45 – 50 Gy in 25 fractions over 5 weeks*, followed by  
2) VIPD (etoposide, ifosfamide, cisplatin, dexamethasone) chemotherapy every 3 weeks x 3 cycles

Stage III/IV

Treatment: **SMILE chemotherapy (dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide) 3-6 cycles**

Alternative regimens (CHOP, L-asparaginase, methotrexate, dexamethasone) should be considered for patients with comorbidities, who are unable tolerate SMILE.
6.2 Surgery
Surgery does not play a role in the primary management of most patients with aggressive lymphoma, outside of the need for an adequate excisional biopsy for accurate diagnosis.

6.3 Chemotherapy
The role of chemotherapy for primary therapy of aggressive lymphoma is described above in the treatment algorithms.

6.4 Radiation Therapy
The role of radiation for primary therapy of aggressive lymphoma is described above in the treatment algorithms.

6.5 Other Therapy
Autologous or allogeneic stem cell transplantation do not have a role in the primary therapy of aggressive lymphomas; the exception to this is ASCT as consolidation for younger patients with mantle cell lymphoma in first remission, discussed above.

6.6 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

Follow up guidelines (NHL):

Response assessment one month post treatment:

- document with P/E, CT of previously involved areas, FDG-PET scan (if previously positive) following completion of chemotherapy for aggressive histology lymphomas; a repeat biopsy is only indicated if there is a strong suspicion of disease progression, as the false positive rate for PET in patients with DLBCL is very high. 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.

At each subsequent visit:

- Document history and physical examination, document toxicity and performance status; repeat CBC if blood counts have not returned to normal at prior visit, (add TSH every 6 months if radiation to thyroid gland). 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.

- For women who had radiation therapy to breast tissue: screening mammography and/or MRI (at recommendation of radiologist or ACR guideline) starting 8-10 years post treatment, or age 30, whichever comes later. MRI + mammogram is recommended for survivors under age 40. Survivors over age 50 can be screened with mammography alone.
Oncology Clinic Follow-up Frequency:

<table>
<thead>
<tr>
<th>Time Frame</th>
<th>Follow-up Frequency</th>
</tr>
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<tbody>
<tr>
<td>First year</td>
<td>Visits every 3 months</td>
</tr>
<tr>
<td>2 - 3 years</td>
<td>Visits every 4 months</td>
</tr>
<tr>
<td>4 - 5 years</td>
<td>Visits every 6 months</td>
</tr>
<tr>
<td>&gt; 5 years</td>
<td>annual follow up</td>
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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


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