LYMPHOMA

Effective Date: October 2017

The recommendations contained in this guideline are a consensus of the Alberta Provincial Hematology Tumour Team synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.
# Table of Contents

Background
Guideline Questions
Development and Revision History
Search Strategy
Target Population
Discussion
  I. Diagnosis and Pathologic Classifications
  II. Staging
  III. Treatment of Non-Hodgkin Lymphomas
  IV. Cutaneous Lymphoma
  V. Hodgkin Lymphoma
  VI. HDCT and Hematopoietic Stem Cell Transplantation for Lymphoma
  VII. Supportive Care in the Treatment of Lymphoma
  VIII. Follow-Up Care in the Treatment of Lymphoma

Glossary of Abbreviations
Dissemination
Maintenance
Conflict of Interest
Appendix A (Chemotherapy Regimens)
Appendix B: General Radiotherapy Guidelines
Appendix C: Prognostic Models
Appendix D: Lymphoma Response Criteria
Appendix E: New Lymphoma Patient Data Sheet
Appendix F: Ideal Body Weight
BACKGROUND

Lymphomas encompass a group of lymphoproliferative malignant diseases that originate from T- and B-cells in the lymphatic system. Traditionally, lymphomas have been subcategorized into two groups: Hodgkin lymphoma and non-Hodgkin lymphoma. It is now known however, that Hodgkin lymphoma is simply one of the numerous varieties of lymphoma, and that non-Hodgkin lymphoma is a fairly meaningless term, representing all of the other subtypes of this disease.

Non-Hodgkin lymphoma involves a heterogeneous group of over 40 lymphoproliferative malignancies with diverse patterns of behaviours and responses to treatments. Non-Hodgkin lymphoma is much less predictable than Hodgkin lymphoma and prognosis depends on the histologic type, stage, and treatment. In Canadian males and females, the incidence rates for non-Hodgkin lymphoma showed a marked increase by approximately 50% between 1978 and the late 1990s, but have since stabilized.\(^1\) Mortality rates have followed a similar pattern. The clearest risk factor for the disease is immunosuppression associated with HIV infection, or medications used to prevent rejection in organ transplantation. Other factors that increase risk of non-Hodgkin lymphoma are poorly understood but may include occupational exposures to pesticides, herbicides, and dioxins, as well as chronic immune stimulation associated with autoimmune disorders (e.g. thyroiditis, Sjogren’s Syndrome, SLE) or infections (e.g. *Helicobacter pylori* gastritis, hepatitis C virus).\(^2\) In 2015, it is estimated that 8200 new cases of non-Hodgkin lymphoma will be diagnosed in Canada, and 2650 deaths will occur, making non-Hodgkin lymphoma the sixth most common cause of cancer-related death in Canada.\(^3\)

Hodgkin lymphoma is a malignancy characterized histopathologically by the presence of Reed-Sternberg cells in the appropriate cellular background. Although rare, Hodgkin lymphoma is one of the best-characterized malignancies of the lymphatic system and one of the most readily curable forms of malignant disease.\(^5\) The incidence rate has remained fairly steady over time, it is estimated that approximately 1000 new cases of Hodgkin lymphoma are diagnosed in Canada each year.\(^3\) It is important to note that lymphoma also represents the most commonly diagnosed non-epithelial cancers in adolescents and young adults in Canada. Between 1992 and 2005, 5577 new cases of Hodgkin and non-Hodgkin lymphoma were diagnosed in Canadians aged 15-29 years.\(^1\) **The following guidelines do not address lymphoma in the pediatric or adolescent populations.**

GUIDELINE QUESTIONS

- What are the diagnostic criteria for the most common lymphomas?
- What are the staging and re-staging procedures for Hodgkin and non-Hodgkin lymphomas?
- What are the recommended treatment and management options for Hodgkin and non-Hodgkin lymphomas?
- What are the recommended follow-up procedures for patients with malignant Hodgkin and non-Hodgkin lymphoma?

DEVELOPMENT AND REVISION HISTORY

This updated guideline was reviewed and endorsed by the Alberta Provincial Hematology Tumour Team. Members of this team include hematologists, medical oncologists, radiation oncologists, surgical oncologists, nurses, nurse-practitioners, hematopathologists, and pharmacists. Updated evidence was selected and reviewed by members from the Alberta Provincial Hematology Tumour Team and a Knowledge Management Specialist from the Guideline Resource Unit. The draft guideline was circulated to all tumour team members for comment and approval, and all comments were reviewed by the tumour team lead and incorporated into the final version of the guideline, where appropriate. A detailed
description of the methodology followed during the guideline development and updating process can be found in the Guideline Resource Unit Handbook. The original guideline was developed in March 2006 and was revised on the following dates: May 2007, June 2009, November 2009, January 2011, December 2011, September 2012, April 2013, December 2014, December 2015, February 2016 and April 2016.

SEARCH STRATEGY

Medical journal articles were searched using Medline (1950 to October Week 1, 2015), EMBASE (1980 to October Week 1, 2015), Cochrane Database of Systematic Reviews (3rd Quarter, 2015), and PubMed electronic databases. An updated review of the relevant existing practice guidelines for lymphoma was also conducted by accessing the websites of the National Comprehensive Cancer Network (NCCN), Cancer Care Ontario (CCO), the British Columbia Cancer Agency (BCCA), the European Society for Medical Oncology (ESMO), and the British Committee for Standards in Haematology.

TARGET POPULATION

The following guidelines apply to adults over 18 years of age. Different principles may apply to pediatric and adolescent patients.
REFERENCES


I. DIAGNOSIS AND PATHOLOGIC CLASSIFICATION¹-⁶

An excisional lymph node biopsy of the largest regionally involved lymph node is the optimal specimen for initial diagnostic assessment. Similarly, a sizable biopsy from the organ of origin in extranodal lymphomas is also suitable. Compelling clinical contraindications to an open biopsy should be present before considering any other options. A careful clinical examination or radiological investigations for more accessible or palpable pathologic adenopathy could be useful in decision making prior to opting for a lesser diagnostic specimen. Fine needle aspirate biopsies are inadequate for the initial diagnosis of lymphoma. These latter specimens may provide adequate material for evaluating possible relapse, clarification of staging at questionable sites and as a source of additional specimen where required for further special testing or research. Occasionally, a generous core needle biopsy comprising many core samples with sufficient material to perform the appropriate ancillary techniques required for diagnostic assessment (immunohistochemistry, flow cytometry, PCR for IgH and TCR gene rearrangements, and FISH for major translocations) may supply adequate tissue, in cases when a lymph node is not easily accessible for excisional or incisional biopsy. A reference lymphoma pathologist should confirm lymphoma diagnoses in each and every case. This is particularly important in cases when only a core needle biopsy is available, and whenever requested by the treating clinician.

Table 1 describes the histologic subclassification of the malignant lymphomas, and is an adaptation of the most recent WHO classification⁶. This classification is based on the light microscopic interpretation complemented by special stains, immunophenotyping, cytogenetics and other ancillary information as available. The specific lymphomas are divided into three major groups, according to the degree of clinical aggressiveness, for treatment planning. All B-cell lymphomas should be immuno-phenotyped to determine if they are CD20 positive.
### Table 1. Lymphoma classification.⁶

<table>
<thead>
<tr>
<th>B-cell</th>
<th>T-cell</th>
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<tr>
<td><strong>Indolent</strong></td>
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<tr>
<td>Follicular, grades 1-2, 3a</td>
<td>Mycosis fungoides /Sezary syndrome</td>
</tr>
<tr>
<td>Small lymphocytic Lymphoma/Chronic Lymphocytic Leukemia</td>
<td>Primary cutaneous, CD30+</td>
</tr>
<tr>
<td>Marginal zone, extranodal (MALT)</td>
<td>Primary cutaneous periportal T-cell lymphoma PTCL, CD30-</td>
</tr>
<tr>
<td>Splenic marginal zone</td>
<td>T-cell large granular lymphocytic leukemia</td>
</tr>
<tr>
<td>Marginal zone, nodal (monocytoid B-cell)</td>
<td></td>
</tr>
<tr>
<td>Lymphoplasmacytic (Waldenström’s macroglobulinemia)</td>
<td></td>
</tr>
<tr>
<td>Primary cutaneous, follicle centre</td>
<td></td>
</tr>
<tr>
<td>Hairy cell leukemia</td>
<td></td>
</tr>
<tr>
<td>Nodular lymphocyte predominant Hodgkin Lymphoma</td>
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<tr>
<td>Mantle cell (can be aggressive)</td>
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| **Aggressive** | |
| Diffuse large B-cell | Peripheral T-cell, unspecified |
| o T-cell/histiocyte-rich DLBCL | Angioimmunoblastic (AITL, formerly AILD) |
| o Primary DLBCL of the CNS | Enteropathy associated T-cell |
| o Primary cutaneous DLBCL, leg-type | Hepatosplenic T-cell |
| o EBV-positive DLBCL of the elderly | Subcutaneous panniculitis-like |
| DLBCL associated with chronic inflammation | Anaplastic large cell (CD30+) ALK+ |
| Lymphomatoid granulomatosis | Anaplastic large cell (CD30+) ALK- |
| Primary mediastinal large B-cell | Extranodal NK/T-cell, nasal type |
| Intravascular large B-cell | |
| ALK positive large B-cell | |
| Plasmablastic lymphoma | |
| LBCL in HHV8-associated Castleman disease | |
| Primary effusion lymphoma | |
| Follicular grade 3b (large cell) | |
| Classical Hodgkin lymphoma | |
| ⇒ Nodular sclerosis | |
| ⇒ Mixed cellularity | |
| ⇒ Lymphocyte rich | |
| ⇒ Lymphocyte depleted | |

| **Special** | |
| Burkitt lymphoma | T lymphoblastic leukemia/lymphoma |
| Intermediate between DLBCL and BL | Adult T-cell leukemia/lymphoma (ATLL) |
| Intermediate between DLBCL and Hodgkin lymphoma | T prolymphocytic leukemia |
| B lymphoblastic leukemia/lymphoma | |
| B prolymphocytic leukemia | |
| Lymphomas associated with HIV infection | |
| Lymphomas associated with primary immune disorders | |
| Post-transplant lymphoproliferative disorders (PTLD) | |
| o Plasmacytic hyperplasia and infectious mononucleosis-like PTLD | |
| o Polymorphic PTLD | |
| o Monomorphic PTLD | |
| o Classical Hodgkin-type PTLD | |
| Other iatrogenic immunodeficiency-associated lymphomas | |
Required Immunohistochemical and Ancillary Testing for Lymphoma

In general, guidelines for using the various ancillary methods, including immunohistochemical and fluorescence in situ hybridization (FISH) testing as outlined in the most recent version of the World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues should be followed so as to confirm a specific diagnosis and provide necessary prognostic and/or predictive information. In addition, the following are recommended by the Alberta Provincial Hematology Tumour Team:

1. **Classical Hodgkin Lymphoma**: The immunohistochemical panel may include CD45/CD3/CD20/CD30/CD15/ PAX5/MUM1 and should be selected on a case by case basis at the discretion of the hematopathologist. EBV studies by in situ hybridization (EBER) may be considered if difficulty exists diagnostically, as most cases of the mixed-cellularity subtype of classical Hodgkin lymphoma are EBER positive.

2. **Diffuse Large B-Cell Lymphoma (DLBCL)**:
   - Immunohistochemical (IHC) panels to distinguish between Activated B Cell (ABC) type and Germinal Centre B-cell (GCB) cell of origin (COO) types have limitations (regardless of which algorithm is employed) when compared to gene expression profiling. However, GCB vs non-GCB COO by IHC does correlate with survival rates following RCHOP chemotherapy, and therefore adds prognostic information when managing DLBCL. The Alberta hematopathologists currently use a simple algorithm published by Hans et al, requiring IHC stains for CD10, BCL6 and MUM1, in which CD10+ or BCL6+/MUM1- cases are designated as GCB COO, whereas cases negative for both CD10 and BCL6 or cases with a CD10 negative/BCL6+/MUM1+ phenotype are considered to have a non-GCB COO.
   - EBER and CD5 expression confer worse prognosis, and may be used to identify various clinical-pathological entities with distinct implications. Determining CD5 expression should be considered on all DLBCL cases. EBER should be performed in patients with immune suppression related lymphomas, or those who possibly have EBV-related DLBCL (consider past the age of 50).
   - Rearrangements of the C-MYC gene as determined by FISH, especially in association with BCL2 and/or BCL6 (so called "double hit" or "triple hit" disease) are associated with very poor outcomes following R-CHOP therapy, as well as high rates of central nervous system relapse. Patients with a double-hit or triple-hit lymphoma under age 70 years should receive more aggressive therapy and possibly stem cell transplantation. Though it represents approximately only 5-10% of DLBCL cases, it is very important to recognize these patients, and therefore, MYC rearrangement testing by FISH is to be performed on all patients younger than 70 y.o. with the appropriate lymphoma histology, i.e. DLBCL or lymphoma that are so called “unclassifiable” with intermediate morphological features between DLBCL and Burkitt. If MYC is rearranged, the case should also undergo BCL2 and BCL6 rearrangement testing by FISH. MYC and BCL2 test results are required within 2 weeks of diagnosis for all new patients within the appropriate diagnostic category and age group. FISH testing may also be performed in select instances at the discretion of the reporting hematopathologist if such studies are deemed diagnostically useful.
   - Immunohistochemical studies cannot be used as a surrogate for MYC rearrangement.
   - However, the detection of MYC and BCL2 concurrent overexpression by IHC in so-called “dual expressor” DLBCL, identifies a numerically significant subset of the DLBCL with potentially similar aggressive behavior compared to double-hit lymphoma cases, but representing a distinct group of patients (more often an ABC subtype as opposed to double hit DLBCL which are usually GCB). This group is also associated with a high rate of CNS relapse. Therefore, provided adequate benchmarks and interpretation standards can be established for reproducibility, IHC for MYC and BCL2 expression should also be strongly considered on all DLBCL cases.
3. **Follicular Lymphoma**: must document grade (1-2, 3a or 3b), because all grade 3b should receive R-CHOP rather than other chemotherapy regimens. Also, if a diffuse pattern is present, this should be specified and a relative proportion noted, as outlined in the WHO Classification.

4. **Peripheral T-Cell Lymphoma**: cytotoxic T-cell markers (CD8/CD57/Granzyme B) correlate with poor prognosis and should be considered. Notably, however, peripheral T cell lymphomas are not classified on the basis of these phenotypic markers. EBV studies by in situ hybridization (EBER) should be performed in cases where angioimmunoblastic T cell lymphoma (AITL) and extranodal T/NK cell lymphoma, nasal type enter in the differential diagnosis.

5. **Mantle Cell Lymphoma**: Evidence of CyclinD1 deregulation confirmed by IHC (positive staining for CyclinD1) and/or FISH (positive for t(11;14)) is needed to confirm the diagnosis, provided other morphophenotypic findings are consistent with the diagnosis. Poor prognostic features must be mentioned in the report, including blastoid and pleomorphic morphologic variants. The proliferation index as measured by Ki67 or Mib-1 (used to calculate MIPI score) is to be reported. In cases where it is difficult to differentiate MCL from CLL, flow cytometry for CD200 and IHC for SOX11 may be performed.
REFERENCES


II. STAGING

Mandatory Staging Procedures

- Pathology review whenever possible (essential for core needle biopsies)
- Complete history and physical examination stating ECOG Performance Score, B symptoms
- CBC & differential, creatinine, electrolytes, Alk P, ALT, LDH, bilirubin, total protein, albumin, calcium
- Hepatitis B Surface Antigen, Hepatitis B Surface Antibody, and Hepatitis B Core Antibody must be done prior to initiating chemo/immunotherapy. Patients who are Hepatitis B Surface Antigen positive, and those who are Hepatitis B Core Antibody positive with detectable HBV DNA by Q-PCR should receive suppressive therapy with Lamivudine during and for 3-6 months after completing chemoimmunotherapy. Those who are Hepatitis B Core Antibody positive and Hepatitis B Surface Antibody negative and have no detectable HBV DNA, should undergo serial Q-PCR testing q1-2mo for HBV DNA.
- ESR (for early stage Hodgkin lymphoma)
- Beta-2-microglobulin
- Serum protein electrophoresis and quantitative IgG, IgA, and IgM for indolent B-cell lymphomas
- Pregnancy test: if at risk
- Bone marrow aspiration and 2cm biopsy (BMasp/bx) with flow cytometry for patients with indolent B-cell and a marrow biopsy (without flow cytometry) for aggressive T-cell non-Hodgkin lymphomas. BMasp/bx is not required for Hodgkin lymphoma or DLBCL if a staging PET/CT is performed.
- FDG-PET and Diagnostic CT NeckChestAbdomenPelvis for FDG-avid, nodal lymphomas, which includes all histologies except chronic lymphocytic leukemia/small lymphocytic lymphoma, lymphoplasmacytic lymphoma, mycosis fungoides, and marginal zone NHLs (unless there is a suspicion of aggressive transformation). Nodal lymphomas that are not FDG avid should have a staging diagnostic CT scan of NCAP. PET-CT is especially important for patients who otherwise have non-bulky, stage I-IIA lymphoma, and are being considered for involved field radiation (IFRT) following abbreviated (or no) chemotherapy. PET/CT is not necessarily required for Follicular Lymphoma if the results will not change management, particularly for a patient who will likely undergo watchful waiting.

Table 1. Selected non-routine tests and required presentation

<table>
<thead>
<tr>
<th>Test</th>
<th>Required Presentation/Condition</th>
</tr>
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<tbody>
<tr>
<td>CSF and MRI Brain with gad Brain, intraocular, epidural, testicular, paranasal sinus, kidney, adrenal, or symptoms referable to CNS or nerve roots. Consider for elevated LDH, ECOG 2-4, and &gt;1 ENS.</td>
<td></td>
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<tr>
<td>ENT exam</td>
<td>Suprahyoid cervical lymph node or stomach</td>
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<tr>
<td>UGI &amp; SBFT</td>
<td>Waldeyer’s ring involvement</td>
</tr>
<tr>
<td>Ophthalmologic (slit lamp) exam</td>
<td>Primary brain lymphoma</td>
</tr>
<tr>
<td>HIV serology</td>
<td>If any HIV risk factors. Lymphomas with unusual presentations or aggressiveness including Primary CNS.</td>
</tr>
<tr>
<td>Cardio-oncology imaging (MR or Echocardiogram)</td>
<td>All patients who are planned to receive anthracycline or high dose chemotherapy (esp. &gt; 50 years of age, or with history of hypertension or cardiopulmonary disease)</td>
</tr>
<tr>
<td>Pulmonary function tests</td>
<td>if bleomycin chemotherapy is planned</td>
</tr>
</tbody>
</table>

Table 2. Staging system

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Stage I</td>
<td>Single lymph node region (I) or one extralymphatic organ (IE)</td>
</tr>
<tr>
<td>Stage II</td>
<td>Two or more lymph node regions, same side of the diaphragm (II), or local extralymphatic extension plus lymph nodes, same side of the diaphragm (IIIE)</td>
</tr>
<tr>
<td>Stage III</td>
<td>Lymph node regions on both sides of the diaphragm either alone (III) or with local extra-lymphatic extension (IIIIE)</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Diffuse involvement of one or more extralymphatic organs or sites</td>
</tr>
<tr>
<td></td>
<td>A: No B symptoms</td>
</tr>
<tr>
<td></td>
<td>B: at least one of the following: unexplained weight loss &gt;10% baseline within 6 months of staging, unexplained fever &gt;38°C, or drenching night sweats</td>
</tr>
</tbody>
</table>
For treatment planning, patients are divided into two groups by stage:

1. **Limited Stage**: Non-bulky stage IA(E) or IIA(E) ($\leq$ 3 adjacent lymph node regions)
2. **Advanced Stage**:  
   - Stage II involving $>3$ or non-adjacent lymph node regions  
   - or stage III or IV  
   - or B symptoms  
   - or bulky tumour mass ($\geq 10$cm)

### Restaging Schedule

1. The following are to be performed prior to each chemotherapy treatment:
   - Clinical parameters: brief history and physical examination, toxicity notation, ECOG status  
   - Bloodwork:  
     - CBC/differential/platelet  
     - also consider EP/creatinine and LFTs

2. Requirements for CT scanning of chest/ abdomen/ pelvis:  
   - Routine CT scanning:  
     - after 3 months (4 cycles) of therapy and again after completion of all therapy for Non-Hodgkin Lymphomas  
     - if a residual mass is seen on the CT after completion of all therapy, then repeat a PET/CT for aggressive lymphoma to determine partial or complete remission.  
     - a repeat CT scan should be considered 6-12 months post-treatment; otherwise, no further routine CT scans are required  
     - Hodgkin lymphoma patients should undergo a PET/CT after 2 cycles ABVD (rather than CT after 4 cycles) as outlined below in the Hodgkin Lymphoma treatment guidelines.
   - Other requirements for CT scanning:  
     - as indicated to investigate clinical signs or symptoms, or abnormal laboratory tests

3. Bone marrow aspirate & biopsy (with sample sent for flow cytometry):  
   - Repeat for transplant-eligible patients with aggressive histology lymphomas who otherwise are in complete remission after completion of chemotherapy, if marrow was positive at diagnosis

4. PET/CT Imaging:  
   - Assessment of residual radiographic or clinical abnormalities of uncertain significance at the time of re-staging following completion of therapy.  
   - Hodgkin lymphoma patients should undergo a PET/CT after 2 cycles ABVD (rather than CT after 4 cycles) as outlined below in the Hodgkin Lymphoma treatment guidelines.

### Table 3. PET result significance and treatment recommendations.

<table>
<thead>
<tr>
<th>PET Result</th>
<th>Final Response</th>
<th>Treatment Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>Complete</td>
<td>Observation</td>
</tr>
<tr>
<td>Positive</td>
<td>Partial</td>
<td>Consider biopsy, IFRT, or HDCT/ASCT versus observation</td>
</tr>
</tbody>
</table>
REFERENCES

Treatment of non-Hodgkin lymphomas is based on histologic subtype, extent of disease, and age of the patient. In the case of discordant (2 separate sites of disease with differing types of lymphoma), composite (1 site of disease with 2 discrete types of lymphoma at that site), or transformed (a second lymphoma developing out of a background of previously known lymphoma) lymphoma, treatment must be directed at the most aggressive phase of the disease. Approaches outlined for aggressive lymphomas are generally applicable to both B- and T-cell types. However, treatments for lymphomas presenting at special sites, poor prognosis lymphomas in younger patients, and lymphomas arising in association with immunodeficiency (HIV, post-organ transplant) are outlined in the section titled “Special Problems in Lymphoma Management” below.

### Diffuse Large B-Cell Lymphoma (DLBCL)

<table>
<thead>
<tr>
<th>Stage</th>
<th># Risk Factors*</th>
<th>Treatment**</th>
</tr>
</thead>
</table>
| Limited | 0 | • R-CHOP x 4 cycles if CR by PET/CT 14-21 days after 4th cycle.  
• R-CHOP x6 with IFRT (30-35Gy) if PR by PET/CT after 4th cycle RCHOP  
• RCHOP x3 plus IFRT if patients unable to tolerate more than 3 cycles RCHOP |
| Limited | 1-4 | • R-CHOP x6 cycles with no IFRT if CR by PET/CT 14-21 days after 4th cycle RCHOP  
• R-CHOP x 6 cycles plus IFRT (30-35Gy) if only PR by PET/CT after 4th cycle RCHOP |
| Advanced*** | 0-2 or age>65 yrs | • R-CHOP x 6 cycles possibly followed by IFRT (30-35Gy) to site of prior bulk disease (>10 cm mass) if no CR by PET/CT 21-28 days after 6th cycle RCHOP**** |
| Advanced*** | 3-5 and age <70 yrs | • Acceptable alternatives:  
• R-CHOP x 6, then high-dose therapy/ASCT if no CR or relapse, or  
• R-CHOP x4-6 then high-dose chemotherapy/ASCT in first remission if:  
  • non-GCB COO, or  
  • GCB COO and MYC/BCL2 dual protein expression or PET+ after RCHOPx4.  
• R-CHOEP-14 x 6 cycles (an option only for pts <60yo)  
• IFRT (30-35Gy) to site of prior bulk disease (>10 cm mass) if no CR to chemotherapy**** |

* IPI Risk Factors for Limited Stage: increased LDH, stage II, ECOG performance status 2-4, age>60 years.

**IPI Risk Factors for Advanced Stage: increased LDH, stage III/IV, >1 Extranodal Site, ECOG 2-4, age>60 years.

**R-CEOP should be used for DLBCL patients who have prior cardiac disease and reduced left ventricular ejection fraction. As presented by the BC Cancer Agency at the ASH 2009 Meeting (abstract 408), R-CEOP (etoposide 50mg/m² IV day 1 and 100mg/m² po days 2-3) resulted in a 5 year TTP of 57% for 81 patients with DLBCL.

***For patients >age 60 years, 3-7 days of prednisone 100mg/day pre-R-CHOP as well as G-CSF prophylaxis are recommended to decrease toxicity.

**Important: Patients who present with masses >10cm or bone involvement (esp. stage I-II) should be considered for radiation oncology consultation, even if CR to RCHOP chemotherapy by PET/CT.**

Prophylactic intrathecal chemotherapy has not been proven to decrease meningeal or parenchymal brain relapse of lymphoma in well-designed studies. Due to the lack of proven benefit, intrathecal chemotherapy cannot be recommended even in high risk situations where the risk of CNS relapse is approximately 10% or higher. Also, primary CNS and intraocular lymphomas do not require intrathecal chemotherapy as long as they are treated with IV high-dose methotrexate-based regimens (discussed in “Special Problems in Lymphoma Management” section).
HDCT/ASCT as Part of Initial Therapy for DLBCL

Randomized phase 3 trials have not proven an OS benefit for first remission consolidation with ASCT compared to RCHOP alone for aalPI=2-3 DLBCL patients. Most recently, Chiapella et al. (2017) evaluated Rituximab-dose-dense chemotherapy with or without HDCT/ASCT in 412 patients with aalPI=2-3 DLBCL (DLCL04), and reported improved PFS but not OS with ASCT consolidation53. This is similar to the US intergroup/NCIC study reported by Stiff PJ et al. (2013)54, however, in the latter study, patients who had aalPI=3 experienced statistically significant improvements in 2yr PFS (75% vs 43%) as well as OS (82% vs 64%) with ASCT compared to RCHOP alone, respectively. aalPI does not adequately identify poor prognosis DLBCL in young patients, as evidenced by the OS of 75-80% for aalPI=2 patients in the RCHOP-only arms of the US intergroup trial and the Italian DLCL04 trial. This is supported by unpublished retrospective Alberta population data from a 2013 analysis, wherein 112 HIV-, CNS- patients 18-65 yo with IPI=3-5 DLBCL experienced 5yr OS of 68% with ASCT (n=37) vs 56% without ASCT (n=75), however, including 166 IPI=2-5 patients, the OS difference was not significantly different with (n=46) or without (n=120) ASCT (72% vs 64%). Newer methods of identifying poorly prognosis DLBCL patients include the use of interim or final PET+ response to RCHOP, as well as cell of origin (COO) GCB vs non-GCB, and MYC/BCL2 expression. Ennishi et al. (2017) reported very poor outcomes (5yr TTP <30%) for GCB DLBCL patients associated with high IPI scores and BCL2 translocations, as well as ABC DLBCL associated with high IPI scores and BCL2 gain/expression55. In addition, several investigators have reported very low salvage rates for the use of ASCT for relapsed/refractory MYC/BCL2 dual protein expression DLBCL. As such, patients who present with DLBCL and IPI=3-5 who also have a non-GCB type of DLBCL (esp BCL2+) or GCB DLBCL with MYC/BCL2 expression or PET+ after 4-6 cycles RCHOP are reasonably treated with ASCT consolidation after upfront RCHOP therapy.

Recommendations for CNS Prophylaxis23,48,49,56

For DLBCL, factors associated with high risk (>10%) for relapse in the central nervous system include 4-6 of the following factors: 1) Age >60 years, 2) elevated LDH, 3) ECOG=2-4, 4) Stage 3-4, 5) >1 extranodal site of involvement, and 6) kidney or adrenal involvement. For such high risk patients, CNS prophylaxis should involve high dose intravenous methotrexate 3.5g/m² x 3 doses mid-cycle (~day15) of R-CHOP or R-CHOEP cycles 2, 4, 6. This is particularly the case for patients with 4-6 of the above risk factors who also have DLBCL pathology demonstrating non-GCB cell of origin (eg. CD10- and BCL6- or MUM1+), or dual expression of MYC+ and BCL2+ by immunohistochemistry, where the risk of CNS relapse is 15-20%, as well as those with double hit lymphoma (MYC and BCL2 mutations/rearrangements by FISH). The other high risk presentation is that of testicular lymphoma where CNS prophylaxis should involve high dose intravenous methotrexate 3.5g/m² every 14-28 days x 2-3 doses after completion of all 6 cycles of R-CHOP. The overall chance of cure and patient co-morbidities should be considered before proceeding with methotrexate. For example, high risk IPI DLBCL in patients over age 70 years is associated with low progression-free survival rates, and poor tolerance of methotrexate, so CNS prophylaxis is probably not appropriate.

Treatment of relapsed DLBCL. All patients younger than 65-70 years of age who experience disease persistence or progression after initial RCHOP chemotherapy should be considered for high dose salvage therapy with autologous stem cell transplantation (SCT). These patients should be referred to the BMT clinic as soon as possible, or a transplant physician should be contacted directly to discuss management decisions. Often these patients will require special salvage therapy recommendations that may necessitate management by the transplant program in a hospital setting (e.g., R-DICEP or R-MICE). Potential transplant candidates should receive rituximab with the salvage chemotherapy to maximize the chance of response, and in-vivo purge blood of tumour cells. Other patients who are not transplant candidates could receive conventional salvage therapy regimens such as DHAP, ICE, GDP, CEPP or
MEP. Amongst these options, GDP is generally preferred because it can be given on an outpatient basis. Prognosis of relapsed DLBCL patients who do not undergo high-dose chemotherapy (HDCT) and SCT is extremely poor, with median survival rates of less than 6 months. Palliation is the main goal for non-transplant candidates. Involved field radiotherapy (IFRT) to symptomatic sites may also benefit these palliative patients. Third-line chemotherapy for relapsed DLBCL is rarely of benefit. If done, there has usually been a definite response to second line therapy, with disease control during and for a few months after the second-line treatment finished. Some palliative patients at or beyond second relapse may have symptomatic benefit from prednisone alone, or low dose daily oral chemotherapy with chlorambucil 0.1mg/kg/day or etoposide 50mg/day, or combination oral therapy such as PEPC.

Secondary CNS Lymphoma: 57-60
Selected patients with CNS relapse/progression may be candidates for aggressive therapy as outlined in Appendix A, subheading VIII. One of 3 induction regimens is recommended for transplant-eligible patients and one of two options for transplant in-eligible patients, based on presentation:

1) Isolated CNS lymphoma: HDMTX-based induction then RDHAP for stem cell mobilization and collection, then R-TBUm/ASCT for transplant eligible (table A) or HDMTX/AraC then Ifosfamide for transplant inelgible (table D).

2) Early Systemic and CNS lymphoma (prior to completing RCHOP x6): RCHOP and HDMTX x4 cycles then RDHAP for stem cell mobilization and collection, then R-TBUm/ASCT for transplant eligible (table B) or RCHOP/MTX followed by AraC then ifosfamide in transplant inelgible (table E).

3) Late relapse (prior RCHOP x6) with systemic and CNS lymphoma: HDMTX-Ifosfamide-etopside x2 then RDHAP for stem cell mobilization and collection, then R-TBUm/ASCT for transplant eligible (table C) or palliation for transplant inelgible (table F).

Unfortunately, most patients with secondary CNS lymphoma experience poor response to salvage therapy, including high dose methotrexate/cytarabine-based regimens. These patients who are unfit to receive or do not respond to high dose methotrexate/cytarabine-based therapy are best managed with palliative intent, including possible use of intrathecal chemotherapy or palliative cranial radiotherapy.

Treatment of special DLBCL entities: 24-27,56

Double Hit Lymphoma with MYC and BCL2 mutations/rearrangements by FISH:
The largest multicentre retrospective analysis of 311 double hit lymphoma patients reported an OS rate of <50% if IPI=2-5 vs 65% for IPI=0-1, and >80% if IPI=0 (Petrich AM, Gandhi M, Jovanovic B: Blood 2014;124:2354-61). In addition, the OS rate was approximately 90% for 39 patients who achieve CR following induction chemotherapy and then underwent SCT compared to 60% for 112 patients who achieved CR but did not receive SCT. Although this numerical difference was not statistically significant (p=0.1), it was very clinically significant, indicating that the study was underpowered to draw any meaningful conclusions regarding the role of ASCT consolidation. More recently, Landsburg et al. (2017) reported outcomes of 159 patients with Double-Hit Lymphoma who achieve CR following induction therapy and then underwent SCT compared to 60% for 112 patients who achieved CR but did not receive SCT. Although this numerical difference was not statistically significant (p=0.1), it was very clinically significant, indicating that the study was underpowered to draw any meaningful conclusions regarding the role of ASCT consolidation. More recently, Landsburg et al. (2017) reported outcomes of 159 patients with Double-Hit Lymphoma who achieve CR following induction therapy and then underwent SCT compared to 60% for 112 patients who achieved CR but not an intensive regimen. 61 These studies suggest that DHL patients treated with RCHOP should be considered for ASCT consolidation, esp with IPI=2-5 at diagnosis, however other patients who achieve CR after an intensive induction regimen (such as DA-EPOCH-R or R-CODOXM/IVAC) probably should not receive ASCT consolidation. Due to the lack of prospective randomized controlled studies, however, it is impossible to determine if the optimal approach involves RCHOP induction followed by ASCT or an intensive induction chemotherapy regimen.
Alberta recommendations for special DLBCL entities:

1. DLBCL with MYC mutation by FISH
   - MYC mutated DLBCL (or Intermediate Between DLBCL and Burkitt Lymphoma) but no translocation of BCL2 or BCL6: R-CHOP x 6 cycles for most patients. However, for the poor prognosis situation of MYC mutated and age <70 years and IPI 3-5: R-CHOP x4 then RDHAP or RDICEP x1, then HDCT/ASCT. Alternatively R-CODOX-M/IVAC should be considered
   - MYC mutated and BCL2 or BCL6 mutated (DOUBLE HIT) or BCL2 and BCL6 mutated (TRIPLE HIT).
     - IPI=0-1:
       - RCHOP or RCHOEPx6 with HDMTX after cycles 2,4,6
       - DA-EPOCH-R
     - IPI=2-5: Options include:
       - A. RCHOP or RCHOEPx2-4 with HDMTX after cycles 2 (+4) then RDICEPx1 then HDCT/ASCT using CNS penetrating regimen with either R-BuMel/ASCT or R-MelTBI/ASCT (not BEAM)
         - Note: it is difficult to mobilize autologous blood stem cells after multiple cycles of intensive chemotherapy + G-CSF (eg. RCHOEP or RCODOXM/IVAC), particularly for older patients. Therefore, if the goal is to proceed to transplant, then RCHOPx4 + HDMTXx2 is generally preferred for patients >60 years, or those who received prior chemotherapy for indolent lymphoma in the past and now have transformed disease.
       - B. DA-EPOCH-R or R-CODOX-M/IVAC

2. Intermediate Between DLBCL and Hodgkin Lymphoma:
   - R-CHOP x 6 cycles for most patients
   - consider R-CHOEP x 6 cycles or RCHOP followed by ASCT if high risk factors are present (IPI=3-5)
Figure 1. Treatment algorithm for diffuse large B-cell lymphoma with no double hit (MYC/BCL2 mutations)

### Limited Stage
- Stage I-II and
- No B symptoms and
- No Bulk ≥ 10cm

### STAGE
- Modified IPI (mIPI) score
  - Stage II
  - Age >60 years
  - ECOG 2-4
  - LDH elevated

### Advanced Stage
- IPI score and Age (co-morbid health)
  - IPI=0-2 or
  - Age >65yrs
  - IPI=3-5 &
  - Age <65yrs

### Treatment
- R-CHOP x 4 then PET/CT
- PET –ve: observation (RT if bone)
- PET+: RCHOPx2+IFRT in the site of prior bulk

- R-CHOP x6, PETpost RCHOP4
- PET-ve: no IFRT (RT if bone)
- PET+: IFRT 30-35Gy

- R-CHOP x 6 ± IFRT
- IFRT 30-35Gy esp. if localized PET+ residual

- RCHOPx 6 ± HDCT/ASCT
- or R-CHOEP 14 x6
  - IFRT to bulk if PET + after chemo
  - ± IV HDMTX
  - CNS prophylaxis

- PR/CR (<10cm masses)

Yes

### Possibly Transplant Eligible
- Age <70 years, ECOG 0-2
- LVEF >45%, PFTs >50% predicted
- No active infection or cirrhosis

- R-DICEP or
- R-GDP or

No

### Palliative Rx
- decreased GDP
- CEPP or
- PEPC or
- IFRT

- NR/PD

- High Dose Therapy/ASCT

<table>
<thead>
<tr>
<th>Limited Stage</th>
<th>STAGE</th>
<th>Advanced Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I-II and No B symptoms and No Bulk ≥ 10cm</td>
<td>mIPI=0</td>
<td>mIPI=1-4</td>
</tr>
<tr>
<td>Modified IPI (mIPI) score Stage II Age &gt;60 years ECOG 2-4 LDH elevated</td>
<td>IPI=0-2 or Age &gt;65yrs</td>
<td>IPI=3-5 &amp; Age &lt;65yrs</td>
</tr>
<tr>
<td>R-CHOP x 4 then PET/CT PET –ve: observation (RT if bone) PET+: RCHOPx2+IFRT in the site of prior bulk</td>
<td>R-CHOP x6, PETpost RCHOP4 PET-ve: no IFRT (RT if bone) PET+: IFRT 30-35Gy</td>
<td>R-CHOP x 6 ± IFRT IFRT 30-35Gy esp. if localized PET+ residual</td>
</tr>
<tr>
<td>PR/CR (&lt;10cm masses)</td>
<td>Probably Transplant Eligible</td>
<td>No</td>
</tr>
<tr>
<td>R-DICEP or R-GDP or</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>High Dose Therapy/ASCT</td>
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Follicular Lymphoma

Throughout the following suggested treatment approach, three over-riding principles should be considered:

1. These are guidelines only. This disease often carries a long, incurable, remitting/relapsing natural history and, therefore, several treatment approaches are reasonable.
2. The mere presence of disease does not alone imply the need for treatment.
3. If therapy is required for predominantly localized disease, IFRT should be considered in lieu of systemic pharmacological treatment as long as the radiotherapy can be done with minimal early or delayed side-effects (e.g., xerostomia, severe nausea/vomiting) and without eliminating future treatment options (e.g., should not radiate ≥25% bone marrow). Figure 2 outlines the treatment algorithm for follicular lymphoma.
Figure 2. Treatment algorithm for follicular lymphoma.

**Stage IA or contiguous stage IIA**
- IFRT 24Gy/12 – 30Gy/20 or Consider observation if disease in Chest, abdo, or pelvis

**Advanced stage disease** (Stage III/IV, B symptoms, or bulky mass > 10cm)
- **Indications for Systemic Therapy**
  - Patient symptoms (eg. fever, night sweats, weight loss, malaise, pain, nausea)
  - Significant lymphadenopathy: > 7cm mass, > 3 sites and > 3 cm, rapidly progressive
  - Splenomegaly ≥ 6cm below costal margin or hypersplenism or pain
  - Impending organ compromise (compression, pleural/pericardial effusions, ascites)
  - Cytopenias secondary to bone marrow infiltration
  - Patient preference because of anxiety and poor quality of life without treatment

- **No**
  - Observe (or arrange follow-up)
  - Clinical assessments q3-6 months (*watchful waiting*)

- **Yes**
  - Grade 1,2,3a B-R x 6
  - Then if PR/CR rituximab q3 months x 2 years

  - Grade 3b
    - R-CHOP x 6

  - Serious co-morbidity limited life expectancy
    - Chlorambucil p.o. or fludarabine p.o.

---

**Initial therapy of stage IA and contiguous stage IIA.** IFRT 24Gy/12-30Gy/20 fractions is recommended for newly diagnosed patients with peripheral stage IA or contiguous non-bulky stage IIA follicular lymphoma, even if the patient is asymptomatic.

**Initial therapy of advanced stage disease (stage III/IV, B symptoms, or bulky stage I/II).** Indications for systemic therapy (usually stage III/IV or bulky stage I/II) include:
- Patient symptoms (fever, night sweats, weight loss, malaise, pain, nausea)
- Significant lymphadenopathy (> 7 cm mass, > 3 sites and > 3cm, rapidly progressive)
- Splenomegaly ≥ 6 cm below costal margin, or hypersplenism, or pain
- Impending organ compromise (compression, pleural/pericardial effusions, ascites)
- Cytopenias secondary to bone marrow infiltration
- Patient preference because of anxiety and poor quality of life without treatment

For patients who do not have any of the above indications for therapy, the recommended approach is to observe with (or arrange) follow-up clinical assessments every 3-6 months (“watchful waiting”).

For grades 1,2,3a follicular lymphoma who have an indication for therapy, the recommended therapy involves 6 cycles of B-R (bendamustine-rituximab) chemotherapy, followed in responding patients by 2 years of maintenance rituximab (375mg/m² IV single dose every 3 months for total of eight doses). In patients with previously untreated indolent lymphoma. B-R can be considered as a preferred first-line treatment approach to R-CHOP because of increased progression-free survival and fewer side-effects. Patients who have limited life-expectancy from serious co-morbid illness, or who do not want intravenous therapy, may be treated with oral chlorambucil or fludarabine monotherapy.
The recently reported GALLIUM clinical trial investigated the value of obinutuzumab in combination with chemotherapy followed by maintenance therapy compared to standard therapy with rituximab chemo-immunotherapy plus maintenance in the firstline treatment of follicular lymphoma. The study demonstrates superiority of obinutuzumab over rituximab in terms of PFS (3-year PFS was 81.9% (95%CI: 77.9-85.2%) vs. 77.9% (95%CI: 73.8-81.4%), respectively, HR: 0.71 (95%CI: 0.54-0.93), p=0.014) with acceptable increased toxicity with the use of obinutuzumab (74.6% vs 67.8% of patients experienced a grade ≥3 toxicity, respectively). However, the study is reported with short follow-up (median 34.5 months) and as such, demonstrates no clear OS advantage to the replacement of rituximab with obinutuzumab (p=0.210). Based on the lack of an OS advantage and the greater cost of obinutuzumab (particularly when compared to currently available subcutaneous rituximab), longer follow-up is required before considering the replacement of rituximab with obinutuzumab in frontline therapy for FL.

For grade 3b follicular lymphoma or DLBCL with areas of follicular lymphoma, R-CHOP should be used. Rituximab maintenance has not been proven effective following R-CHOP therapy for large B-cell lymphoma, and therefore is not recommended.

**Therapy of relapsed disease.** Therapeutic recommendations for recurrent follicular lymphoma need to be individualized, and no one recommendation is suitable for all patients. Numerous factors need to be taken into consideration before recommending therapy for recurrent follicular lymphoma, including:

- **Patient Factors:** Age, co-morbidity, symptoms, short vs. long-term goals, preservation of future options, reimbursement/ability to pay for expensive treatments, acceptance of risks/toxicities of treatment option relative to potential benefit (RR, PFS, OS).
- **Disease Factors:** Stage, sites of involvement, grade, transformation, prior therapy, time from prior therapy (disease-free interval).

For example, previously healthy patients younger than 70 years who relapse within 2 years of initial chemotherapy have a median life expectancy of <5 years, and are best managed with HDCT/autologous SCT. HDCT/SCT maximizes the length of disease control for all patients less than 70 years, regardless of length of initial remission, and as such is a reasonable treatment option for those who accept potential risks/toxicities. Therefore, patients younger than 70 years without serious co-morbid disease, and who respond to salvage therapy should be considered for high dose chemotherapy and autologous (relapse 1-2) or allogeneic stem cell transplantation (relapse 3). A large retrospective study of consecutively treated relapsed follicular lymphoma patients in Alberta and BC reported 5 year overall survival rates following relapse of ~90% for those who received ASCT vs ~60% for those who did not receive ASCT. This marked difference in survival retained significance in multivariate as well as instrumental variable analyses.

Conversely, some patients may be best managed by repeating their initial treatment regimen, especially if they achieved an initial remission greater than 5 years. Other patients should be changed to a second line standard-dose chemotherapy regimen (bendamustine, chlorambucil, CVP, fludarabine, etoposide, CEPP, GDP, FND, PEC, or MEP). For patients who have rituximab, it is reasonable to re-treat with rituximab alone or with chemotherapy as long as the patient attained at least a 6 month remission to prior rituximab-based therapy. Rituximab maintenance should only be used once in the course of a patient’s disease (first remission or first relapse). Palliative, symptomatic care (possibly including palliative IFRT 4Gy/2 fractions) is usually the best option for patients who were refractory to their 2 most recent treatment regimens, those with CNS involvement, or those with an ECOG score of 3-4.

A phase 3, open-label, two-arm parallel, randomized trial (GADOLIN), compared obinutuzumab and bendamustine followed by obinutuzumab maintenance to bendamustine alone in patients with rituximab-
refractory, indolent non-Hodgkin lymphoma (failure to respond or progress during or within 6 months of a rituximab containing regimen). The primary outcome was PFS, and other outcomes included OS, overall response, duration of response, quality of life, and adverse events. In the subgroup of patients with follicular lymphoma, the median PFS was 25.3 months in patients treated with obinutuzumab plus bendamustine versus 14 months in patients treated with bendamustine alone (HR[95%CI]: 0.52[0.39,0.69]; p<0.0001). From the April 2016 data cut-off, median OS for obinutuzumab plus bendamustine was not estimable (NE) and median OS for bendamustine alone was 53.9 months (40.9 to NE) (HR[95%CI: 0.58[0.39,0.86]; p=0.0061). While there was no significant advantage reported for patients with other subtypes of iNHL, this was deemed to be based purely on the small numbers in other subgroups. Based on these results, it is recommended that obinutuzumab chemo-immunotherapy be considered in patients with rituximab-refractory iNHL. While the study used bendamustine as a chemotherapy backbone, few patients on the study had received bendamustine as their frontline therapy. Given current practice to use BR for the frontline treatment of FL and the fact that there is no biological reason that the same clinical benefit of obinutuzumab would not be seen in combination with other chemotherapies, alternate NHL chemotherapy backbones could be considered for patients deemed inappropriate for bendamustine retreatment. While there was a higher frequency of serious adverse events in the obinutuzumab plus bendamustine arm, many of these were infusion-related reactions which can be safely managed. Relatively frequent infections were also noted so prophylactic antibiotics and antivirals should be considered, especially when obinutuzumab is combined with bendamustine.
Indolent Lymphomas (Excluding Follicular Histology) 1,110-118

Indolent lymphomas should generally be treated similarly to follicular grade 1-2 lymphomas.

Recurrent CD20+ indolent B-cell lymphomas should be considered for rituximab therapy alone (375mg/m² weekly x 4) or rituximab plus chemotherapy (B-R, R-fludarabine, R-FC, R-FND, R-CVP), or chemotherapy alone (chlorambucil, fludarabine, etoposide, CEPP, GDP, FND, PEC, or MEP). Patients less than 70 years of age without serious co-morbid disease, and who respond to salvage therapy could be considered for high dose chemotherapy and autologous or allogeneic stem cell transplantation.

Table 2. Treatment of Indolent Lymphomas 110

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited</td>
<td>IFRT (24Gy/12 - 30Gy/20)</td>
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</table>
| Advanced| **Asymptomatic:** observation until treatment indication  
|        | **Symptomatic:**  
|        | • majority should receive B-R, then rituximab maintenance  
|        | • alternatives in special situations include IFRT, fludarabine, or chlorambucil |

Splenic Marginal Zone Lymphoma

Splenic marginal zone lymphoma is an uncommon type of non-Hodgkin lymphoma characterized by splenomegaly, cytopenias, lymphocytosis, and less commonly lymphadenopathy. Revised diagnostic criteria now specify the typical blood and bone marrow findings of SMZL and splenic biopsy is not usually required to establish the diagnosis 119. It is still reasonable, however, to proceed with splenectomy if the cause of splenomegaly is not determined following peripheral blood and bone marrow evaluation.

The disease course is indolent and many patients can be managed expectantly until symptomatic splenomegaly or pronounced cytopenias develop. SMZL prognostic scoring systems have been described, with low hemoglobin, low platelets, elevated lactate dehydrogenase and extra-hilar lymphadenopathy as adverse markers 120.

In rare cases, SMZL has been associated with hepatitis C infection (HCV), so all patients should be screened at diagnosis. Those who are HCV+ should first be offered HCV-directed therapy, as the lymphoma may regress avoiding the immediate need for further therapy 121,122. Splenectomy has otherwise been the standard approach to treat SMZL for over two decades 123. The role of splenectomy as frontline treatment of SMZL is now controversial 124,125. One large SEER database review found no improvement on overall survival or lymphoma specific survival following splenectomy 126. On the other hand, a recent single centre registry review suggested that splenectomy remains superior over chemotherapy with improved overall survival (61 vs 42%) and failure free survival (39 vs 13%) at 10 years 127. However, almost half of the patients in the chemotherapy arm were treated in the pre-rituximab era which may have skewed the results in favour of splenectomy. Risks posed by splenectomy include operative morbidity and mortality, particularly in the elderly, or those with multiple comorbidities. However, surgical outcomes are improving at experienced centres. The risk of infection with encapsulated organisms is a serious concern, but may be mitigated with timely vaccination and long-term antibiotic prophylaxis 128.

Monotherapy with rituximab has recently emerged as a non-operative alternative 125,129 with reports suggesting survival outcomes similar to historical patients treated with splenectomy. Chemo-
immunotherapy such as rituximab-bendamustine (BR) is also a rational approach for SMZL given the recent favourable results of a large scale RCT of iNHL, including marginal zone histology\textsuperscript{106}.

Although existing evidence is inadequate to conclude which treatment approach is superior, we propose the following strategy for managing SMZL:

1. Rituximab monotherapy is recommended as frontline therapy for most patients. A standard regimen is rituximab 375mg/m\textsuperscript{2} once weekly for 4 weeks, followed by a response assessment 4-6 weeks later.
   a. Those achieving at least a partial response, defined by conventional response criteria\textsuperscript{119}, should subsequently receive maintenance rituximab (375mg/m\textsuperscript{2} every 3 months for 2 years).
   b. Non-responders or those with progressive disease should proceed with either:
      i. Splenectomy if the spleen is the major site of disease or
      ii. BR for those with additional nodal disease, extensive bone marrow involvement, or non-operative candidates, then followed by maintenance rituximab (375mg/m\textsuperscript{2} every 3 months for 2 years)

2. Select patients who require a splenectomy to establish the diagnosis and have no bone marrow, peripheral blood, or nodal involvement, do not require maintenance rituximab and may simply be observed.
Lymphoplasmacytic Lymphoma (LPL)

**Diagnostic criteria for Waldenström macroglobulinemia (WM):**
- IgM monoclonal gammopathy of any concentration
- Bone marrow infiltration by small lymphocytes showing plasmacytoid/plasma cell differentiation, usually with intertrabecular pattern of bone marrow infiltration
- LPL immunophenotype:
  - surface IgM+ CD5- CD10- CD19+ CD20+ CD22+ CD23- CD25+ CD27+ FMC7+ CD103- CD138-
- Recent findings documented a strong association between WM and the MYD88 L265P variant, which might serve as an additional tool to diagnose WM and to separate it from other entities such as multiple myeloma, monoclonal gammopathy of undetermined significance, splenic marginal zone lymphoma and MALT lymphoma

**Diagnostic approach to confirm a suspected case of WM:**
1. Serum protein electrophoresis with immunofixation: to characterize the type of light and heavy chains.
2. 24-Hour urine for protein electrophoresis: 40%-80% have detectable Bence Jones proteinuria.
4. Bone marrow biopsy: intratrabecular monoclonal lymphoplasmacytic infiltrate, ranging from predominantly lymphocytic to lymphoplasmacytic to overt plasma cells.
5. CT of the abdomen and pelvis: to detect organomegaly and lymphadenopathy (skeletal surveys and bone scans are not necessary in absence of symptoms).
6. Blood or plasma viscosity: if signs and symptoms of hyperviscosity syndrome (HVS) or IgM> 50 g/L.
7. Direct antiglobulin test and cold agglutinin titre if positive.
8. Cryoglobulins.

**IgM monoclonal protein response assessment in WM.** Serum IgM monoclonal protein should be measured by serum protein electrophoresis. The use of nephelometry to determine total serum IgM should be discouraged because this method is unreliable, especially when the levels of monoclonal protein are high. The presence of cryoglobulin or cold agglutinin may affect determination of IgM; therefore, testing of cryoglobulin and cold agglutinin at baseline should be considered, and if present, serum samples should be reevaluated at 37°C to ensure accurate and consistent determination of the monoclonal protein levels.

**Hyperviscosity syndrome (HVS) in LPL.** Symptoms and signs of hyperviscosity include spontaneous bleeding, neurological symptoms and retinopathy. Patients with HVS have an expanded plasma volume and cardiac failure may also occur. There are several published reports demonstrating the efficacy of plasmapheresis in HVS although randomised data are lacking. There is not, however, a simple linear relationship between paraprotein concentration and either plasma viscosity, whole blood viscosity or symptoms. An increase in IgM concentration from 20 to 30 g/L results in an increase in plasma viscosity of <2 centipoise (cP) but an increase from 40 to 50 g/L increases the plasma viscosity by around 5 cP. Indeed, a 1-volume plasma exchange results in a 35-40% decrease in IgM concentration but in up to a 60% reduction in plasma viscosity. In patients with WM the actual plasma volume may exceed that calculated and, given the data above, a 1–1.5 volume exchange is therefore advisable.

**General treatment guidelines for LPL/WM.** The usual indications for starting patients with LPL/WM on active therapy consist of clinical evidence of adverse effects of the paraprotein (HVS with neurological or ocular disturbance, peripheral neuropathy, amyloidosis, symptomatic cryoglobulinemia), symptomatic anemia (Hb<100 g/L...beware of pseudo-anemia from hemodilution), platelets <100, progression to high-grade lymphoma, significant adenopathy or organomegaly, or constitutional symptoms.
**Plasmapheresis:** 1-2 procedures, exchanging 1-1.5 calculated plasma volumes, are advised for the treatment of HVS in WM, followed by chemotherapy to prevent paraprotein re-accumulation. In patients who are drug-resistant, plasmapheresis may be indicated for long-term management. Although there are few studies that consider the role of plasma exchange in the treatment of cryoglobulinemia, there is a clear rationale for its use. The treatment room should be warm and blood warmers used in the cell separator circuit to prevent precipitation during the procedure.

**Chemotherapy:** The most common initial chemotherapy for LPL is B-R (Bendamustine-Rituximab) followed by rituximab maintenance, similar to other indolent B-cell lymphomas. For patients who do not tolerate B-R, CDR (Cyclophosphamide, Decadron, Rituximab) or Bortezomib-based therapy (eg. R-Bortezomib, R-CyBorD) should be considered. Rituximab is active in the treatment of WM but associated with the risk of transient exacerbation of disease-related complications and should be used with caution in patients with symptoms of hyperviscosity and/or IgM levels >40 g/L. In patient with hyperviscosity and/or IgM levels >40 g/L, it is advised to hold rituximab for cycle 1, and start rituximab with cycle 2 chemotherapy. In retrospective studies, purine analogue therapy is associated with higher rates of prolonged cytopenias, infections, secondary MDS/AML, and transformation to large cell lymphoma when compared to therapy with alkylating agents. Autologous SCT is used with increasing frequency for LPL, and as such, purine analogues and chlorambucil should be avoided as initial therapy for transplant-eligible patients to prevent risk of blood mobilization failure in the future.

- Second-line therapy commonly involves a Bortezomib-based regimen (eg. R-Bortezomib, R-CyBorD). Purine analogues (Fludarabine) are usually reserved for multiply relapsed disease.
- Non-chemotherapy options for multiply relapsed patients may involve Ibrutinib, Everolimus, or Thalidomide. Among these options, Ibrutinib is the most effective and least toxic, and is considered the option of choice. In a study of 31 multiply relapsed, rituximab refractory patients, the response rate to ibrutinib was 90% and 18mo PFS was 86% (Dimopoulos MA, Lancet Oncol. 2017 Feb;18(2):241-250)
- **High-dose therapy supported by autologous SCT** has a role in the management of selected patients with WM who have chemosensitive primary induction failure or relapsed disease (preferably first or second relapse). Autologous stem cell collection is often not possible for patients who have received more than 4 months of prior chlorambucil or purine analogue (fludarabine or 2-CDA) therapy. Re-induction therapy prior to ASCT can usually be achieved with R-CyBorD (Cyclophosphamide, Bortezomib, Dexamethasone). As with other indolent lymphomas, allogeneic SCT should be considered at second or third relapse, before the disease develops absolute chemoresistance. Allogeneic transplantation is rarely done prior to autologous SCT for patients in first or second relapse.

**Special Lymphomas**

These diagnoses sometimes constitute an oncologic emergency. Treatment may require intensive high dose chemotherapy with central nervous system prophylaxis, and may need to begin within 48 hours, whether staging is complete or not. Patients should be seen for consultation at a major referral centre and may require complicated high dose chemotherapy regimens. Acceptable treatment approaches for some of the entities are outlined below.

**Mantle cell lymphoma.**

Characteristics of mantle cell lymphoma include: male predominance, median age approximately 65 years, advanced stage with multiple extranodal sites (marrow, blood, and intestinal tract), relative chemoresistance, no evidence for curability following R-CHOP chemotherapy, median time to relapse after initial chemotherapy of 12-18 months and median survival following RCHOP induction of 3-5 years. Significant improvements in PFS over RCHOP alone have been demonstrated for RCHOP/RDHAP induction followed by high dose therapy and ASCT for transplant eligible patients, and for B-R induction for
transplant ineligible patients, as well as for prolonged rituximab maintenance after completing initial chemotherapy.

**Recommendation regarding Watchful Waiting for MCL:**

Although most patients with MCL have relatively aggressive disease, and even those asymptomatic patients initially managed with watchful waiting have median times to first systemic therapy of 11-12 months, a small proportion of patients can be managed expectantly for over 5 years. Features suggestive of indolent MCL include leukemic non-nodal presentations, predominantly hypermutated immunoglobulin heavy chain variable regions, non complex karyotypes and absence of SOX11 expression by immunohistochemistry. Occasionally, nodal MCL can also follow an indolent course. Prognostic indices such as the MIPI have not been shown to identify indolent MCL. Poor prognostic features associated with shorter survivals and response durations, for which expectant management is not appropriate, include high burden nodal disease, Ki-67 positivity >20-30%, blastoid histology, p53 or Notch1 mutation, gene expression profiling and altered microRNA signature. No prospective randomized trials, or properly designed retrospective comparative effectiveness research studies have compared immediate treatment versus watch-and-wait for MCL patients without clear indications for therapy. Poorly designed retrospective studies suggest similar survival outcomes to immediate therapy, however these studies were biased because patients were selected for watchful waiting based upon better prognostic factors (eg. younger age, better performance status) and did not routinely administer immediate aggressive therapy according to current standards to all patients in the control groups. Prospective randomized trials have demonstrated that more aggressive therapy improves PFS and OS rates relative to less aggressive therapy for MCL. Extrapolating these data to the hypothetical question of aggressive therapy vs no immediate therapy leads to the logical conclusion that immediate therapy is likely the superior approach for most MCL patients.

Given the lack of high quality evidence from properly conducted comparative studies to prove the W&W is non-inferior to immediate therapy, W&W should only be considered for patients who present with all of the following features:

1. Non-nodal disease such as CLL-like presentation (lymphocytosis without associated cytopenias) or stage IAE marginal zone-like presentation. Patients presenting with nodal disease should generally receive immediate chemo-immunotherapy as indicated in treatment sections below unless they have significant co-morbidity that will limit life-expectancy, low tumor burden, and meet other criteria listed in this section below.
2. No disease-related symptoms
3. No adverse pathology features such as blastoid variant, Ki67>20% of cells, or complex cytogenetic changes. Other adverse features include SOX11 expression and complex cytogenetic changes, however, SOX11 immunohistochemistry is not currently available in Alberta.
4. Patient consent to forgo immediate therapy despite knowledge of demonstrated survival benefits of aggressive vs less aggressive therapy. Patient agreement to surveillance disease monitoring.

**Treatment – Transplant Eligible Patients (Age <60-65yrs)**

The accepted standard of care for newly diagnosed MCL patients < 60-65 years of age without co-morbidities involves chemoimmunotherapy followed by high dose therapy and ASCT. Progression free and overall survival benefit has been established in a prospective randomized trial for patients treated with myeloablative radiochemotherapy followed by autologous stem cell transplant in first remission as consolidation after CHOP-like chemotherapy. This strategy was compared to interferon alpha...
maintenance and demonstrated a 22mo improvement in progression free survival and 20.5mo improvement in overall survival with ASCT. These benefits of ASCT were seen in patients who had low risk MIPI, and who attained CR after RCHOP induction. Studies from the GELA and the European MCL Network have reported that R-CHOP/R-DHAP induction prior to ASCT (R-CHOP-21 x 3 followed by R-DHAP x3 , or alternating RCHOP/RDHAP x 6 cycles) improves rates of CR, PFS and OS relative to RCHOP x6 induction for transplant-eligible MCL.144 Alternating or sequential R-CHOP/R-DHAP induction is now considered a standard treatment option prior to HDCT/SCT for transplant-eligible mantle cell lymphoma patients, especially those with low or intermediate MIPI scores. If a patient is not considered a good candidate for cisplatin (in DHAP), then a reasonable alternative is the Nordic regimen published as a phase II trial involving RCHOP-21 alternating with Ara-C [3gm² for patients under age 60 years or 2g/m² for patients over 60 years, repeated every 12 hours for a total of 4 doses], for a total of 6 cycles, then ASCT.150 Allogeneic SCT is preferred over autologous SCT for patients less than 65 years of age who have an HLA-matched donor if they have relapsed disease or present with high risk MIPI scores at diagnosis (peripheral blood involvement associated with bulky nodal or other extranodal disease, especially Blastoid variant). Maintenance rituximab was recently shown in the elderly population (age > 60) treated with either R-CHOP or FC-R followed by either Rituximab or IFN-alpha maintenance to prolong overall survival (4 year OS 87% vs. 63%).151

A phase III trial (LyMa) of patients with mantle cell lymphoma who received 4 courses of R-DHAP followed by R-BEAM/ASCT (patients who did not achieve at least PR after R-DHAP could receive 4 additional courses of R-CHOP to facilitate ASCT) randomly assigned PR or CR responders after ASCT to receive 3 years of rituximab maintenance therapy (375 mg/m², one injection every two months) or watch and wait. An interim analysis of all patients (n=299) reported estimated 3 year PFS and OS of 73.7% (95%CI: 67.8-78.7) and 82.6% (95%CI: 77.3-86.8), respectively, after a median follow-up of 35.8 months. Amongst patients who successfully proceeded to randomization (n=119 per arm), median 2-year EFS was 93.2% in the rituximab arm versus 81.5% in the watch and wait arm (p=0.015), after a median follow-up of 29.7 months. However, OS was not significantly different between groups.152 A second interim analysis of the LyMa group found that minimal residual disease (determined through Q-PCR for clonal Ig gene rearrangements on bone marrow and/or peripheral blood) is an early predictor of PFS in younger mantle cell lymphoma patients. The group reported 72% and 79% of patients in the watch and wait arm and 59% and 80% in the rituximab arm were negative for minimal residual disease by bone marrow and peripheral blood, respectively. The estimated 3 year PFS for MRD positive/watch and wait, negative/ watch and wait, positive/rituximab, negative/rituximab patients, according to BM and PB MRD status were: 61.6% (95%CI: 35.4-79.8), 83.9% (95%CI: 73.5-93.4), 80% (95%CI: 50-93.1), vs 92.8% (95%CI: 81.6-97.3), respectively (p=0.0027)153. Additionally, a retrospective review of 72 patients previously enrolled in a phase II trial showed a progression free survival benefit in patients who received maintenance Rituximab vs those who did not (2 year PFS 90% vs. 65%).154 It is reasonable to offer maintenance Rituximab every 3 months x 2 years to patients post ASCT, similar to other indolent lymphoma in first remission.

Treatment – Role of Allogeneic Stem Cell Transplantation

Allogeneic stem cell transplant has the potential to cure MCL, as is evident from a plateau in the survival curves that is often seen post transplant. Because most patients present over the age of 60 and with multiple comorbidities, allogeneic stem cell transplant is not often offered. Currently it is not recommended outside of a clinical trial in front line therapy but is suggested in relapsed or refractory disease for those patients who are young and fit, even after autologous stem cell transplant.
Several retrospective reviews have looked at the outcomes of allogeneic stem cell transplant in the relapsed/refractory setting. Le Gouill et al. have shown a 2 year EFS of 50%, 2 year OS of 53% and 1- and 2-year transplant related mortality of 22% and 32% respectively. Long term follow up has demonstrated 6 year PFS and OS rates of 46% and 53%, respectively confirming the plateau in response that is often seen to allogeneic stem cell transplantation. Response to chemotherapy has consistently been shown to predict both success of allogeneic stem cell transplant and transplant related mortality, with the best outcomes in those who have achieved a CR or CRu. Chronic GVHD has been shown in retrospective reviews to reduce the risk of relapse and DLI has been shown to salvage some patient who relapse or progress post allogeneic stem cell transplant, suggesting a graft-versus-tumour effect in MCL. Reduced intensity Allo SCT in the MCL setting has also been looked at retrospectively with 5 year PFS and OS rates of 14% and 37% respectively, and 1 year non relapse mortality of 18%.

The Calgary experience suggests no difference in OS or PFS when allogeneic vs. autologous stem cell transplantation are used in front-line therapy however, in the relapsed/refractory setting, allogeneic stem cell transplantation appears to offer superior OS and PFS.

**Treatment – Transplant Ineligible Patients (Age >60-65yrs)**

For patients with mantle cell lymphoma over 60-65 years of age, B-R induction x6 cycles followed by rituximab maintenance q2mo until progression is the standard of care. Results from a recently published
open-label, multicentre, randomized, phase 3 non-inferiority trial found a significant benefit for progression-free survival in patients with mantle cell lymphoma treated with B-R versus R-CHOP (HR 0.61, 95%CI 0.42-0.87, p=0.0072). The recently completed European Mantle Cell Lymphoma Elderly trial reported the results of different maintenance therapy regimens for patients older than 60 years of age with stage III-IV mantle cell lymphoma who were not eligible for HDCT. Initially, patients were randomized to 8 cycles of 3 weekly R-CHOP or 6 cycles of 4 weekly R-FC. Patients in complete or partial remission were then randomized to maintenance with rituximab 375 mg/m² every 2 months or interferon-α 2a or 2b; both were continued until progression. After a median follow-up of 30 months, rituximab maintenance was associated with a significantly longer remission duration compared to interferon maintenance (51 vs. 24 months; HR=0.56, 95% CI 0.36-0.88; p=0.0117). While there was no difference in overall survival between the two groups, a subcohort of patients treated with R-CHOP appeared to show an advantage in 3-year overall survival with rituximab versus interferon maintenance (85% vs. 70%, p=0.0375). Grade III-IV hematologic toxicity was higher in the patients treated with interferon. The investigators concluded that R-CHOP induction followed by rituximab therapy should be the standard of care for elderly patients with mantle cell lymphoma. The rare patient who has stage I-IIA, non-bulky mantle cell lymphoma could be considered for B-R + IFRT, or even IFRT alone if they are older than 70 years of age or have significant co-morbidities.

Summary Initial Treatment Recommendations for Mantle Cell Lymphoma:

Watchful waiting should only be considered for patients who present with all of the following features:
1) Non-nodal disease such as CLL-like presentation (lymphocytosis without associated cytopenias) or stage IAE marginal zone-like presentation. Patients presenting with nodal disease should generally receive immediate chemo-immunotherapy as indicated in treatment sections below unless they have significant co-morbidity that will limit life-expectancy, low tumor burden, and meet other criteria listed in this section below.
2) No disease-related symptoms
3) No adverse pathology features such as blastoid variant, Ki67>20% of cells, or complex cytogenetic changes. Other adverse features include SOX11 expression and complex cytogenetic changes, however, SOX11 immunohistochemistry is not currently available in Alberta.
4) Patient consent to forgo immediate therapy despite knowledge of demonstrated survival benefits of aggressive vs less aggressive therapy. Patient agreement to surveillance disease monitoring.

Treatment – Transplant Eligible Patients (Age <60-65yrs)

1) Induction: Alternating or sequential R-CHOP/R-DHAP induction x6 cycles. If a patient is not considered a good candidate for cisplatin (in DHAP), then a reasonable alternative is the Nordic regimen published as a phase II trial involving RCHOP-21 alternating with Ara-C [3g/m² for patients under age 60 years or 2g/m² for patients over 60 years, repeated every 12 hours for a total of 4 doses], for a total of 6 cycles, then ASCT.
2) Autologous blood stem cell collection after cycle 4 induction using R-DHAP and G-CSF mobilization
3) Consolidation: High dose chemotherapy and ASCT
4) Maintenance rituximab 375mg/m2 every 3 months x 2 years post ASCT
Allogeneic SCT should be offered if the following conditions are met:
1) Chemosensitive disease (PR/CR to most recent chemotherapy)
2) ECOG 0-2
3) Disease status first remission to 2nd relapse:
   a. First remission only if: blastoid variant, or high risk MIPI (full myeloablative conditioning).
   b. Relapsed MCL (1st or 2nd relapse only):
      i. >1 year following ASCT (reduced intensity conditioning for alloSCT if prior ASCT)
      ii. If no prior ASCT (full myeloablative conditioning pre-AlloSCT)

Treatment – Transplant Ineligible Patients (Age >60-65yrs)
1) Induction: Bendamustine-Rituximab x6 cycles
2) Rituximab maintenance q2mo until progression or for maximum 4 years

The rare patient with stage I-IIA, non-bulky mantle cell lymphoma could be considered for B-R + IFRT, or even IFRT alone if they are older than 70 years of age or have significant co-morbidities.

Lymphoblastic lymphoma. 158-164
Patients with lymphoblastic lymphoma require aggressive combination chemotherapy, similar to regimens used in acute lymphoblastic leukemia (ALL), involving induction, consolidation, prophylactic intrathecal chemotherapy and either maintenance therapy or first remission allogeneic SCT (occasionally autologous SCT). Refractory or relapsed patients should be considered for allogeneic SCT if not done previously.

Burkitt lymphoma. 165-167
Patients with classical Burkitt Lymphoma require aggressive combination chemotherapy with prophylactic intrathecal chemotherapy. Acceptable regimens such as R-CODOX-M/IVAC are described in Appendix A. First-remission autologous SCT should be considered for patients who cannot tolerate timely administration of full dose R-CODOX-M/IVAC (particularly with adverse prognostic features). Patients who do not have classical Burkitt Lymphoma (eg. Double hit DLBCL, Unclassifiable with features intermediate between DLBCL and Burkitt Lymphoma, etc) do not seem to achieve high cure rates with R-CODOX-M/IVAC, and instead should receive different induction therapy, often with first remission ASCT (see section on DLBCL above).

Special Problems in Lymphoma Management

Gastric MALT lymphoma. 168-176
For complete staging evaluation, patients with gastric MALT lymphoma require gastroscopy and multiple mucosal biopsies for Helicobacter pylori. Stage IAE low grade gastric MALT should be treated with omeprazole 20mg twice daily, clarithromycin 500mg twice daily and either metronidazole 500mg twice daily or amoxicillin 1000mg twice daily for one week, 177 or an equally effective regimen such as the Hp-PAC. After treatment with antibiotics, patients should undergo repeat gastroscopy at 3 months, then every 6 months for 2 years, then annually for 3 years. Biopsies should be taken for lymphoma and H pylori each time. One re-treatment should be tried if H pylori persists. MALT lymphoma may slowly regress over 12-18 months after H pylori eradication. If lymphoma recurs or persists more than 12-18 months after eradication of H pylori, the patient should receive upper abdominal irradiation (30 Gy/20 fractions with POP if anatomy permits, otherwise 4-5 field plan with superior portion AP/PA and inferior portion AP, R lateral and L lateral). Patients with localized MALT lymphomas are reported to have excellent clinical outcomes after moderate-dose radiation, significantly less risk of distant recurrence, and good overall survival. 178 Patients could also be considered for IFRT rather than H pylori therapy if the tumour is associated with t(11;18),
NFkB, or nuclear bcl-10 expression. Stage IIAE or greater gastric MALT should be managed as advanced low grade lymphoma plus eradication of H pylori with antibiotics. Other histologies of gastric lymphoma should be managed as per the sections on aggressive lymphomas or follicular lymphomas above.

**Testicular lymphoma.**

In contrast to other patients with localized large B-cell lymphoma, patients with stage IAE or IIAE testicular lymphoma are cured less than 50% of the time using brief chemotherapy and irradiation. Thus, the recommended treatment for all stages of testicular lymphoma is a full course of chemotherapy (R-CHOP x 6 cycles). An additional problem often seen in these patients is relapse in the opposite testicle. This can be prevented by scrotal irradiation (25-30Gy/10-15 fractions). Finally, these patients are at high risk for CNS relapse. Although some experts recommend prophylactic intrathecal chemotherapy, especially for stage 3-4 disease, this has not been proven effective. Unfortunately, many of the CNS relapses occur within the brain parenchyma, and are not prevented by intrathecal chemotherapy. For this reason, CNS prophylaxis should involve high dose intravenous methotrexate 3.5g/m² every 14-28 days x 2-3 doses after completion of all 6 cycles of R-CHOP.

**Primary CNS lymphoma (PCNSL).**

Diagnosis of PCNSL is based on a biopsy of the brain lesion, or pathological examination of a vitrectomy or CSF specimen. A bone marrow biopsy and CT scan of the chest, abdomen, and pelvis is required to rule out systemic disease. Required staging tests include ophthalmologic slit lamp exam and CSF cytology (only if lumbar puncture is not contraindicated because of intracranial hypertension and midline shift). HIV serology should also be obtained. If initial CSF cytology is obtained while the patient is receiving corticosteroids and is negative, it should be obtained one month after completing all therapy, after corticosteroids have been discontinued.

Treatment of PCNSL involves induction chemotherapy based upon high dose methotrexate 3.5-5g/m² every 2 weeks for 4 to 5 doses. Intrathecal methotrexate has not been shown to be beneficial if high-dose methotrexate is used. In a recent phase II trial, 79 patients aged 18 to 75 years with ECOG 0-3 and mostly low-to-intermediate IELSG risk were randomized to treatment with high dose methotrexate plus cytarabine or high-dose methotrexate alone for 4 cycles every 3 weeks, followed by whole brain radiotherapy (WBRT). The investigators reported superior CR (18% vs. 46%, p=0.006), ORR (40% vs. 69%, p=0.009) and 3 year EFS (24% vs. 35%, p=0.02) for patients treated with high-dose methotrexate and cytarabine versus high-dose methotrexate alone. It is therefore recommended to use high-dose methotrexate and cytarabine during induction therapy for PCNSL.

Whole brain radiotherapy (WBRT) has fallen out of favour for PCNSL, based in part upon high rates of severe neurotoxicity following high-dose methotrexate, and in part due to the results of the G-PCNSL-SG1 randomized controlled trial. In this recently completed trial, 551 immunocompetent PCNSL patients (median age 63 years) were randomized to chemotherapy followed by WBRT (arms A1, B1) or chemotherapy alone (arms A2, B2). 411 patients entered the post-high dose methotrexate phase, and 318 of these patients were treated per protocol. For this per protocol population, there were no differences in median OS (32.4 vs. 37.1 months, p=0.8) or median PFS (18.3 vs. 12 months, p=0.13) between the chemotherapy plus WBRT arms (A1+B1, n=154) or chemotherapy alone arms (A2+B2, n=164), respectively. A recent study suggests neurotoxicity can be reduced by decreasing WBRT dose to 23.4Gy after CR to induction HDMTX-based chemotherapy. The 2-year PFS was 78% in these patients.

Although patients with refractory or relapsed PCNSL typically have dismal outcomes, autologous stem cell transplantation (ASCT) has shown promising results in this setting. Soussain et al. (2001) have reported a
3-year event-free survival (EFS) rate of 53% for patients with relapsed/refractory PCNSL undergoing ASCT following high dose thiotepa, busulfan and cyclophosphamide (TBC) conditioning.\textsuperscript{192}

We previously reported a series of 7 patients treated with TBC/ASCT for PCNSL, including 6 patients who were transplanted as part of planned initial therapy.\textsuperscript{195} At a median follow-up of 24 months, 4 of these 6 patients remained progression-free. Other small studies have also demonstrated durable responses with ASCT for PCNSL, however, the optimal conditioning regimen remains undefined.\textsuperscript{196-198} With the knowledge of our initial encouraging experience with TBC/ASCT,\textsuperscript{195} and the lack of any widely accepted standard treatment for PCNSL, TBC/ASCT consolidation was considered an acceptable option to treat consenting PCNSL patients at our centre. PCNSL patients were initially treated with HDMTX/Cytarabine-based therapy alone. WBRT was reserved for non-transplant eligible patients who did not attain complete remission to chemotherapy alone, or for patients who were not considered candidates for any chemotherapy such as the very elderly, or patients with severe co-morbidities including advanced human immunodeficiency virus (HIV) infections. Other patients were offered planned consolidation TBC/ASCT as part of initial treatment, especially if their disease did not attain complete remission to induction HDMTX-based therapy. We proceeded to treat 21 PCNSL patients aged 34-69 years (median 56) with high dose thiotepa, busulfan, cyclophosphamide (TBC), and autologous stem cell transplant (ASCT) as part of frontline therapy, without WBRT.\textsuperscript{199} Patient characteristics included: Karnofsky performance status (KPS) <70% (n=17), age >60 years (n=8), deep brain involvement (n=16). Treatment-induced neurotoxicity was not observed in any of these patients. Three of the 21 patients experienced primary refractory/progressive disease during HDMTX/Ara-C induction. Currently, 11 of 21 patients (52%) are alive and progression-free at a median follow-up of 60 (6-125) months post-ASCT. Causes of death included progressive PCNSL (n=4), progressive systemic lymphoma (n=1), early treatment-related mortality (transplant-related mortality [TRM], n=3), and 2 late deaths from pneumonia 3 years post-ASCT. All patients who died of TRM were over 60 years of age and had poor performance status. A recent report from centres in the USA confirms these findings. They treated 32 PCNSL patients with 5-7 cycles R-MPV. A total of 25 patients received TBC/ASCT. The 1-year EFS was 78%, the 2-year OS was 76%, TRM was 8% and no patient developed delayed neurotoxicity.\textsuperscript{200}

The important role of Rituximab in treating PCNSL was reported at the June 2015 13th International Conference on Malignant Lymphoma in Lugano, Switzerland. Specifically, the International Extranodal Lymphoma Study Group (IELSG) 32 study\textsuperscript{201} randomized patients with histologically-proven primary CNS lymphoma to receive a maximum of four 3-week cycles of methotrexate at 3.5 g/m\textsuperscript{2} on day 1 and cytarabine at 2 g/m\textsuperscript{2} twice daily on days 2 and 3, either alone (arm A; n = 75), in combination with 375 mg/m\textsuperscript{2} of rituximab on day -5 and 0 (arm B; n = 69), or combined with rituximab at the same dose plus 30 mg/m\textsuperscript{2} of thiotepa on day 4 (MATRIX arm; n = 75). The study was conducted at 52 locations across five countries. The median patient age was 58 years (range, 18-70) and all patients were HIV-negative. Overall, patients had an ECOG PS ≤3, with patients aged 66 to 70 years having an ECOG PS ≤2. Patient characteristics were well balanced among the study arms. Autologous stem cells were collected after the second treatment course. A total of 733 (84%) of planned treatment courses were delivered. Successful collection of autologous stem cells was possible in 152 patients (94%). At a median follow-up of 20 months, 118 patients were failure-free: 48 patients in the MATRIX arm, 35 patients in arm B, and 35 patients in arm A. Responding patients underwent a second randomization comparing consolidation with whole-brain irradiation or autologous stem cell transplantation. Two-year OS rates were 66% (±6%; P = .01) in the MATRIX arm, 58% (±6%) in arm B, and 40% (±6%) in arm A. At 2 years, 124 patients are still alive: 52 patients in the MATRIX arm, 41 patients in arm B, and 31 patients in arm A. FFS rates at 2 years were 64% (±6%) with MATRIX (P = .0006), 52% (±6%) in arm B, and 34% (±6%) in arm A. Five-year FFS rates were 54% (±11%), 43% (±8%), and 34% (±10%), respectively (P = .0001 for arm A vs C). In the
MATRIX arm, the overall response rate was 87% (95% CI, 80-94) compared with 74% (95% CI, 64-84), and 53% (95% CI, 42-64) in arms B and A, respectively (P = .00001 for A vs C). The CR rate was 49% (95% CI, 38-60) in the MATRIX arm, compared with 31% in arm B (95% CI, 21-42), and 23% (95% CI, 14-31) in arm A (P = .00007 for A vs C). A partial response was achieved by 1%, 4%, and 8% in the three arms, respectively. Stable disease was reported for 1%, 16%, and 29% of patients in the MATRIX arm, arm B, and arm A, respectively.201.

In conclusion, the 5 year cause-specific survival rate of 65% and lack of neurotoxicity we observed following first-line consolidation therapy with TBC/ASCT compares favourably to outcomes with non-transplant approaches for PCNSL. However, the high NRM we observed with TBC/ASCT, resulting in an overall 5 year PFS rate of 44%, is concerning. Efforts should be made to better select patients for transplant, including those who are immune competent, under 60 years of age or perhaps 65 years without co-morbidities, and those who have KPS>60% at the time of transplant. Furthermore, we hypothesize that the elimination of cyclophosphamide from the TBC regimen might decrease NRM without substantially decreasing efficacy, and suggest that high dose thiopeta and busulfan (TB) with ASCT be examined in a future PCNSL study.

Rationale behind 2012 PCNSL Treatment Protocol:

1) Induction chemotherapy:
   a. Rituximab to be given for a total of 6 doses during induction therapy to improve response rates.
   b. First 2 cycles: HDMTX 3.5g/m2 d1,15 with procarbazine 100mg/m2 po d1-7. This treatment has been shown to induce response and is tolerable for patients who may be debilitated at the time of initial diagnosis of PCNSL. Cytarabine will not be added to first cycle HDMTX because patients may not tolerate intensive therapy well until performance status improves.
   c. Stem Cell Chemo-Mobilization and Apheresis: Should be done with first dose of Cytarabine because stem cells may not mobilize well after multiple cycles Cytarabine/G-CSF. Rituximab will be used in addition to Cytarabine due to reports that lymphoma cells can circulate in blood and marrow in patients with PCNSL, and Rituximab may decrease risk of collecting contaminated autograft as has been shown for other B-cell lymphomas. The regimen will include Rituximab 375mg/m2 IV d1 and Cytarabine 3 g/m2 d2,3, G-CSF 480-600 μg subcutaneous d9-14 until apheresis completed (plan for apheresis approximately day 13-15, once ANC>5, Plt >75 and CD34>20)
   d. Final 2 Cycles will combine Cytarabine with HDMTX as done in the prior IELSG study to improve response rates and decrease frequency of primary progressive disease.

2) High Dose Chemotherapy (patients <65yo with no significant co-morbidities, KPS>60% after induction therapy, and PCNSL not secondary to immune suppression):
   a. Thiopeta 300mg/m2 x2d and Busulfan 3.2mg/kg x3d without cyclophosphamide. Because cyclophosphamide does not penetrate the blood brain barrier particularly well, its omission may decrease treatment-related mortality without decreasing cure rates compared to the previous TBC regimen.

3) Ifosfamide consolidation (transplant refusal or ineligible patients):
   a. Ifosfamide crosses BBB approximately 30%, and gives some exposure of PCNSL to alkylating agent therapy.
For a detailed description of recommended PCNSL treatment regimens, please refer to Appendix A, subheading VII, sections A and B.

For palliative therapy, doses of cranial radiotherapy should be 30Gy in 10-20 fractions.

**Eye lymphoma.**

*Orbital or peri-orbital lymphoma.*\(^{171,205}\) Peri-orbital lymphoma of the bony orbit or the soft tissues in and around the orbit but outside of the globe and optic nerve should be managed as indicated in the earlier sections on aggressive lymphomas, marginal zone lymphomas or follicular lymphoma, as appropriate for the type and stage of the lymphoma. Approximately 40% of such patients have advanced disease discovered when carefully staged. In general, 25-30Gy/20 fractions radiotherapy to whole orbit/periorbital tissue is recommended for indolent peri-orbital lymphomas.

*Conjunctival lymphoma.*\(^{171,205}\) Lymphoma involving the conjunctiva but not the structures within the globe or the optic nerve is usually of low grade and should be treated with 25-30Gy/20 fractions of radiotherapy. Doses, fields, and shielding specifically modified for treatment of the eye are necessary to minimize long-term complications such as xerophthalmia or cataract formation.

*Intra-ocular and optic nerve lymphoma:*\(^{171,206}\)
- Lymphoma involving the vitreous, retina or other structures within the optic nerve or globe is usually of large cell type and is equivalent to PCNSL. Bilateral involvement is common. Evaluation and management should be the same as for PCNSL. Acceptable treatment involves induction chemotherapy with high dose methotrexate and high dose cytarabine as described for PCNSL in Appendix A.
- Lymphoma involving the uveal structures (choroid) is a rare presentation of lymphoma, and is usually of indolent type. This disease is best managed with treatment appropriate for stage and local extent of disease.
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### IV. Cutaneous Lymphomas

#### Table 1. Classification criteria of primary cutaneous lymphomas (WHO 2016)

<table>
<thead>
<tr>
<th>Disease entity</th>
<th>Subtype</th>
<th>Minimum diagnostic workup</th>
<th>Other useful diagnostic tests</th>
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<tr>
<td><strong>PRIMARY CUTANEOUS T-CELL LYMPHOMAS</strong></td>
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| Mycosis fungoides (MF) | • Classic MF*  
• Folliculotropic MF (fMF)  
• Pagetoid reticulosis  
• Granulomatous slack skin disease | Clinico-pathological correlation supported by immunohistochemistry (CD3, CD4, CD8) and clonality by TCRr | • IHC: CD2, CD5, CD7, CD30, PD1  
• DUSP22-IRF4 translocations (tumor stage)
| | | | |
| Sezary’s syndrome (SS) | | Clinico-pathological correlation supported by skin biopsy (IHC and TCRr as in MF)  
• blood: CD4/CD8 ratio (FC), clonality by TCRr or TCRVbeta chain Abs | PD-1 (IHC and FC)  
Blood: CD5, CD7, CD26, CCR4, CD158k, Sezary cell absolute count in blood smear
| | | | |
| Primary cutaneous CD30+ lymphoproliferative disease | • lymphomatoid papulosis (LyP, types A,B,C,D,E)  
• pcALCL (anaplastic large cell lymphoma) | Typical skin lesions and histopathology  
• IHC: CD3, CD4, CD8, CD30, ALK,EMA  
• TCRr | • IHC: CD2, 3, 5, 7, 15, CD15, CD56, betaF1, MUM-1  
• FISH: 6p25 rearrangement (DUSP22-IRF4)  
• TCRr
| | | | |
| Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) | | Typical skin lesions and histopathology  
• IHC: CD3, CD8, CD4, TIA-1, CD56, CD30, EBER  
• TCRr | • IHC: TIA-1, granzyemeB, CD56, PD-1, CXCL13, CD10, bcl-6, CD20
| | | | |
| EBV-associated T-cell especially extranodal NK/T cell lymphoma | nasal type angioimmunoblastic hydroa vacciniforme-like lymphoproliferative disorder | • EBER by ISH  
• CD3, CD56, CD4, CD8, CD2, CD5, CD7  
• Clinical features: systemic symptoms  
• EBV antibody profile and DNA load  
• TCR and IgH clonality status | IHC: TIA-1, granzyemeB, CD56, CD30, EBER
| | | | |
| Primary cutaneous acral CD8+ lymphoma | | Clinicopathological correlation; typical skin lesions and histopathology  
• IHC: CD4, CD8, CD3, CD2, CD7 7  
• TCRr | IHC: TIA-1 granzyemeB, perforin, KI67, betaF1
| | | | |
| pc CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma | | Clinicopathological correlation; typical skin lesions and histopathology  
• IHC: CD2, 3, 4, 5, 7, 8, 15, 30, 45RA, TIA-1, CD56, betaF1, EBER by ISH  
• TCRr | IHC: TCR-gamma, granzyemeB, perforin
| | | | |
| pc gamma-delta T-cell lymphoma | | • IHC: CD2, 3, 4, 5, 7, 8, 30, 45RA, TIA-1, CD56, betaF1, EBER by ISH  
• TCRr | IHC: TCR-gamma, granzyemeB, perforin
| | | | |
| pc CD4+ small/medium cell T-cell lymphoproliferative | | • Clinical picture, sudden  
• CD4, CD8, CD3, PD-1, CD30, CD7, | IHC: CXCL13, BCL6

*not included in formal WHO classification of pc lymphomas

† DUSP22-IRF4 translocation FISH assay is not routinely available in Alberta
### PRIMARY CUTANEOUS B-CELL LYMPHOMAS

<table>
<thead>
<tr>
<th>Disorder</th>
<th>IHC/TCRr</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>pcPTL NOS</td>
<td>CD2, 3, 4, 5, 7, 8, 30, TIA-1, CD56, betaF1, EBER, TIA-1</td>
<td>TCR-gamma, CXCL13, CD10, bcl-6, CD20</td>
</tr>
</tbody>
</table>

### OTHER LYMPHOMAS PRESENTING IN THE SKIN (not included in WHO2016 classification)

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Clinical Presentation</th>
<th>IHC/TCRr</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravascular B-cell lymphoma</td>
<td>* Intravascular B-cell lymphoma*&lt;sup&gt;*&lt;/sup&gt;</td>
<td>CD2, 3, 4, 5, 7, 8, 30, TIA-1, CD56, betaF1, EBER</td>
<td>-CD30, CD138, FOX-P1, EBER by ISH (in DLBL), Ki-67, Cyclin D1, CD79a, CD21, CD23, MYD88L265P mutation in DLBLLT</td>
</tr>
<tr>
<td>pc follicle center lymphoma (pc FCL)</td>
<td>* Typical skin lesions and histopathology—R/O EBV+ mucocutaneous ulcer*</td>
<td>CD2, 3, 4, 5, 7, 8, 30, TIA-1, CD56, betaF1, EBER, TIA-1</td>
<td>TCR-gamma, CXCL13, CD10, bcl-6, CD20</td>
</tr>
<tr>
<td>pc diffuse large B-cell lymphoma, leg type</td>
<td>* Typical skin lesions and histopathology—R/O EBV+ mucocutaneous ulcer*</td>
<td>CD2, 3, 4, 5, 7, 8, 30, TIA-1, CD56, betaF1, EBER, TIA-1</td>
<td>TCR-gamma, CXCL13, CD10, bcl-6, CD20</td>
</tr>
</tbody>
</table>

---

**Abbreviations:** Pc = primary cutaneous, IHC = immunohistochemistry, TCRr = TCR rearrangement, FC = flow cytometry.
Table 2. Mycosis fungoides and Sézary’s syndrome (Staging (2007 ISCL/EORTC))

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T (skin)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>No clinically and/or histopathologically suspicious lesions</td>
<td>Patch indicates any size skin lesion without significant elevation or induration. Presence/absence of hypo- or hyperpigmentation, scale, crusting, and/or poikiloderma should be noted. Tumor indicates at least one 1-cm diameter solid or nodular lesion with evidence of depth and/or vertical growth. Note total number of lesions, total volume of lesions, largest size lesion, and region of body involved.</td>
</tr>
<tr>
<td>T1</td>
<td>Limited patches, papules, and/or plaques covering &lt;10% of the skin surface.</td>
<td></td>
</tr>
<tr>
<td>T1a</td>
<td>patch only</td>
<td></td>
</tr>
<tr>
<td>T1b</td>
<td>plaque +/- patch</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>Patches, papules or plaques covering =&gt; 10% of the skin surface.</td>
<td></td>
</tr>
<tr>
<td>T2a</td>
<td>patch only</td>
<td></td>
</tr>
<tr>
<td>T2b</td>
<td>plaque +/- patch</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>One or more tumors (=&gt;1-cm diameter)</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>Confluence of erythema covering =&gt;80% body surface area</td>
<td></td>
</tr>
<tr>
<td><strong>N (lymph nodes)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>No clinically abnormal peripheral lymph nodes</td>
<td>Abnormal peripheral lymph node indicates any palpable peripheral node that on physical examination is firm, irregular, clustered, fixed or 1.5 cm or larger in diameter. Node groups examined on physical examination include cervical, supraclavicular, epitrochlear, axillary, and inguinal. Central nodes, which are not generally amenable to pathologic assessment, are not currently considered in the nodal classification unless used to establish N3 histopathologically.</td>
</tr>
<tr>
<td>N1</td>
<td>Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 1 or NCI LN0-2.</td>
<td></td>
</tr>
<tr>
<td>N1a</td>
<td>– clone negative</td>
<td></td>
</tr>
<tr>
<td>N1b</td>
<td>– clone positive</td>
<td></td>
</tr>
<tr>
<td>N2</td>
<td>Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 2 or NCI LN3</td>
<td></td>
</tr>
<tr>
<td>N2a</td>
<td>– clone negative</td>
<td></td>
</tr>
<tr>
<td>N2b</td>
<td>– clone positive</td>
<td></td>
</tr>
<tr>
<td>N3</td>
<td>Clinically abnormal peripheral lymph nodes; histopathology Dutch grades 3-4 or NCI LN4; clone positive or negative</td>
<td></td>
</tr>
<tr>
<td>Nx</td>
<td>Clinically abnormal peripheral lymph nodes; no histologic confirmation</td>
<td></td>
</tr>
<tr>
<td><strong>B (peripheral blood)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B0</td>
<td>Absence of significant blood involvement: &lt;=5% of peripheral blood lymphocytes are atypical (Sézary) cells</td>
<td>For blood, Sézary cells are defined as lymphocytes with hyperconvoluted cerebriform nuclei. Alternatives to Sézary cell count: (1) expanded CD4+ or CD3+ cells with CD4/CD8 ratio of 10 or more, (2) expanded CD4+ cells with abnormal immunophenotype including loss of CD7 or CD26</td>
</tr>
<tr>
<td>B0a</td>
<td>– clone negative</td>
<td></td>
</tr>
<tr>
<td>B0b</td>
<td>– clone positive</td>
<td></td>
</tr>
<tr>
<td>B1</td>
<td>Low blood tumor burden: &gt;5% of peripheral blood lymphocytes are atypical (Sézary) cells but does not meet the criteria of B2</td>
<td></td>
</tr>
<tr>
<td>B1a</td>
<td>– clone negative</td>
<td></td>
</tr>
<tr>
<td>B1b</td>
<td>– clone positive</td>
<td></td>
</tr>
<tr>
<td>B2</td>
<td>High blood tumor burden: =&gt;1000/uL Sézary cells with positive clone</td>
<td></td>
</tr>
<tr>
<td><strong>M (visceral organs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>No visceral organ involvement</td>
<td>For viscera, spleen and liver may be diagnosed by imaging criteria</td>
</tr>
<tr>
<td>M1</td>
<td>Visceral involvement (must have pathology confirmation and organ involved should be specified)</td>
<td></td>
</tr>
</tbody>
</table>
Table 3. Staging of mycosis fungoides and Sezary’s syndrome

<table>
<thead>
<tr>
<th>Staging of MF and SS</th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0,1</td>
</tr>
<tr>
<td>IB</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0,1</td>
</tr>
<tr>
<td>IIA</td>
<td>1-2</td>
<td>1.2</td>
<td>0</td>
<td>0,1</td>
</tr>
<tr>
<td>IIB</td>
<td>3</td>
<td>0-2</td>
<td>0</td>
<td>0,1</td>
</tr>
<tr>
<td>III</td>
<td>4</td>
<td>0-2</td>
<td>0</td>
<td>0,1</td>
</tr>
<tr>
<td>IIIA</td>
<td>4</td>
<td>0-2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IIIB</td>
<td>4</td>
<td>0-2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>IVA&lt;sub&gt;1&lt;/sub&gt;</td>
<td>1-4</td>
<td>0-2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>IVA&lt;sub&gt;2&lt;/sub&gt;</td>
<td>1-4</td>
<td>3</td>
<td>0</td>
<td>0-2</td>
</tr>
<tr>
<td>IVB</td>
<td>1-4</td>
<td>0-3</td>
<td>1</td>
<td>0-2</td>
</tr>
</tbody>
</table>

Staging procedures

- **Complete physical examination:** all stages
- **Skin biopsy:** all stages
- **Lymph node biopsy:** excisional biopsy in patients with N1 or higher or in strong PET-positive nodes
- **Imaging:** For stages T1-2&N0 no additional imaging techniques are necessary. For patients T3 or N1 imaging including CT scan of thorax and abdomen or FDG-PET/CT scan are recommended.
- **Clinical biochemistry:** not included in staging but recommended tests are: CBC with differential, liver function tests, creatinine, LDH
- **TCR rearrangement:** all stages
- **Bone marrow biopsy:** Bone marrow biopsy and aspiration should be carried out in cutaneous lymphomas with an intermediate or aggressive clinical behaviour, but is not required in cutaneous lymphomas with an indolent clinical behaviour (MF, cutaneous anaplastic large-cell lymphoma and cutaneous marginal zone lymphoma), unless indicated by other staging assessments. The significance of bone marrow examination in primary cutaneous follicle centre lymphoma (pcFCL) is controversial.
Treatment of Mycosis Fungoides

MF at early stages (I-IIA) has excellent prognosis and should preferentially be treated with skin-directed therapies (phototherapy, topical steroids, nitrogen mustard). In more resistant cases treatment can be combined with biological response modifiers (IFN-α) and local radiation. Chemotherapy with single agents (gemcitabin, vorinostat, brentuximab vedotin) should be preferred for multiagent chemotherapy (e.g. CHOP). The optimal conditions for bone marrow transplant have not been elucidated, but there is consensus that allogeneic transplant using reduced risk protocol may provide cure in selected cases.

<table>
<thead>
<tr>
<th>Stage</th>
<th>First line</th>
<th>Second line and supportive</th>
<th>Third line</th>
</tr>
</thead>
</table>
| I A   | • Topical steroids  
        • PUVA  
        • UVB-311nm  
        • Topical Carmustine | • Radiotherapy 15-30 Gy  
        • Topical PUVA | • Topical bexarotene  
        • Topical Carmustine |
| I B – II A | • PUVA  
        • UVB-311nm  
        • PUVA + IFN-α  
        • Topical Carmustine | • RePUVA  
        • TSEB 10-40 Gy  
        • Radiotherapy 15-30 Gy  
        • Topical PUVA | • PUVA + oral Bexaroten  
        • Oral Bexaroten  
        • Topical bexaroten  
        • Topical tazarotene  
        • Topical Carmustine |
| II B  | • Radiotherapy for tumors, if required with PUVA/UVB-311nm  
        • PUVA + IFN-α  
        • Topical Carmustine | • TSEB 10-40 Gy  
        • Low-dose MTX  
        • Gemcitabine | • Brentuximab Vedotin  
        • Praletrexate  
        • Bortezomib  
        • Vorinostat  
        • Romidepsin |
| III and Sezary’s syndrome | • As stage IIB  
        • ECP | • TSEB 10-40 Gy  
        • Low-dose MTX | • Alemtuzumab (low dose)  
        • Other agents as in stage IIB, alone or in combination |
| IV A-B | • As stage IIB  
        • Clinical trials | • As stage IIB  
        • CHOP or CEOP | • Other agents as in stage IIB, alone or in combination  
        • Allogeneic bone marrow transplant, reduced risk conditioning |

2 not available in Canada - requires Special Access Program (SAP).  
3 mechlorethamine is no longer available. Topical Carmustine ointment is available and is able to be compounded.  
4 Total skin electron beam irradiation: Not available in Alberta; the only Canadian center is Credit Valley Hospital, Mississauga (Glenn Jones).  
5 Not available in Canada - requires Special Access Program (SAP).  
6 available through AHS Cancer Control  
7 Not covered by AHS Cancer Control. Patient assistant program available. Drug dispensed through patients retail pharmacy  
8 ECP (extracorporeal phoropheresis): available at the Apheresis Unit in the Foothills Hospital in Calgary. The patient is given a psoralen derivative and then undergoes leukopheresis. The blood is passed through an aperture that exposes it to UV light, activating psoralen in the lymphoma cells, killing the cells. The dead cells may then act as better antigens and generate an immune response to the CTCL. Best suited for erythrodermic CTCL and Sezary’s syndrome.  
9 requires request through pharmaceutical company Clinigen.
### Staging and Treatment of Non-MF Cutaneous Lymphomas

#### Table 5. Diagnostic workup and staging

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T</strong></td>
<td>Solitary skin lesion</td>
</tr>
</tbody>
</table>
| T1 | • T1a: a solitary lesion with diameter <5cm  
• T1b: a solitary lesion with diameter >5cm |
| T2 | Regional skin involvement (multiple lesions limited to 1 body region or 2 contiguous body regions) |
| T2a | • skin lesions present in a <15-cm diameter circular area  
• skin lesions present in a >15-cm and <30-cm diameter circular area  
• skin lesions present in a >30-cm diameter circular area |
| T3 | Generalized skin involvement |
| T3a | • multiple lesions involving 2 noncontiguous body regions  
• multiple lesions involving 3 or more body regions |
| **N** | No clinical or pathologic lymph node involvement |
| N0 | No clinical or pathologic lymph node involvement |
| N1 | Involvement of 1 peripheral lymph node region that drains an area of current or prior skin involvement |
| N2 | Involvement of 2 or more peripheral lymph node regions or involvement of any lymph node region that does not drain an area of current or prior skin involvement |
| N3 | Involvement of central lymph nodes |
| **M** | No evidence of organ disease |
| M0 | No evidence of organ disease |
| M1 | Extracutaneous organ disease |
### Staging and Treatment of Other Types of Cutaneous Lymphomas

**Table 6. Diagnostic workup**

<table>
<thead>
<tr>
<th>Disease entity</th>
<th>Laboratory and radiologic workup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphomatoid papulosis</td>
<td>• Screening for concurrent cancer may be warranted in elderly patients or presence of risk factors</td>
</tr>
</tbody>
</table>
| pcALCL                                                                        | • CBC with diff, blood chemistries and LDH  
• PET/CT or CT  
• Lymph node biopsy (if clinically or radiologically abnormal)  
• Bone marrow biopsy in patients with evidence of extracutaneous disease or multiple tumors |
| Subcutaneous panniculitis-like T-cell lymphoma (SPTCL)                        | • CBC with diff, blood chemistries and LDH,  
• PET/CT or CT  
• Lymph node biopsy (if clinically or radiologically abnormal)  
• Bone marrow biopsy in patients with evidence of extracutaneous disease, multiple tumors or hematocytophagic syndrome |
| CD4+ small/medium cell primary cutaneous T-cell lymphoproliferative disorder | • None                                                                                                                                                                                                                           |
| Aggressive pcCTCL: Extranodal NK/T-cell lymphoma, CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma; gamma-delta T-cell lymphoma, Blastic plasmacytoid dendritic cell neoplasm | • As other aggressive lymphomas                                                                                                                                                                                                    |
| Extracutaneous MZL with cutaneous presentation                               | • CBC with diff, blood chemistries and LDH  
• Borrelia serology                                                                                                                                                                                                                   |
| pcFCL                                                                         | • CBC with diff, blood chemistries and LDH  
• PET/CT or CT  
• Lymph node biopsy (if clinically or radiologically abnormal)  
• Bone marrow biopsy                                                                                                                                                     |
| pc diffuse large B-cell lymphoma,                                           | • CBC with diff, blood chemistries and LDH  
• PET/CT  
• Lymph node biopsy (if clinically or radiologically abnormal)                                                                                                                                                                  |
| Primary cutaneous acral CD8+ lymphoma                                        | None                                                                                                                                                                                                                             |
### Table 7. Treatment of other types of cutaneous lymphomas

<table>
<thead>
<tr>
<th>CTCL Subtype</th>
<th>First line treatment</th>
<th>Second or third line treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphomatoid papulosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Solitary lesion</td>
<td>Observation</td>
<td>Topical carmustine 0.2-0.4%*</td>
</tr>
<tr>
<td></td>
<td>Topical high potency corticosteroids</td>
<td></td>
</tr>
<tr>
<td>• Large/stigmitizing lesion</td>
<td>Surgical excision</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Local radiotherapy</td>
<td></td>
</tr>
<tr>
<td>• Multifocal or frequently recurrent</td>
<td>Narrow band UVB</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Psoralen UVA light therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low dose MTX (5-25mg/wk)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary Cutaneous ALCL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Solitary lesion</td>
<td>Surgical excision</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Local radiotherapy (15Gy)</td>
<td></td>
</tr>
<tr>
<td>• Multifocal or frequently recurrent</td>
<td>Low dose MTX (5-25mg/week) maintenance</td>
<td></td>
</tr>
<tr>
<td>• Extracutaneous involvement</td>
<td>CHOP or CEOP</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subcutaneous panniculitis-like T-cell</td>
<td>Systemic corticosteroids, alone, or in combination with</td>
<td></td>
</tr>
<tr>
<td>lymphoma</td>
<td>methotrexate</td>
<td></td>
</tr>
<tr>
<td>• Associated hemophagocytic syndrome</td>
<td>CHOP or CEOP x 6 +/- HDT-ASCT in eligible patients</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary cutaneous acral CD8+ T-cell</td>
<td>Intralesional corticosteroids</td>
<td></td>
</tr>
<tr>
<td>lymphoma Provisional entity</td>
<td>Local radiotherapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary cutaneous CD4+ small/medium T-</td>
<td>Observation</td>
<td></td>
</tr>
<tr>
<td>cell lymphoproliferative disorder</td>
<td>Topical corticosteroids</td>
<td></td>
</tr>
<tr>
<td>• If tumour rapidly growing or &gt; 5cm,</td>
<td>Intralesional corticosteroids</td>
<td></td>
</tr>
<tr>
<td>High Ki67</td>
<td>Local radiotherapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary cutaneous aggressive</td>
<td>Multiagent chemotherapy (CHOP or CEOP) plus IFRT 30Gy/10 or</td>
<td></td>
</tr>
<tr>
<td>epidermotropic CD8+ cytotoxic T-cell</td>
<td>or 45Gy/25</td>
<td></td>
</tr>
<tr>
<td>lymphoma or Primary cutaneous γδ T-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cell lymphoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blastic plasmacytoid dendritic cell</td>
<td>Multiagent chemotherapy (CHOP or CEOP)</td>
<td>Single agent chemotherapy (Gemcitabine)</td>
</tr>
<tr>
<td>neoplasm (CD4+/CD56+ hematodermic</td>
<td>Acute lymphoblastic leukemia type protocol if concurrent</td>
<td></td>
</tr>
<tr>
<td>neoplasm)</td>
<td>bone marrow involvement</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Allogeneic stem cell transplantation in eligible candidates</td>
<td></td>
</tr>
<tr>
<td>Primary cutaneous extranodal NK/T</td>
<td>Combined Modality (CHOP or CEOP plus IFRT) for localized</td>
<td></td>
</tr>
<tr>
<td>cell lymphoma, nasal type</td>
<td>presentation SMILE or equivalent for advanced stage</td>
<td></td>
</tr>
<tr>
<td>Primary Cutaneous Marginal Zone</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Lymphoma or Primary Cutaneous Follicle Center Lymphoma

<table>
<thead>
<tr>
<th>Primary Cutaneous Large B cell lymphoma, leg type</th>
<th>Surgical excision</th>
<th>Local radiotherapy (15-35Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solitary lesion</td>
<td>Observation</td>
<td>Chlorambucil</td>
</tr>
<tr>
<td>Multifocal lesions</td>
<td></td>
<td>Rituximab monotherapy*</td>
</tr>
<tr>
<td><em>B. burgdorferi</em> associated pcMZL</td>
<td></td>
<td>Antibiotics (cephalosporin or doxycycline)</td>
</tr>
</tbody>
</table>

| Primary Cutaneous Large B cell lymphoma, leg type | R-CHOP x 6 +/- IFRT | IFRT +/- rituximab monotherapy* if frail |

- **Short term director’s privilege (STDP) required**
- **Short term exceptional drug therapy (STEDT) approval required**
- **Health Canada Special Access Program required**
- **Not covered by AHS Cancer Control Drug Benefit list. Manufacturer’s reimbursement assistance program available. Dispensed through retail pharmacy**
- **Manufacturer application required for access. Drug not funded.**
Aggressive T-Cell Lymphomas

NK/T-cell lymphoma, nasal type.\textsuperscript{29-37} Natural killer (NK)/T-cell lymphoma, nasal type is a rare and aggressive extranodal neoplasm that almost exclusively affects Asian and South American adults in the fifth decade of life, with a male:female ratio of approximately 3:1. It typically arises in the nasal cavity or surrounding structures, such as the sinuses, palate, nasopharynx, tonsils, hypopharynx, and larynx. While the pathogenesis of NK/T-cell lymphoma, nasal type is not well understood, the Epstein-Barr virus (EBV) is implicated in almost all cases. Approximately 25% of cases show a p53 mutation; in addition, p21 over-expression is also frequent in nasal NK/T-cell lymphoma, and seems to be independent of p53 gene status.\textsuperscript{32}

Hematopathological evaluation of a biopsy specimen from the site of involvement is the basis for diagnosis of nasal NK/T-cell lymphoma. The recommended immunohistochemistry panel includes:\textsuperscript{30,38}

- B-cell: CD20
- T-lineage antigens: CD2, CD7, CD8, CD4, CD5, CD3
- NK lineage markers: CD56
- Cytotoxic granules (granzyme B and/or TIA-1)
- Ki-67
- In situ hybridization for EBV-encoded RNA (EBER)

For patients with early-stage nasal NK/T-cell lymphoma, early or upfront radiotherapy (intensive regimens such as a total dose ≥ 50 Gy) plays an essential role in therapy, and has been associated with higher overall survival and complete response rates compared to chemotherapy alone.\textsuperscript{33} However, radiotherapy alone is also associated with high relapse rates. Combined modality therapy is recommended. In a phase II trial involving 30 patients treated with concurrent radiation (40–52.8 Gy) and weekly cisplatin (30mg/m\textsuperscript{2}) followed by 3 cycles of VIPD chemotherapy (etoposide 100mg/m\textsuperscript{2} d1-3 + ifosfamide 1.2g/m\textsuperscript{2} d1-3 + cisplatin 33mg/m\textsuperscript{2} d1-3 + dexamethasone 40mg d1-4), \textit{Kim et al.} reported an overall response rate of 83.3\%, and a complete response rate of 80\%.\textsuperscript{33} The 3-year progression-free and overall survival rates were 85.2\% and 86.3\%, respectively. While 26 patients completed all 3 cycles, there was a high rate of grade 4 neutropenia (41.4\%). Similar results have been described in a phase I/II study involving 26 assessable patients treated with radiotherapy (50 Gy) and 3 courses of dexamethasone, etoposide, ifosfamide, and carboplatin (DeVIC).\textsuperscript{35} In another recently completed phase II trial, 31 patients with stage I or II disease were treated with radiotherapy 40–50.4 Gy plus cisplatin 30mg/m\textsuperscript{2} weekly, followed by 2 cycles of VIDL (etoposide 100mg/m\textsuperscript{2} d1-3, ifosfamide 1200mg/m\textsuperscript{2} d1-3, dexamethasone 40mg d1-3, and L-asparaginase 4000U/m\textsuperscript{2}).\textsuperscript{36} The overall response rate after the concurrent chemo-radiotherapy was 90\%, and after VIDL was 92.6\%; one-year progression-free survival was approximately 75\%; lower than with VIPD, though a lower total dose of radiation was provided in this study and is postulated as the cause of the reduced PFS. Grade 3-4 leucopenia was reported in 85.1\% of patients, and hepatic toxicity associated with L-asparaginase, the majority of which was grade 1 or 2, was reported in 55\% of patients. Despite these results, L-asparaginase appears to be an active agent in this disease and most novel regimens incorporate L-asparaginase into treatment. One such regimen, GOLD (gemcitabine, oxaliplatin, L-asparaginase, dexamethasone) was recently reported in N=55 patients of whom 10 had stage III/IV disease. Amongst patients treated with the GOLD regimen, 91\% (48/55) experienced a response, with 62\% (34/55) having a complete response, and 29\% (15/55) a partial response. In patients with stage I/II disease, 1-year PFS and OS were 87\% and 98\%, respectively. In patients with stage III/IV disease, 1-year PFS and OS were 66\% and 75\%, respectively.\textsuperscript{39}

For patients with stage III-IV disease, complete remission rates are less than 15\%, and the median overall survival is approximately 4 months.\textsuperscript{37} The recommended options for therapy include either enrollment in a
clinical trial or treatment with an L-asparaginase-based combination chemotherapy regimen. The most well-studied regimen is the SMILE regimen with several small series of patients reported. While the SMILE regimen was first reported to have excellent response rates (overall, and complete in 79% and 45%, respectively) in relapsed/refractory patients, an updated study of the use of the SMILE regimen as frontline therapy for advanced stage patients reported a short median OS (12.2 months; 1-year OS was 45%) with a high rate of TRM (5 of 87 patients died of sepsis). While the GOLD regimen has less reported patients, the toxicity is significantly less (Grade 3-4 neutropenia of 16% compared to SMILE of 92% with serious infections in 4% and 31-45% of patients treated, respectively). For this reason, patients of advanced age or with comorbidities or a history of infections should be considered for therapy with GOLD for 2-4 cycles followed by SCT if possible while younger, fit patients can be treated with SMILE x 2 cycles with a goal of proceeding to SCT as consolidation. The role of allogeneic or autologous SCT is not yet well defined however, as data is limited but it is suggested when possible for advanced stage or relapsed/refractory patients.

**Peripheral T-cell lymphomas (PTCL).**

With the exception of ALK-positive anaplastic large cell lymphoma, CHOP chemotherapy cures less than 30% of patients with PTCL. Options that may be associated with higher cure rates include CHOP x 4-6 cycles followed by HDCT/ASCT in responding patients or intensification of CHOP with etoposide (CHOEP). The German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL) analyzed results of 343 PTCL patients treated within their trials. The majority belonged to the four major T-cell lymphoma subtypes: anaplastic large cell lymphoma (ALCL), ALK-positive (n=78); ALCL, ALK-negative (n=113); peripheral T-cell lymphoma, unspecified (PTCLU; n=70); and angioimmunoblastic T-cell lymphoma (AITL; n=28). Treatment consisted of 6-8 courses of CHOP or etoposide plus (CHOEP). Three-year event-free and overall survival rates were 75.8% and 89.8% for the ALCL, ALK-positive patients, 50.0% and 67.5% for the AITL patients, 45.7% and 62.1% for the ALCL, ALK-negative patients, and 41.1% and 53.9% for the PTCLU patients. The International Prognostic Index (IPI) was effective in defining risk groups with significantly different outcomes. For patients, 60 years of age or younger with LDH levels ≤ upper normal value, etoposide was associated with an improvement in 3-year EFS (75.4% vs. 51.0%, p=0003). Aviles and colleagues recently reported the results of a phase III trial involving 217 patients with PTCL unspecified. Patients were treated with either CMED every 14 days x 6 cycles or standard CHOP. The 10-year PFS was 70% in the CMED group versus 43% in the CHOP group (p<0.01), and the 10-year OS was 60% in the CMED group versus 34% in the CHOP group (p<0.01).

Retrospective and prospective phase II trials support the use of SCT as part of upfront therapy for PTCL. Sieniawski and colleagues reported 5-year PFS rates of 60% for 26 patients with enteropathy associated T-cell lymphoma treated with IVE-methotrexate induction therapy followed by autologous SCT, compared to only 22% for 54 patients treated with CHOP-like therapy alone. Two prospective trials have also been reported. In the first, Reimer and colleagues reported results of CHOP x 4-6 cycles followed by dexabeam or ESHAP followed by CyTBI/ASCT for 83 patients (including 32 with PTCL-not otherwise specified, and 27 with angioimmunoblastic T-cell lymphoma). Fifty-five of the 83 patients received transplantation. In an intent-to-treat analysis, with a median follow-up time of 33 months, the estimated 3-year OS, DFS, and PFS rate were 48%, 53%, and 36%, respectively. In the second prospective trial, Rodriguez and colleagues from the Spanish Lymphoma and Autologous Transplantation Cooperative Group reported the results of 74 patients transplanted in the first complete response (65% had 2-3 aPI risk factors). With a median follow-up of 67 months from diagnosis, the 5-year OS and PFS rates were 68% and 63%, respectively.
For PTCL patients who relapse following CHOP-type induction and respond to salvage therapy, ASCT should be recommended, as several studies report similar ASCT outcomes to those seen with relapsed DLBCL. Brentuximab vedotin may be considered for those patients with CD30+ anaplastic large cell lymphoma who have had failure of initial chemotherapy.54

**Summary of treatment recommendations for PTCL:**
1. Anaplastic large cell lymphoma, ALK positive: CHOP x 6 cycles
2. NK/T-cell lymphoma, nasal type:
   - recommendation for stage I-II NK/T cell lymphoma: IFRT as initial therapy (either 30Gy/10 fractions IFRT or concurrent 40-50Gy IFRT+ weekly cisplatin 30mg/m²) then follow IFRT with VIPD x 3 cycles (etoposide 100mg/m² d1-3 + ifosfamide 1.2g/m² d1-3 + cisplatin 33mg/m² d1-3 + dexamethasone 40mg d1-4)
   - if IFRT must be delayed for 2 or more weeks after diagnosis due to scheduling issues, then d1-4 of GDP could be administered while waiting for IFRT
3. All other subtypes of PTCL:
   - <60 years of age with IPI=0-2: CHOEP x 6 cycles
   - <60 years of age with IPI=3-5: CHOP or CHOEP x 4 cycles, then mobilize stem cells with high-dose MTX 3.5g/m² IV d1 and cytarabine 3g/m² IV d9-10, G-CSF 480-600 mg SC daily d16-21 followed by apheresis d22-23, then HDCT/ASCT
   - >60 years of age: CHOP or CEOP x 6 cycles +/- HDCT/ASCT

**AIDS-related lymphomas:**55-60
In general, the treatment of AIDS-related lymphoma should be the same as for non-AIDS related lymphoma if the AIDS does not otherwise compromise the patient’s performance status and he/she is free of coincident serious opportunistic infection. HAART should be given with CHOP chemotherapy. Treatment should be planned in conjunction with the patient’s HIV physician and an antiviral regimen without overlapping toxicity should be chosen. R-CHOP results in the highest rates of disease-free survival, but may also increase the risk of infectious complications and treatment-related mortality in patients with CD4 counts below 50.

**Post-transplant lymphoproliferative disease (PTLD) after Solid Organ Transplant in Adults:**
1. **Epidemiology.** Post-transplant lymphoproliferative disorder (PTLD) is a heterogeneous disease with clinical and pathologic manifestations ranging from benign lymphoid hyperplasia (ie. early lesions) to aggressive lymphoma (ie. monomorphic PTLD)61,62. PTLD and its treatment cause a high rate of mortality and graft loss in patients with solid organ transplants (SOT)63. The incidence of PTLD is highest in multivisceral (>10%) and lowest in renal transplants (1-5%), attributed to intensity of immunosuppression and amount of lymphoid tissue in the allograft64-66. Epstein-Barr virus (EBV) infection drives the pathogenesis in PTLDs occurring early post-transplant; conversely, PTLDs occurring after prolonged immunosuppression tend to be monomorphic with no detectable EBV genome, calling an infectious etiology into question67. An epidemiologic shift in PTLD has occurred in the most recent decade: the median latency time from transplant to PTLD has increased from 1 to 3 years68,69 and the proportion of EBV-positive vs. -negative PTLD has decreased70, attributed to EBV viral load monitoring in EBV seronegative (ie. high risk) patients.

2. **Diagnosis and staging.** Diagnostic tissue must be reviewed by expert pathologists and subtyped according to the WHO[1]. Several small case series have confirmed that PET-CT is an effective imaging modality for staging in PTLD71-76. However, some subtypes of PTLD, such as early lesions and T-cell lymphomas, may not be FDG-avid, necessitating CT as an alternate staging modality.
3. **Management.** Recommendations for the management of PTLD in SOT are based on few phase II clinical trials, retrospective case series, and expert opinion. The mainstays of therapy for CD20-positive PTLD in SOT include reduction of immune suppression (RIS), rituximab, and chemotherapy; adoptive immunotherapy is promising but considered experimental and is unavailable in Alberta. All patients should undergo RIS to the lowest tolerated levels under the direction of the transplant physician as soon as the diagnosis of PTLD is confirmed. A recommended strategy is to discontinue antiproliferative agents and reduce the calcineurin inhibitor by 25-50% while maintaining the steroid.

Published response rates vary widely (0-73%) and responses are seen within 2 to 4 weeks.

3a. **Early lesions, polymorphic and CD20-positive monomorphic PTLD.** RIS may serve as definitive treatment of early lesions, but if response is incomplete further treatment with surgery or radiation is favored. In contrast, polymorphic and monomorphic PTLDs require definitive treatment along with RIS, discussed in further detail below (Figure 3).

**Surgery and radiation.** Patients with localized PTLD, such as isolated skin, GI or renal allograft lesions, can achieve prolonged remissions with surgery or localized radiation. Some experts consider surgical resection of isolated GI lesions prior to initiating systemic therapy to reduce early mortality from bowel perforation. Radiation alone is generally not curative, with exception of plasmacytoma-like PTLD, and should not be used as primary treatment. Radiation may be used for palliating obstructive or compressive symptoms where systemic therapy fails or is not possible.

**Chemotherapy.** SOT patients do not tolerate chemotherapy well, often developing severe infection or prolonged cytopenias. Estimates of efficacy of chemotherapy in treatment of PTLD in SOT are limited by the almost entirely retrospective nature of publications. Results of retrospective studies of anthracycline-based chemotherapy, mainly CHOP, show ORRs of 65-73% and 5-year OS of 25-78%; however, treatment-related mortality (TRM) is up to 31%.

**Rituximab.** Several retrospective reviews and phase II clinical trials have confirmed the efficacy of rituximab monotherapy in CD20-positive PTLD post-SOT in patients that fail to respond to RIS. Phase II trials show overall response rates (ORR) of 44% to 71% and CR rates of 26% to 53% after 4 weekly doses with no reported TRM. However, 57% of patients treated with rituximab monotherapy in 2 prospective trials had progressive disease within 12 months; risk factors for survival and need for further treatment included age > 60, ECOG ≥ 2, elevated LDH, and lack of CR after rituximab. Therefore rituximab causes minimal toxicity but remissions achieved are durable in only a minority of patients.

**Sequential therapy.** Efficacy of a sequential treatment regimen (4 weekly doses of rituximab followed by 4 cycles of CHOP) was established in a phase II international multicentre trial in adult CD20-positive PTLD in SOT (n=70) in an attempt to improve upon the success of rituximab monotherapy and diminish the toxicity of chemotherapy. The ORR was 60% after initial rituximab, increasing to 90% after sequential chemotherapy. EBV-positive and –negative PTLDs responded equally. OS was 61% at 3 years and time to progression was 69% at 3 years. There were no TRM events related to rituximab and 11% ascribed to CHOP. In a subsequent analysis, the authors concluded that patients who achieved CR and those in PR with a low-risk IPI score after rituximab monotherapy had a low risk of disease progression.

A subsequent phase II trial utilized risk-stratified sequential therapy, in which patients in CR (by CT) after 4 doses of rituximab received 4 further 3-weekly doses of rituximab, and those not in CR after initial rituximab proceeded to RCHOP (4 cycles supported with GCSF). With 152 patients treated, endpoints
were superior to sequential therapy (3-year OS 70%, 3-year TTP 73%, TRM 7%), and response to initial rituximab was highly predictive of OS, TTP and PFS (p<0.001)\textsuperscript{97,98}

In summary, rituximab monotherapy is effective first-line treatment in most CD20-positive PTLDs with minimal toxicity. Risk-stratified sequential therapy offers the highest survival rates published to date, and allows patients in CR after rituximab monotherapy to avoid chemotherapy. Close follow-up for disease progression is recommended for patients that received rituximab alone. For PTLD that behaves aggressively (ie. IPI 3-5) or progresses during initial treatment with rituximab, proceed directly to RCHOP before completing 4 doses of rituximab (Figure 3).

3b. Primary CNS PTLD. In the largest reported retrospective series of primary CNS PTLD (n=84), patients treated with rituximab and/or cytarabine (most often given after MTX) survived longer, but significant variation in regimens precluded firm conclusions\textsuperscript{99}. Patients with acceptable renal function and performance status should be offered high-dose methotrexate and rituximab, and others may benefit from palliative radiation\textsuperscript{78,99}.

3c. Burkitt Lymphoma PTLD. Several case series cite acceptable outcomes in this rare subtype of PTLD with chemotherapy regimens ranging in intensity\textsuperscript{100-102}. However, no definite recommendations can be made and treatment should be considered individually.

3d. CD20-negative monomorphic PTLDs. Rare subtypes of PTLD that resemble non-transplant lymphomas, such as Hodgkin Lymphoma-like PTLD, T cell monomorphic PTLD, plasmablastic PTLD and plasma cell dyscrasias, require specific chemotherapeutic treatment similar to their non-transplant counterparts (reviewed by\textsuperscript{77,78}).

4. Prognosis. The risk of death from NHL is significantly higher in SOT compared to non-transplant patients\textsuperscript{103}, and PTLD increases the graft failure rate 5-fold\textsuperscript{104}. Retrospective series of PTLD post-SOT report OS of 30-68% at 5 years, with excess mortality in the first year post-diagnosis\textsuperscript{64,69,105-107}. Adverse prognostic factors from retrospective studies include monomorphic subtype, monomorphic T-cell, bone marrow or CNS involvement, advanced stage, poor performance status, advanced age, elevated LDH, and hypoalbuminemia\textsuperscript{66,69,91,107-109}. Risk factors for worsened OS in the PTLD-1 prospective trial include IPI 3-5, thoracic organ transplant and lack of CR after rituximab monotherapy\textsuperscript{96}. A prognostic score developed from 500 PTLD cases in renal transplant patients is described in Table 8; the score was calculated with the exclusion of patients with monomorphic T-cell and CNS PTLD, both of which carried an adverse prognosis, but the score maintains its ability to discriminate risk groups in the whole population\textsuperscript{105}. 

\textsuperscript{78,99}
Figure 1. Treatment Algorithm for Polymorphic or Monomorphic (DLBCL) PTLD Post-SOT

1. Polymorphic OR CD20-positive Monomorphic B-cell (DLBCL)
2. Reduce immunosuppression (RIS)
3. Rituximab weekly x 4
   - IPI 3-5 at diagnosis OR progression on Rituximab
     - CR
     - No CR
       - Rituximab q 3 weeks x 4
       - RCHOP x 4 cycles
         - GCSF support
Table 8. Post-Transplant Lymphoproliferative Disorders in Renal Transplant Prognostic Score\textsuperscript{105}. (One point is given for each of elevated LDH, disseminated PTLD (ie. higher than stage 1), monomorphic PTLD, and serum creatinine level >133 µmol/L; 2 points are given for creatinine >133 µmol/L if age > 55 at PTLD diagnosis.)

<table>
<thead>
<tr>
<th>Risk Group (# Risk Factors)</th>
<th>% Alive at 1/5/10 years</th>
</tr>
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<tbody>
<tr>
<td>Low (0)</td>
<td>100/92/85</td>
</tr>
<tr>
<td>Moderate (1)</td>
<td>89/83/80</td>
</tr>
<tr>
<td>High (2-3)</td>
<td>74/59/56</td>
</tr>
<tr>
<td>Very High (4-5)</td>
<td>52/35/0</td>
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REFERENCES


V. HODGKIN LYMPHOMA

Pathologic Classification

The histological sub-classification of Hodgkin lymphoma is based on the light microscopic H&E interpretation. If problems with differential diagnosis arise, staining for CD15, CD30, T-cell and B-cell panels and EMA may be helpful. For lymphocyte predominant Hodgkin lymphoma, CD20, CD45, +/- CD57 are recommended.

Table 1. WHO classification of histologic subtypes of Hodgkin lymphoma

<table>
<thead>
<tr>
<th>Classical</th>
<th>Nodular Sclerosis</th>
<th>Mixed Cellularity</th>
<th>Lymphocyte Rich</th>
<th>Lymphocyte Depleted</th>
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<tr>
<td>Nodular Lymphocyte Predominant</td>
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Staging

Mandatory staging procedures include:2-8

- Pathology review whenever possible (essential for core needle biopsies)
- Complete history and physical examination (B symptoms, Etoh intolerance, pruritis, fatigue, ECOG performance score, examination of nodes, Waldeyer’s ring, spleen, liver, skin)
- CBC & differential, creatinine, electrolytes, Alk P, ALT, LDH, bilirubin, total protein, albumin, calcium
- ESR (required for limited stage patients)
- If a PET/CT is not done, then perform a bone marrow aspiration and biopsy (2cm core preferable) for patients with stage IIB-IV or cytopenias (note: flow cytometry on the marrow aspirate does not add useful information and should not be done)
- Chest x-ray (PA and lateral)
- CT scan of the neck, chest, abdomen, and pelvis
- A PET scan with body CT is preferred as initial staging and after 2 cycles of ABVD.9-14
- Pregnancy test, if at risk (consider fertility and/or psychosocial counseling)
- Semen cryopreservation if chemotherapy or pelvic radiotherapy is contemplated
- HIV: if HIV risk factors or unusual disease presentations

Primary Treatment of Classical Hodgkin Lymphoma15-19

**General principles:** For treatment planning, supradiaphragmatic clinical stage (CS) I or II without bulk (mass >10cm or >1/3 maximal transthoracic diameter (MTD) on CXR) or significant B symptoms is considered limited stage. Initial treatment options for classical Hodgkin Lymphoma involve the chemotherapy regimens ABVD or escalated BEACOPP as well as involved field radiotherapy (IFRT). Multiple studies phase III studies conducted by the German Hodgkin Study Group (GHSG) and other cooperative study groups have demonstrated that optimal cure rates are achieved with: 1) ABVD x2 cycles followed by 20Gy IFRT for favorable risk limited stage disease (5yr PFS >90%); 2) ABVD x4 cycles followed by 30Gy IFRT for unfavorable risk limited stage (> 3 nodal sites, ESR > 50 or >30 with B symptoms, or extranodal disease) (5yr PFS >85%); 3) escalated BEACOPP x 6 cycles for young healthy patients with advanced stage disease; and 4) ABVD x6 cycles for patients >60 years or with co-
morbidities. Advanced stage patients also receive IFRT following chemotherapy to localized PET+ residual disease >2.5cm, and is considered to sites of prior bulk after ABVD.

Data supporting escalated BEACOPP for advanced stage disease: The GHSG HD9 trial conducted in the 1990s demonstrated that 8 cycles of an escalated-dose BEACOPP regimen were superior to 8 cycles of a COPP/ABVD regimen or 8 cycles of a baseline-dose BEACOPP regimen in terms of freedom from treatment failure and overall survival rates in patients with advanced-stage Hodgkin lymphoma. Each regimen was followed by consolidative radiation therapy to sites of initial bulky disease greater than 5 cm. At the 10-year analysis, freedom from treatment failure was 64% for the COPP/ABVD group, 70% for the baseline BEACOPP group, and 82% for the escalated BEACOPP group (p<0.001); overall survival rates were 75%, 80%, and 86%, respectively (p<0.001). There were higher rates of hematologic toxicities, grades 3-4 infections and higher rate of AML/MDS in the escalated BEACOPP group, but not an increase in all second malignancies. A meta-analysis of 4 subsequent phase III trials confirmed superior PFS (OR 0.56, 95%CI 0.38, 0.81) and long-term overall survival (OR 0.64, 95%CI 0.51, 0.81) with escBEACOPP compared to ABVD. Of importance, escBEACOPP is associated with infertility, especially in male patients. Sieniawski et al. (2008) reported that 34 of 38 patients with advanced-stage Hodgkin lymphoma became azoospermic after treatment with 8 cycles of BEACOPP, and that of the remaining 4 patients, 2 had impaired spermatogenesis.

The German Hodgkin Study Group recently published the results of their HD15 prospective randomized clinical trial. 2182 patients with newly diagnosed Hodgkin lymphoma aged 18-60 years with stage IIB (large mediastinal mass or extranodal lesions), or stage III-IV disease were randomly assigned to receive either 8 cycles of escalated BEACOPP (8Besc), 6 cycles of escalated BEACOPP (6Besc), or 8 cycles of BEACOPP14 (8B14). After completion of chemotherapy, patients in partial response with a persistent mass measuring 2.5 cm that was positive on centrally-reviewed PET scan received additional radiotherapy with 30Gy. The full analysis set comprised 2126 patients: 705 treated with 8Besc, 711 treated with 6Besc and 710 treated with 8B14. Baseline characteristics were balanced between groups with a median age of 33 years and 334 patients (15.7%) in stage II disease. 32.1% had an International Prognostic Score (IPS) of 0-1, 52.4% had a score of 2-3, and 15.5% had a score of 4-7. Hematological toxicities occurred in 92.4% (8Besc), 91.7% (6Besc), 91.7% (8B14) of cases. After a median follow-up of 48 months, there were 53 deaths (7.5%) in the 8Besc group, 33 (4.6%) in the 6Besc group and 37 (5.2%) in the 8B14 group. The higher number of deaths in the 8Besc group mainly resulted from acute toxicity of chemotherapy and secondary neoplasms. There were 72 secondary cancers including 29 secondary acute myeloid leukemias and myelodysplastic syndromes: 19 (2.7%) in the 8Besc group, 2 (0.3%) in the 6Besc group and 8 (1.1%) in the 8B14 group. Complete response was achieved in 90.1% of patients after 8Besc, 94.2% after 6Besc and 92.4% after 8B14 (p=0.01). Five year OS rates were 91.9% in the 8Besc group, 95.3% in the 6Besc group, and 94.5% in the 8B14 group. PET scans performed after chemotherapy for 822 patients revealed that 739 were in PR with residual mass ≥ 2 cm having no other exclusion criteria. 548 patients were PET-negative (74.2%) and 191 were PET-positive (25.8%). PFS was comparable between patients in CR or those in PET-negative PR after chemotherapy with 4-year PFS rates of 92.6% and 92.1%, respectively. Only 11% of all patients in the HD15 trial received additional radiotherapy as compared to 71% in the prior HD9 study. Based on results from this HD15 trial, the investigators concluded that 6 cycles of escalated BEACOPP followed by PET-guided IFRT is the new standard of care for the German Hodgkin Study Group.
Due to concerns of toxicity, escalated BEACOPP in Alberta should only be considered for the following patients: 2,21,22,26-30

- Age < 60 years
- KPS score > 70 (ECOG 0-2)
- HIV negative, no other major co-morbidities
- Patients must be made aware of infertility implications, and consent to proceed

Although the above-described treatment approaches (outlined in Figure 4B) currently optimize cure rates from initial therapy, they result in: 1) the frequent use of radiotherapy that contributes to late mortality from second cancers and cardiac disease; 2) the use of multiple cycles of Bleomycin that may cause serious lung toxicity; or 3) the use of escalated BEACOPP that increases the risk of serious infections and therapy-related MDS/AML. By avoiding these added risks of non-relapse mortality, it is estimated that similar long-term survival rates can be achieved with a PET-guided approach that minimizes therapy for patients whose lymphoma is highly sensitive to ABVD, while only subjecting less responsive patients to the potential toxicities of IFRT or escalated BEACOPP.

Data Supporting a PET-Guided Treatment Approach:31-34: In the UK Rapid trial, patients with stage I-IIA non-bulky HL received ABVD x3 cycles then underwent a PET scan. If the PET was positive (uptake more than blood pool, Deauville score 3-5) the patients received one more cycle ABVD then IFRT, whereas if the PET was negative patients were randomized to observation or IFRT. The 3yr PFS was 85.9% in the 145 PET+ patients, 94.6% in the PET- patients who received IFRT and 90.8% in PET- patients who were observed. The difference in PFS was -3.8% (95%CI: -8.8%, 1.3%) exceeding -7% non-inferiority margin. Of interest, the per-protocol PFS was 97% vs 90.7% because 28pts did not get allocated IFRT. The respective 3 year overall survival rates were 97.1% vs 99.0%. In the EORTC/LYSA/FIL HD10 trial, stage I-II HL patients were randomized between control arm therapy with ABVD x3 +INRT (favorable risk) or ABVD x4 +INRT (unfavorable risk), with all patients undergoing PET after cycle 2 ABVD. In the experimental arm of the study, patients received ABVD x2 then a PET scan, followed by ABVD x 2 (favorable) or 4 (unfavorable) if PET-, or escBEACOPP x2 cycles +INRT if PET+. Comparing control (INRT) and experimental (no INRT) arms for patients with negative PET after 2 cycles ABVD, the difference in PFS was -11.9% (95%CI -16.9%, -8.2%) for favorable risk (not meeting non-inferiority endpoint) and -2.5% (95%CI -6.6%, 0.5%) for unfavorable risk (meeting non-inferiority). For patients with PET+ disease after ABVD, the 5y PFS 77% vs 91% (p=0.002) and 5yr OS 89% vs 96% (p=0.06) was superior with escBEACOPP than further ABVD. Regarding advanced stage disease, a UK RathL trial treated patients with 2 cycles ABVD then performed a PET scan. In total, 172 patients with PET+ disease (uptake > liver, Deauville 4-5) received BEACOPP whereas PET- patients were randomized to ABVD x4 (n=470) or AVD x4 (n=465). For PET- patients, 3yr PFS was 85.7% vs 84.4% for ABVD vs AVD (95%CI crossed 5% difference non-inferiority limit), the respective 3yr OS rates were 97.2% vs 97.6%, and the rate of grade 3-4 pneumonitis was 1% vs 0.2%, respectively. Of interest, a prior phase GHSG III trial found that omitting agents from ABVD x2 prior to IFRT for favorable risk limited stage HL resulted in lower 5 PFS rates (5yr FFTF 93.1% ABVD, 89.2% AVD, 77.1% AV, 81.4% ABV) and did not recommend this strategy. In view of the fact that the RathL trial failed to meet its non-inferiority endpoint and only demonstrated a small reduction is serious pulmonary toxicity by eliminating bleomycin from the final 4 cycles of ABVD, it seems most reasonable to adopt this strategy only for those patients with risks factors for bleomycin lung toxicity (COPD / ↓PFTs, CrCl <80ml/min, Stage IV, Age >40yr), or those with any clinical or PFT evidence of acquiring bleomycin lung toxicity at any time during therapy.

Based upon the above data, it is reasonable to adopt a PET-guided therapy approach for early and advanced staged Hodgkin lymphoma, which will minimize the long-terms risks of cytotoxic chemotherapy.
and radiotherapy for PET- patients after ABVD x2, while maintaining PFS rates <5% inferior to conventional combined modality treatments. This PET-guided approach is illustrated in Figure 4A, and is currently the preferred approach in Alberta, especially at centres where PET scans are more easily available. For centres where PET scanning is not available, or in situations when patients prefer to prioritize their initial cure rate and avoidance of intensive salvage therapy with autologous SCT rather than prioritize a similar long-term survival while minimizing therapy-related second cancers, cardiovascular mortality or bleomycin lung toxicity, the more traditional therapy approach illustrated in Figure 4B is still very reasonable.
Figure 1. Treatment algorithm for Hodgkin lymphoma using PET-Guided therapy (Preferred Approach)

**Limited Stage**
- Stage I-II and
- No B symptoms (unless other cause) and
- No mass > 10cm or >1/3 maximal transthoracic diameter (MTD) on CXR

ABVD x2

PET/CT

-ve

+ve

F: ABVD x2
U*: ABVD x4

Omit Bleo if:
- COPD / ↓PFTs
- CrCl <80ml/min
- Age >40yr

eBEACOPP* x2
IFRT 30Gy

If Age <60yrs & fertility not NB (esp if IPS high)

Consider IFRT alone for favorable CS IA NS HL involving <3cm high neck or epitrochlear nodes only

**Advanced Stage**
- Stage III-IV or
- Definite B symptoms or
- Bulky mass > 10 cm or
- >1/3 MTD on CXR

ABVD x2

PET/CT

-ve

+ve

Risk for Bleo Lung Toxicity
- COPD / ↓PFTs
- CrCl <80ml/min
- Stage IV
- Age >40yr

eBEACOPP* x4
If Age <60yrs & fertility not NB (esp if IPS high)
IFRT to final PET+ residual mass

Yes

AVD x4

No

AVD x4

*Unfavourable Risk Limited Stage:
Any of:
- ESR > 50 (or >30 with B symptoms)
- ≥ 3 sites disease
- extranodal disease

IPS Risk Factors
- Age ≥ 45years
- Stage IV
- Male
- Lymphocyte < 0.6 or <8%WBC
- Hb < 105
- WBC ≥ 15
- Albumin <40

IFRT = Involved field radiotherapy; 20-30Gy/ 20 fractions

For ABVD x4-6: Perform pulmonary function test at baseline and after cycles 3 and 5; omit bleomycin if >25% decrease in DLCO or FVC; decrease bleomycin dose by 50% if 10-24% decrease in DLCO or FVC

*escBEACOPP should only be considered for the following patients:
- Age < 60 years
- KPS score ≥ 70 (ECOG 0-2)
- HIV negative, no major co-morbidities
- Pts must be made aware of infertility implications, and consent to proceed
Figure 2. Treatment algorithm for Hodgkin lymphoma without using PET-Guided therapy.

Limited Stage
Stage I-II and
No B symptoms and
No bulk > 10cm

Advanced Stage
Stage III-IV or
B symptoms or
Bulk > 10 cm mass

STAGE

Unfavourable Risk
ESR > 50
≥ 3 sites disease or
extranodal disease

IPS Risk Score
- Age ≥ 45 years
- Stage IV
- Male
- Albumin <40

0-2
3-7

Abnormal Risk

ABVD x 2 then IFRT 20Gy

ABVD x 4 then IFRT 30Gy

ABVD x 6 ± IFRT 30Gy
IFRT to prior bulk with
PET positive residual
Mass >2.5cm

escBEACOPP* x6
or ABVD x 6
then
IFRT to prior bulk > 10 cm
(if PET positive residual
mass >2.5cm)

Recurrent Hodgkin Lymphoma

Re-biopsy and re-stage

Initial Relapse:
GDP or DICEP
then
high dose therapy and autologous SCT
± IFRT 20-30Gy to prior bulk site at relapse

Second or Subsequent Relapse
- IFRT if localized relapse in previously non-irradiated site
- Brentuximab vedotin if chemotherapy and ASCT failed
- Palliative chemotherapy for symptomatic patients (COPP, CHIVPP, PEPC, GDP, vinblastine, gemcitabine, lomustine)
- Allogeneic SCT only in motivated healthy patients < 60 years with chemosensitive disease, ECOG 0-2, and time to relapse of > 1 year following HDCT/Autologous SCT

*escBEACOPP should only be considered for the following patients:
- Age < 60 years
- KPS score ≥ 70 (ECOG 0-2)
- HIV negative, no major co-morbidities
- Pts must be made aware of infertility implications, and consent to proceed
Management of Recurrent Hodgkin Lymphoma\textsuperscript{2,35-50}

Similar to the initial workup, recurrent disease should involve re-staging tests.

\textit{Initial relapse:}
- Re-induction chemotherapy with GDP or DICEP then high dose therapy and autologous SCT \pm IFRT 20-30Gy to prior bulk site at relapse, or PET-positive residual disease post-ASCT

\textit{Second or subsequent relapse:}
- IFRT if localized relapse in previously non-irradiated site
- Brentuximab vedotin IV q21d for up to 16 doses if prior failure of initial chemotherapy (ABVD or BEACOPP) and prior autologous SCT
- Palliative chemotherapy for symptomatic patients (GDP, COPP, ChlVPP, CEPP, vinblastine)
- Allogeneic SCT only in motivated healthy patients <60 years old with chemosensitive disease, ECOG 0-2, and time to relapse of >1 year following high dose therapy and autologous SCT
- A PD1-inhibitor (eg. Nivolumab or Pembrolizumab) should be considered after prior failure of chemotherapy (and autologous SCT in transplant eligible patients) as well as prior failure of Brentuximab vedotin.

Nodular Lymphocyte Predominant Hodgkin Lymphoma\textsuperscript{51}

This rare subtype comprises \textasciitilde5\% of Hodgkin lymphomas and has a very indolent course with excellent survival. Despite the name, clinical, biological, morphological and immunophenotypic features of NLPHL significantly differ from classical Hodgkin lymphoma. Patients most commonly present with early stage disease, the clinical course is indolent and the prognosis is very favourable. Similar to other indolent CD20+ lymphoma, late relapses as well as transformation to DLBCL (3–5\% of cases) can occur. Even after relapse, patients may survive for many years, and therefore minimizing risk of treatment-related mortality is important.

In terms of treatment recommendations, surgery should be offered to patients with localized, resectable disease and a watchful waiting approach may be considered in patients who have no residual disease after surgery (following discussion with a radiation oncologist). Patients with residual but localized peripheral NLPHL (stage 1-2A with \textlesssim 2 sites of disease) should be offered IFRT. Patients with more advanced stage 2A disease, or those with stage 3-4 disease, should be treated in a similar fashion as those with other forms of indolent CD20+ lymphoma including watchful waiting or chemoimmunotherapy (eg. BR or RCVP) as appropriate. Consider the possibility of high-grade transformation in patients with rapidly progressive disease, marked B symptoms, focal abnormalities in the spleen, extranodal disease, high LDH, or prior bone marrow involvement. R-CHOP is appropriate for patients with transformed disease, with consideration for HDCT/ASCT, especially in those who have relapsed < 2 years after prior chemoimmunotherapy. Consider rituximab monotherapy in patients with advanced stage NLPHL who have serious co-morbidities that would preclude the use of combination chemotherapy.
REFERENCES


49. Schmitz N, Nickelsen M, Ziepert M, Haenel M, Borchmann P, Viardot A. Aggressive chemotherapy (CHOEP-14) and rituximab or high-dose therapy (MegaCHOEP) and rituximab for young, high-risk patients with aggressive B-cell lymphoma: results of the megaCHOEP trial of the German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL). Blood 2009 Nov;(ASH Annual Meeting Abstracts); 114 (22)(Abstract 404).


VI. HDCT AND HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR LYMPHOMA

For detailed information on hematopoietic stem cell transplantation in patients with hematological malignancies, please refer to the Alberta Bone Marrow and Blood Cell Transplant Standard Practice Manual. This manual was developed and is regularly updated by members of the Alberta Provincial Hematology Tumour Team and the Alberta Bone Marrow and Blood Cell Transplant Program, and can be found at: http://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-bmt-manual.pdf

**Summary of Recommendations**

**Eligibility:**
- Patient: age < 70 years, ECOG 0-2, adequate organ function, no active infections
  - HIV not contraindication if CD4>100 and meet other eligibility criteria
- Lymphoma: chemosensitive: partial response (PR) or better to last chemotherapy
  - No active secondary CNS disease (eligible if CNS in PR/CR to salvage therapy)

**HDCT regimen for autologous stem cell transplantation:**
- Indolent (Follicular, SLL/CLL, MZL, LPL) and Mantle Cell: melphalan 180mg/m\(^2\) + TBI 5Gy
- Aggressive systemic non-Hodgkin lymphoma (DLBCL, PTCL): (R)BEAM or Etoposide/Melphalan
- Hodgkin lymphoma: melphalan 200mg/m\(^2\) or Etoposide/Melphalan
- Primary CNS lymphoma: thiopeta 600mg/m\(^2\) + busulfan 9.6mg/kg
- Secondary CNS lymphoma: (R-TBM) thiopeta 500mg/m\(^2\) + busulfan 9.6mg/kg + melphalan 100mg/m\(^2\)

**HDCT regimen for allogeneic stem cell transplantation:**
- Majority of patients: fludarabine 250mg/m\(^2\) + busulfan 12.8mg/kg, 400cGy TBI + ATG
- Reduced intensity: fludarabine 120mg/m\(^2\) + melphalan 140mg/m\(^2\) + ATG
  - co-morbidities (liver, lung, nervous system), prior busulfan, prior ASCT after BEAM or TBI
  - slowly progressive, non-bulky lymphoma

**Indications for HDCT and autologous stem cell transplantation:**
1. Indolent non-Hodgkin lymphoma
   - Follicular, Marginal Zone, Small Lymphocytic, Lymphoplasmacytic Lymphoma
     - chemosensitive first or second chemotherapy failure
   - Mantle Cell Lymphoma (especially low or low-intermediate risk MIPI score)
     - first partial remission (PR) or first complete remission (CR)
2. Aggressive non-Hodgkin lymphoma
   - Part of first salvage therapy for chemosensitive first relapse or first remission-induction failure
   - Part of initial therapy for high IPI=4-5 risk patients or double hit Lymphoma
     - first PR/CR following completion of full induction (i.e. R-CHOP x 6)
     - high-dose sequential remission-induction therapy
3. Hodgkin lymphoma
   - First chemotherapy failure (relapse or 1\(^{st}\) refractory)
Indications for HDCT and allogeneic stem cell transplantation for lymphoma:

1. Indolent non-Hodgkin lymphoma
   - Follicular, Marginal Zone, Small Lymphocytic/CLL, Lymphoplasmacytic Lymphoma
     - chemo-sensitive second to fourth chemotherapy failure (last time to progression <2 years), usually after prior autologous SCT.
   - Mantle cell lymphoma
     - first remission for high risk MIPI score, blastoid variant, or heavy blood/marrow involvement
     - chemo-sensitive first chemotherapy failure

2. Aggressive non-Hodgkin lymphoma
   - Diffuse large B-cell or peripheral T-cell lymphomas
     - chemo-sensitive relapse following HDCT/ASCT if time to relapse >1 year and aalPl=0-1
   - Lymphoblastic lymphoma
     - first remission after induction and CNS therapy if prior blood/marrow involvement and high LDH
     - chemo-sensitive first chemotherapy failure

3. Hodgkin lymphoma
   - Chemo-sensitive relapse following HDCT/ASCT if time to relapse >1 year

4. Any lymphoma with indication for HDCT/ASCT but unable to collect adequate autograft
REFERENCES


VII. SUPPORTIVE CARE IN THE TREATMENT OF LYMPHOMA

Allopurinol

300mg/d x10-14 days starting 1-3 days prior to cycle 1 chemotherapy for Burkitt or Lymphoblastic lymphoma. This should also be considered for rapidly progressive aggressive bulky lymphomas and in patients with impaired renal function.

Pre-Phase Therapy for DLBCL Patients >60 years of Age

Prednisone 100mg/d x 3-7 days prior to cycle 1 R-CHOP or R-CEOP.

Neutropenia Prevention1-5

Primary or secondary prophylaxis to decrease the risk of febrile neutropenia and maintain chemotherapy dose intensity is indicated when treating with curative intent (e.g. preventing treatment delay/dose reduction). The recommendation for R-CHOP, ABVD, CODOX-M/IVAC, HyperCVAD, or intensive salvage therapy regimens, with or without rituximab (e.g. DHAP, ICE, GDP, MICE, DICEP), in patients with aggressive Hodgkin or non-Hodgkin lymphoma older than 60 years of age, or poor prognostic factors (high IPI or IPS) is G-CSF 300μg subcutaneous on days 8 and 12 of a 14- or 21-day chemotherapy regimen.1

For primary prophylaxis of febrile neutropenic infection for similar indications above or co-morbidities that increase risk of infectious complications such as chronic obstructive pulmonary disease, or secondary prevention after a prior episode of febrile neutropenia:

- G-CSF 300 or 480μg/day starting 3 days after chemotherapy completed until post-nadir ANC>1.0 (usually 7-10 days)
- Must monitor CBC
- The alternative is one dose of pegfilgrastim (Neulasta) 6mg on day 4 (without CBC monitoring, but at a cost of ~$2500/dose)

Erythropoeitin

Erythropoeitin is not recommended because of evidence suggesting increased mortality rates. Consider only for symptomatic anemia patients who cannot receive RBC transfusions (i.e., Jehovah’s Witnesses, prior severe transfusion reactions or severe iron overload).

Antimicrobial Prophylaxis for Immunosuppressive Regimens

- For patients receiving fludarabine, high dose cyclophosphamide, >5 days high dose corticosteroids every 21 days, bortezomib, and bendamustine, and for immune-compromised patients (i.e., HIV, post-organ transplant or autoimmune disease patients who develop hematologic cancers) use prophylaxis during and for 3-6 months post-treatment.
- Pneumocystis jiroveci pneumonia (PCP) prophylaxis:
  - choice 1: Septra 1 regular strength tab daily
  - choice 2: dapsone 100mg every Monday/Wednesday/Friday (or daily)
  - choice 3: pentamadine 300mg inhalation monthly
  - choice 4: atovaquone 750mg daily
- Shingles prophylaxis: valacyclovir 500mg daily
Immunizations

Patients should be encouraged to keep all immunizations up to date. The reactivation and/or seroreversion of viruses that patients have been previously vaccinated against, such as hepatitis B, is a major cause of morbidity and mortality in patients with hematologic malignancies treated with cytotoxic chemotherapy. Appendix G outlines the general principles and specific immunization schedules for recipients of blood and marrow transplantations. In addition, separate guidelines outlining influenza and pneumococcal immunization recommendations for all patients with cancer can be found at: www.albertahealthservices.ca/cancerguidelines.asp under the “Supportive Care” heading.

Family members and health care providers in contact with patients who have undergone a transplant should also be strongly encouraged to keep all immunizations up to date.

For patients who have experienced reactivation or seroreversion of hepatitis B virus, prompt administration of nucleoside/nucleotide analogues is essential. Lamivudine 100mg/day during and for 3 months following R-CVP or R-CHOP chemotherapy for lymphoma is recommended for all patients who have a positive hepatitis B surface antigen test.
REFERENCES


VIII. FOLLOW-UP CARE IN THE TREATMENT OF LYMPHOMA

The following late effects should be considered when patients are reviewed during follow-up:

- **Relapse.** Careful attention should be directed to lymph node sites, especially if previously involved with disease. Routine surveillance CT scans are not indicated. Most relapses have been demonstrated to occur between scheduled clinics visit and tests, and are detected by patients themselves. Highly anxious patients who wish surveillance tests could be considered for occasional CXR and abdominal/pelvic ultrasounds (if thin), especially in the setting of indolent lymphoma and prior retroperitoneal and mesenteric disease.

- **Dental caries.** Neck or oropharyngeal irradiation may cause decreased salivation. Patients should have careful dental care follow-up and should make their dentist aware of the previous irradiation.

- **Hypothyroidism.** After external beam thyroid irradiation to doses sufficient to cure malignant lymphoma, at least 50% of patients will eventually develop hypothyroidism. All patients whose TSH level becomes elevated should be treated with life-long T4 replacement in doses sufficient to suppress TSH levels to low normal.

- **Infertility.** Multi-agent chemotherapy and direct or scatter radiation to gonadal tissue may cause infertility, amenorrhea, or premature menopause. However, with current chemotherapy regimens and radiation fields used, most patients will not develop these problems. All patients should be advised that they may or may not be fertile after treatment. In general, women who continue menstruating are fertile, but men require semen analysis to provide a specific answer.

- **Secondary neoplasms.** Although quite uncommon, certain neoplasms occur with increased frequency in patients who have been treated for lymphoma. These include AML, thyroid, breast, lung, and upper GI carcinoma, melanoma and cervical carcinoma in situ. It is appropriate to screen for these neoplasms by careful history, physical examination, mammography and Pap smears for the rest of the patient’s life because they may have a lengthy induction period. Patients should be counseled about the hazards of smoking and excessive sun exposure, and should be encouraged to perform careful breast and skin examinations on a regular basis.

Table 16 outlines the minimum follow-up tests and examinations that should be performed on all patients after treatment for malignant lymphoma. Visits should be scheduled with an oncologist or family physician educated in post-treatment lymphoma surveillance every 3-4 months for 2 years, then every 6 months for 3 years, then annually.

**Table 1. Minimum follow-up tests and examinations for patients with malignant lymphoma**

<table>
<thead>
<tr>
<th>Interval</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Every Visit</td>
<td>• Examination of lymph nodes, thyroid, lungs, abdomen, and skin</td>
</tr>
<tr>
<td></td>
<td>• CBC &amp; differential, LDH (consider ESR AlkP for Hodgkin disease)</td>
</tr>
<tr>
<td></td>
<td>• Consider CXR during first 3 years for patients who previously had intrathoracic disease</td>
</tr>
<tr>
<td>Annually</td>
<td>• TSH (if thyroid was irradiated)</td>
</tr>
<tr>
<td></td>
<td>• Mammogram for women after age 40 if irradiated (otherwise age 50)</td>
</tr>
<tr>
<td></td>
<td>• Pap smear</td>
</tr>
<tr>
<td></td>
<td>• Influenza immunization</td>
</tr>
<tr>
<td>Routine Body CT Scanning</td>
<td>• After 3 months of therapy and if abnormal, again after completion of all therapy</td>
</tr>
<tr>
<td></td>
<td>• If a residual mass is seen on the CT after completion of all therapy, then consider PET/CT scan or consider a repeat CT scan 6 months later. Otherwise, no further routine CT scans are required.</td>
</tr>
</tbody>
</table>
REFERENCES


# Glossary of Abbreviations

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-CDA</td>
<td>2-chlorodeoxyadenosine</td>
</tr>
<tr>
<td>ABVD</td>
<td>adriamycin + bleomycin + vinblastine + dacarbazine</td>
</tr>
<tr>
<td>ALCL</td>
<td>anaplastic large cell lymphoma</td>
</tr>
<tr>
<td>ALK</td>
<td>anaplastic lymphoma kinase (test)</td>
</tr>
<tr>
<td>ALL</td>
<td>acute lymphoblastic leukemia</td>
</tr>
<tr>
<td>ALT</td>
<td>alanine transaminase (test)</td>
</tr>
<tr>
<td>AML</td>
<td>acute myeloid leukemia</td>
</tr>
<tr>
<td>ATCL</td>
<td>adult T-cell lymphoma</td>
</tr>
<tr>
<td>BCNU</td>
<td>carmustine</td>
</tr>
<tr>
<td>BEACOPP</td>
<td>bleomycin + etoposide + adriamycin + cyclophosphamide + vincristine + procarbazine + prednisone</td>
</tr>
<tr>
<td>BEAM</td>
<td>BCNU + etoposide + cytarabine + melphalan</td>
</tr>
<tr>
<td>BL</td>
<td>Burkitt lymphoma</td>
</tr>
<tr>
<td>BMT</td>
<td>bone marrow transplant</td>
</tr>
<tr>
<td>B-R</td>
<td>Bendamustine-rituximab</td>
</tr>
<tr>
<td>CALGB</td>
<td>Cancer and Leukemia Group B</td>
</tr>
<tr>
<td>CAP</td>
<td>cyclophosphamide + adriamycin + prednisone</td>
</tr>
<tr>
<td>CBV</td>
<td>cyclophosphamide + BCNU + etoposide</td>
</tr>
<tr>
<td>CEC</td>
<td>cyclophosphamide + lomustine + vindesine + melphalan + prednisone + epidoxorubicin + vincristine + procarbazine + vinblastine + bleomycin</td>
</tr>
<tr>
<td>CEPP</td>
<td>cyclophosphamide + etoposide + procarbazine + prednisone</td>
</tr>
<tr>
<td>ChIVPP</td>
<td>chlorambucil + vinblastine + procarbazine + prednisone</td>
</tr>
<tr>
<td>CHOP</td>
<td>cyclophosphamide + adriamycin + vincristine + prednisone</td>
</tr>
<tr>
<td>CHOEP</td>
<td>cyclophosphamide + adriamycin + vincristine + etoposide + prednisone</td>
</tr>
<tr>
<td>CLL</td>
<td>chronic lymphocytic leukemia</td>
</tr>
<tr>
<td>CMED</td>
<td>cyclophosphamide + etoposide + methotrexate + dexamethasone + leucovorin + G-CSF</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>CODOX-M</td>
<td>cyclophosphamide + vincristine + adriamycin + methotrexate</td>
</tr>
<tr>
<td>COPP</td>
<td>cyclophosphamide + vincristine + procarbazine + prednisone</td>
</tr>
<tr>
<td>CR</td>
<td>complete remission</td>
</tr>
<tr>
<td>CS</td>
<td>clinical stage</td>
</tr>
<tr>
<td>CSF</td>
<td>cerebrospinal fluid</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography scan</td>
</tr>
<tr>
<td>CTCL</td>
<td>cutaneous T-cell lymphoma</td>
</tr>
<tr>
<td>CVAD</td>
<td>cyclophosphamide + vincristine + adriamycin + dexamethasone</td>
</tr>
<tr>
<td>CVP</td>
<td>cyclophosphamide + vincristine + prednisone</td>
</tr>
<tr>
<td>DHAP</td>
<td>dexamethasone + cytarabine + cisplatin</td>
</tr>
<tr>
<td>DICE</td>
<td>dexamethasone + ifosfamide + cisplatin + etoposide + mesna</td>
</tr>
<tr>
<td>DICEP</td>
<td>dexamethasone + cyclophosphamide + etoposide + cisplatin + mesna + Septra</td>
</tr>
<tr>
<td>DLBCL</td>
<td>diffuse large B-cell lymphoma</td>
</tr>
<tr>
<td>DLCO</td>
<td>diffusing capacity of the lung for carbon monoxide</td>
</tr>
<tr>
<td>EBER</td>
<td>Epstein-Barr virus encoded ribonucleic acid</td>
</tr>
<tr>
<td>EBV</td>
<td>Epstein-Barr virus</td>
</tr>
<tr>
<td>ECOG</td>
<td>Eastern Cooperative Oncology Group</td>
</tr>
<tr>
<td>ENS</td>
<td>extracapsular neoplastic spread</td>
</tr>
<tr>
<td>ENT</td>
<td>ear, nose, and throat</td>
</tr>
<tr>
<td>ESHAP</td>
<td>etoposide + methylprednisolone + cytarabine + cisplatin</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>ESR</td>
<td>erythrocyte sedimentation rate</td>
</tr>
<tr>
<td>FC</td>
<td>fludarabine + cyclophosphamide</td>
</tr>
<tr>
<td>FEV1</td>
<td>forced expiratory volume in one second</td>
</tr>
<tr>
<td>FISH</td>
<td>fluorescent in situ hybridization</td>
</tr>
<tr>
<td>FLIPI</td>
<td>Follicular Lymphoma International Prognostic Index</td>
</tr>
<tr>
<td>FND</td>
<td>fludarabine + mitoxantrone + dexamethasone</td>
</tr>
<tr>
<td>FVC</td>
<td>forced vital capacity</td>
</tr>
<tr>
<td>G-CSF</td>
<td>granulocyte-colony stimulating factor</td>
</tr>
<tr>
<td>GDP</td>
<td>gemcitabine + dexamethasone + cisplatin</td>
</tr>
<tr>
<td>GHSG</td>
<td>German Hodgkin Study Group</td>
</tr>
<tr>
<td>GMALL</td>
<td>German multicentre adult acute lymphoblastic leukemia protocol</td>
</tr>
<tr>
<td>H&amp;E</td>
<td>hematoxylin and eosin stain</td>
</tr>
<tr>
<td>HAART</td>
<td>highly active antiretroviral therapy</td>
</tr>
<tr>
<td>HAMA</td>
<td>human anti-mouse antibodies</td>
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<tr>
<td>HDCT</td>
<td>high dose chemotherapy</td>
</tr>
<tr>
<td>HL</td>
<td>Hodgkin lymphoma</td>
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<tr>
<td>HP-Pac</td>
<td>lansoprazole + clarithromycin + amoxicillin</td>
</tr>
<tr>
<td>HSCT</td>
<td>hematopoietic stem cell transplantation</td>
</tr>
<tr>
<td>HVS</td>
<td>hyperviscosity syndrome</td>
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<tr>
<td>ICE</td>
<td>ifosfamide + carboplatin + etoposide</td>
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<td>IELSG</td>
<td>International Extranodal Lymphoma Study Group</td>
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<td>IFRT</td>
<td>involved field radiation therapy</td>
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<td>IMRT</td>
<td>intensity-modulated radiation therapy</td>
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<tr>
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<td>International Prognostic Index/Score</td>
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<td>IV</td>
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<tr>
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<td>IVE</td>
<td>ifosfamide + vincristine + etoposide</td>
</tr>
<tr>
<td>KPS</td>
<td>Karnofsky Performance Status Scale</td>
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<tr>
<td>LDH</td>
<td>lactate dehydrogenase test</td>
</tr>
<tr>
<td>LPL</td>
<td>lymphoplasmacytic lymphoma</td>
</tr>
<tr>
<td>LVEF</td>
<td>left ventricular ejection fraction</td>
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<tr>
<td>MACOP-B</td>
<td>methotrexate + Adriamycin + cyclophosphamide + vincristine + bleomycin + prednisone</td>
</tr>
<tr>
<td>MALT</td>
<td>mucosa-associated lymphoid tissue</td>
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<tr>
<td>MDS</td>
<td>myelodysplastic syndrome</td>
</tr>
<tr>
<td>MEP</td>
<td>mitomycin C + etoposide + cisplatin</td>
</tr>
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<td>maximum transthoracic diameter</td>
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<td>MTX</td>
<td>methotrexate</td>
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<tr>
<td>MUGA</td>
<td>multiple gated acquisition scan</td>
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<td>PCNSL</td>
<td>primary central nervous system lymphoma</td>
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<td>PCP</td>
<td>Pneumocystis jiroveci pneumonia</td>
</tr>
<tr>
<td>PET</td>
<td>positron emission tomography</td>
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<tr>
<td>PFS</td>
<td>progression-free survival</td>
</tr>
<tr>
<td>PFT</td>
<td>pulmonary function test</td>
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<tr>
<td>POMP</td>
<td>mercaptopurine + vincristine + methotrexate + prednisone</td>
</tr>
<tr>
<td>PR</td>
<td>partial response</td>
</tr>
<tr>
<td>PTCL</td>
<td>peripheral T-cell lymphoma</td>
</tr>
</tbody>
</table>
PTLD  post-transplant lymphoproliferative disorder
PUVA  psoralen + ultraviolet A radiation
R     rituximab
R-CHOP rituximab + cyclophosphamide + adriamycin + vincristine + prednisone
R-CVP rituximab + cyclophosphamide + vincristine + prednisone
R-FCM fludarabine + cyclophosphamide + mitoxantrone + rituximab
RIT  radioimmunoconjugate therapy
RR   response rate
RT   radiotherapy
SBFT  small bowel follow-through (test)
SCT  stem cell transplant
SD   stable disease
SLE  systemic lupus erythematosus
SLL  small lymphocytic lymphoma
SOT  solid organ transplant
STNI  subtotal nodal irradiation
TBUc thiotepa + busulfan + cyclophosphamide
TBI  total body irradiation
TRM  Transplant-related mortality
TSH  thyroid stimulating hormone
UGI  upper gastrointestinal series (test)
VIPD etoposide + ifosfamide + cisplatin + dexamethasone
WHO  World Health Organization
WM  Waldenström macroglobulinemia

DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Hematology Tumour Team Meeting in 2015. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

CONFLICT OF INTEREST

Participation of members of the Alberta Provincial Hematology Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Hematology Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.
APPENDIX A

Information regarding Rituximab 375mg/m² IV or 1400mg SC for B-cell lymphoma treatment

• Indications:
  o All CD 20+ B cell lymphomas (indolent and aggressive)
  o PTLD and MCL
  o Monotherapy or with chemo
  o Maintenance q2m (MCL) and q3m (indolent and FL)
  o Stem cell mobilization and high dose conditioning regimens for ASCT.
Not indicated:
  o Not CLL (Health Canada)
  o not for Ritux treatment of autoimmune cytopenias due to CLL or indolent lymphoma (hematoma risk)
• Timing of sc Rituximab relative to IV:
  o all first exposure to rituximab must be IV
  o before commencing SC the patient must have completed a full rituximab IV infusion dose, regardless if the patient had an infusion reaction or the grade of the reaction. (patient does not have to had 0 reaction to IV). If the patient did not complete* the full IV dose, the next rituximab dose must be by IV infusion. (Roche)
• Pts may start with SC if:
  o going on to maintenance treatment and had SC prior
  o going on to mobilization, high dose chemo and had SC prior
  o undergoing re-treatment (even > 6 months) may start with SC if they had SC prior

I. INITIAL THERAPY FOR DIFFUSE LARGE B-CELL LYMPHOMA

R-CHOP (standard risk)
- rituximab 375mg/m² IV day 1 (premedications: Tylenol, Benadryl, Zantac, hydrocortisone 100mg), then Rituximab 1400mg sc on day 1 from cycle 2 onwards if initial IV dose tolerated well.
- cyclophosphamide 750 mg/m² IV
- adriamycin 50 mg/m² IV day 1
- vincristine 2mg IV day 1
- prednisone 100mg/day p.o. days 1-5
- Cycles: every 21 days

R-CHOEP (high risk, age <60 years)¹⁻³
- rituximab 375mg/m² IV day 1 (premedications: Tylenol, Benadryl, Zantac, hydrocortisone 100mg) then Rituximab 1400mg sc on day 1 from cycle 2 onwards if initial IV dose tolerated well.
- cyclophosphamide 750 mg/m² IV
- adriamycin 50 mg/m² IV day 1
- vincristine 2mg IV day 1
- etoposide 100mg/m² IV days 1-3 (or 200mg/m² p.o. days 2-3 instead of IV; round down to nearest 50mg multiple)
- prednisone 100mg/day p.o. days 1-5
- G-CSF days 7-11 or neulasta day 4 of each cycle
- Cycles: every 14-21 days
R-CEOP (cardiac disease with LVEF <50%)\(^1\)-\(^3\)
- rituximab 375mg/m\(^2\) IV day 1 (premedications: Tylenol, Benadryl, Zantac, hydrocortisone 100mg) then Rituximab 1400mg sc on day 1 from cycle 2 onwards if initial IV dose tolerated well.
- cyclophosphamide 750 mg/m\(^2\) IV
- vincristine 2mg IV day 1
- etoposide 50mg/m\(^2\) IV days 1-3 (or 100mg/m\(^2\) p.o. days 2-3 instead of IV; round up to nearest 50mg multiple)
- prednisone 100mg/day p.o. days 1-5
- Cycles: every 21 days

R-MACOP-B (not recommended unless patient needs to complete therapy in 3 months)
- methotrexate 400mg/m\(^2\) IV on weeks 2, 6, 10 (24 hours later: folinic acid 15mg q6 hours x 6 doses)
- adriamycin 50 mg/m\(^2\) IV weeks 1,3,5,7,9,11
- cyclophosphamide 350 mg/m\(^2\) IV weeks 1,3,5,7,9,11
- vincristine 2mg IV weeks 2,4,6,8,10,12
- bleomycin 10mg/m\(^2\) weeks 4,8,12
- prednisone 75mg/day p.o. daily, taper over last 15 days
- septra for PCP prophylaxis
- suggest adding rituximab 375mg/m\(^2\) IV q14 days x 6 doses then Rituximab 1400mg sc on day 1 from cycle 2 onwards if initial IV dose tolerated well.

DA-EPOCH-R:
Prednisone is a tablet taken by mouth TWICE daily on Days 1, 2, 3, 4, 5 Rituximab is an intravenous (I.V.) infusion on Day 1 (time of infusion varies) Doxorubicin is an I.V. infusion given over 24 hours on Days 1, 2, 3, 4 Etoposide is an I.V. infusion given over 24 hours on Days 1, 2, 3, 4 Vincristine is an I.V. infusion given over 24 hours on Days 1, 2, 3, 4 Cyclophosphamide is an I.V. infusion given over two hours on Day 5 On Day 6, filgrastim (Neupogen®) is started subcutaneously once daily and continued every day until the white blood cell count returns to normal. Alternatively, some Doctors prefer to give one dose of pegfilgrastim (Neulasta®) after each cycle of dose-adjusted EPOCH-R Patients then have labs drawn twice weekly until the white blood cell count has recovered.
Typically, etoposide, doxorubicin, and vincristine are mixed together in one intravenous infusion bag and each bag is infused over 24 hours on Days 1, 2, 3, and 4 of each cycle (96 hours total).

| Day 1-4   | Doxorubicin | 10 mg/m\(^2\)/day |
|          | Vincristine | 0.4mg/m\(^2\)/day (no cap) |
|          | Etoposide   | 50 mg/m\(^2\)/day |
| Day 5    | Ondansetron | 8mg           |
| Day 6    | Cyclophosphamide | 750mg/m\(^2\) |
|          | GCSF (Biosimilar) | 300 micrograms |

Dose Adjustments according to nadir
Doxorubicin, Etoposide and Cyclophosphamide ONLY:
Doses may be adjusted from Cycle 2 based on the previous cycle’s neutrophil (ANC) nadir. This is monitored by obtaining TWICE WEEKLY CBC, i.e. days 9, 12, 15,18:
- If nadir ANC \(\geq 0.5 \times 10^9/l\): **increase by 1 dose level**
- If nadir ANC <0.5x10\(^9\)/l on 1 or 2 measurements: **same dose as last**
**Cycle**
- If nadir ANC <0.5x10^9/l on at least 3 measurements: **decrease by 1 dose level**
- If platelet nadir <25x10^9/l: **reduce by 1 dose level** regardless of ANC
- Life threatening infections: **decrease by 1 dose level**

<table>
<thead>
<tr>
<th>Drug Dose Adjustments</th>
<th>Drug Doses per Dose Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-2</td>
</tr>
<tr>
<td>Prednisolone (mg/m² twice daily)</td>
<td>60</td>
</tr>
<tr>
<td>Rituximab (mg/m²/day)</td>
<td>375</td>
</tr>
<tr>
<td>Doxorubicin (mg/m²/day)</td>
<td>10</td>
</tr>
<tr>
<td>Vincristine (mg/m²/day)</td>
<td>0.4</td>
</tr>
<tr>
<td>Etoposide (mg/m²/day)</td>
<td>50</td>
</tr>
<tr>
<td>Cyclophosphamide (mg/m²/day)</td>
<td>480</td>
</tr>
</tbody>
</table>

**Neurotoxicity:**
If the patient complains of significant constipation or sensory loss in fingers and/or toes, consider dose reduction of vincristine:
- Reduce by 25% for grade 2 motor neuropathy
- Reduce by 50% for grade 3 motor or sensory neuropathy
- For patients who develop ≥ grade 3 ileus, treatment should be delayed until recovery and vincristine introduced at 75% of the normal dose thereafter. If ≥ grade 3 ileus recurs, vincristine should be discontinued

Additional medicines that may be prescribed:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septa</td>
<td>480mg</td>
<td>Oral once daily</td>
</tr>
<tr>
<td>Valacyclovir</td>
<td>500mg</td>
<td>Oral once daily</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>50mg</td>
<td>Oral once daily</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>20mg</td>
<td>Oral once daily for 5 days</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>10mg</td>
<td>Oral four times daily as needed</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>8mg</td>
<td>Oral as a single dose prior to chemotherapy, then twice daily as needed</td>
</tr>
</tbody>
</table>

Docusate/Senna (Senna-S®) to prevent constipation from vincristine

Consider intrathecal prophylaxis for patients with >1 extranodal site and elevated LDH
II. INITIAL THERAPY FOR INDOLENT HISTOLOGY NON-HODGKIN LYMPHOMA

B-R
- bendamustine 90 mg/m² IV day 1, 2
- rituximab 375 mg/m² IV day 1 then Rituximab 1400mg sc on day 1 from cycle 2 onwards if initial IV dose tolerated well.
- Cycles: repeated every 3-4 weeks depending on blood counts (usually administered every 28 days) for a maximum of 6 cycles

CVP
- cyclophosphamide 800 mg/m² IV day 1 (or 400 mg/m²/day p.o. days 1-5)
- vincristine 2mg IV day 1
- prednisone 100mg/day p.o. days 1-5
- Cycles: every 21 days

R-CVP
- rituximab 375mg/m² IV day 1 (premeds: Tylenol, Benadryl, Zantac, hydrocortisone 100mg), then Rituximab 1400mg sc on day 1 from cycle 2 onwards if initial IV dose tolerated well.
- cyclophosphamide 750 mg/m² IV day 1
- vincristine 2mg IV day 1
- prednisone 100mg/day p.o. days 1-5
- Cycles: every 21 days

Maintenance Rituximab in First or Second Remission Following Chemotherapy + Rituximab
- Follicular and other indolent B-cell lymphoma: rituximab 1400mg sc (or 375mg/m² IV if cannot tolerate sc) x 1 dose q3 months x 2 years (8 doses total)
- Mantle cell lymphoma option: rituximab 1400mg sc (or 375mg/m² IV if cannot tolerate sc) q2months until progression

Outpatient R-DHAP
Cycle 1:
Day1: Rituximab 375mg/m² IV (if no rituximab in past 3months and cannot receive sc rituximab)
Day 2: 500mL NS pre, cisplatin 35 mg/m2 in 500 mL NS/mannitol, 500 ml NS post, AraC 2g/m2 in 500 mL NS.
Day 3: 500mL NS pre, cisplatin 35 mg/m2 in 500 mL NS/mannitol, AraC 2g/m2 in 500 mL NS. Total 5 hrs

Cycle 2 onwards:
Day1: Rituximab 1400mg sc, 500mL NS pre, cisplatin 35 mg/m2 in 500 mL NS/mannitol, 500 ml NS post. Then AraC 2g/m2 in 500 mL NS. Total 5 hrs
Day2: 500mL NS pre, cisplatin 35 mg/m2 in 500 mL NS/mannitol, AraC 2g/m2 in 500 mL NS. Total 5 hrs

Chlorambucil (options)
- 0.1-0.2 mg/kg/day for 4-8 weeks then usually reduce for maintenance
- 10-14 mg/m² for 5 to 7 days each 28 days
- 0.5 mg/kg days 1 and 15 q28d cycle
**Fludarabine**
- 25mg/m² IV days 1-5 q28 days (days 1-3 only if frail elderly or renal dysfunction)
- 40mg/m² p.o. days 1-5 q28 days (round down to nearest multiple of 10mg) (d1-3 only if frail or renal dysfunction)

**FND**
- fludarabine 25mg/m² IV days 1-3 or 40mg/m² p.o. days 1-3
- mitoxantrone 10mg/m² day 1
- dexamethasone 40mg p.o. days 1-3
- septra for PCP prophylaxis
- Cycles: every 28 days

**III. INITIAL THERAPY FOR PERIPHERAL T-CELL LYMPHOMA**

**CHOP**
- cyclophosphamide 750 mg/m² IV
- adriamycin 50 mg/m² IV day 1
- vincristine 2mg IV day 1
- prednisone 100mg/day p.o. days 1-5
- Cycles: every 21 days

**CHOEP**
- cyclophosphamide 750 mg/m² IV
- adriamycin 50 mg/m² IV day 1
- vincristine 2mg IV day 1
- etoposide 100mg/m² IV days 1-3 (or 200mg/m² p.o. days 2-3 instead of IV; round down to nearest 50mg multiple)
- prednisone 100mg/day p.o. days 1-5
- G-CSF days 7-11 or neulasta day 4 of each cycle
- Cycles: every 21 days

**VIPD (Nasal NK/T-cell lymphoma)**
- etoposide 100mg/m² days 1-3
- ifosfamide 1.2g/m² days 1-3
- cisplatin 33mg/m² days 1-3
- dexamethasone 40mg days 1-4
- Cycles: 3 cycles after initial radiotherapy

**GOLD (14 day cycle)**
- gemcitabine 1000mg/m² on day 1
- oxaliplatin 100mg/m² on day 1
- L-asparaginase 10,000U/m² on days 1-5*
- dexamethasone (20mg b.i.d.) on days 1-4

*An intradermal test was required prior to the administration of L-ASP
SMILE (28 day cycle)\textsuperscript{5}
- Methotrexate $2g/m^2$ on day 1
- Leucovorin $15mg \times 4$ on day 2, 3, and 4
- Ifosfamide $1500mg/m^2$ on day 2, 3, and 4
- Mesna $300 mg/m^2 \times 3$ on day 2, 3 and 4
- Dexamethasone $40mg/d$ on day 2, 3 and 4
- Etoposide $100mg/m^2$ on day 2, 3 and 4
- L-asparaginase $6000U/m^2$ on day 8, 10, 12, 14, 16, 18 and 20

GCSF should be given from day 6 and discontinued if the leukocyte count exceeds 5000/µL. Antibiotic prophylaxis with sulfamethoxazole-trimethoprim is recommended.
IV. HODGKIN DISEASE CHEMOTHERAPY REGIMENS

Initial Therapy

**ABVD**
- Adriamycin 25 mg/m² IV days 1 and 14
- Bleomycin 10 mg/m² IV days 1 and 14
- Vinblastine 6 mg/m² IV days 1 and 14
- Dacarbazine 375 mg/m² IV days 1 and 14

**ChlVPP**
- Chlorambucil 6 mg/m² p.o. days 1-14
- Vinblastine 6 mg/m² IV days 1 and 8
- Procarbazine 100 mg/m² p.o. days 1-14
- Prednisone 40 mg/m² p.o. days 1-14

**BEACOPP (escalated)**
- Bleomycin 10 mg/m² IV day 8
- Etoposide 200 mg/m² IV days 1-3
- Adriamycin 35 mg/m² IV day 1
- Cyclophosphamide 1250 mg/m² IV day 1
- Vincristine 1.4 mg/m² IV day 8
- Procarbazine 100 mg/m² p.o. days 1-7
- Prednisone 40 mg/m² p.o. days 1-14

**BEACOPP (baseline)**
- Bleomycin 10 mg/m² IV day 8
- Etoposide 100 mg/m² IV days 1-3
- Adriamycin 25 mg/m² IV day 1
- Cyclophosphamide 650 mg/m² IV day 1
- Vincristine 1.4 mg/m² IV day 8
- Procarbazine 100 mg/m² p.o. days 1-7
- Prednisone 40 mg/m² p.o. days 1-14

**CEPP**
- Cyclophosphamide 600 mg/m² IV days 1 and 8
- Etoposide 70 mg/m² days 1-3
- Procarbazine 60 mg/m² p.o. days 1-10
- Prednisone 100 mg/day p.o. days 1-10

**Cycles**: every 21-28 days

V. LYMPHOMA SALVAGE REGIMENS

**Aggressive Histology Hodgkin and Non-Hodgkin Lymphomas**

**DICE**
- Dexamethasone 10 mg IV q6 hours days 1-4
- Ifosfamide 1 g/m² (max 1.75 g) over 15 minutes days 1-4
- Cisplatin 25 mg/m² IV over 1 hour days 1-4
- Etoposide 100 mg/m² over 1 hour days 1-4
- Mesna 200 mg/m² over 5-10 min prior to first dose of ifosfamide, then 200 mg/m² IV at 4 hours and 400 mg/m² p.o. (or 200 mg/m² IV) at 8 hours post-ifosfamide x 4 days
- **Cycles**: every 21-28 days

**CEPP**
- Cyclophosphamide 600 mg/m² IV days 1 and 8
- Etoposide 70 mg/m² days 1-3
- Procarbazine 60 mg/m² p.o. days 1-10
- Prednisone 100 mg/day p.o. days 1-10
- **Cycles**: every 28 days

**GDP**
- Gemcitabine 1000 mg/m² IV days 1 and 8
- Dexamethasone 40 mg p.o. days 1-4
• cisplatin 75mg/m² IV

**DICEP**
- dexamethasone 10mg IV q8 hours x 10 doses
- cyclophosphamide 1.75 g/m² IV over 2 hours days 1-3
- etoposide 350mg/m² IV over 2 hours days 1-3
- cisplatin 35mg/m² IV over 2 hours days 1-3
- mesna 1.75g/m² IV over 24 hours days 1-3
- septra for PCP prophylaxis
- **Cycles:** Once only

*Add rituximab to salvage regimens for transplant eligible patients with relapsed B-cell lymphomas*

**Indolent Histology Non-Hodgkin Lymphoma**

As above, plus:

**R rituximab**
- 375mg/m² IV days 1,8,15, and 22 (Rituximab 1400mg sc from day 8 onwards if initial IV dose tolerated well.
- Pre-medicate with hydrocortisone 100mg IV, Benadryl, Zantac, and Tylenol
- Infuse 50mg/hour initially, then increase by 50mg/hour increments q30 minutes as tolerated to a maximum of 400mg/hour
- Subsequent infusions can begin at 100mg/hour and increase by 100mg/hour increments as tolerated to maximum of 400mg/hour

**FND**
- fludarabine 25mg/m² IV days 1-3 or 40mg/m² p.o. days 1-3
- mitoxantrone 10mg/m² day 1
- dexamethasone 40mg p.o. days 1-3
- septra for PCP prophylaxis
- **Cycles:** every 28 days

**R-FCM**
- fludarabine 25mg/m² IV days 1-3 or 40mg/m² p.o. days 1-3
- cyclophosphamide 200mg/m² IV days1-3
- mitoxantrone 8mg/m² IV day 1
- rituximab 375mg/m² IV day 1 (Rituximab 1400mg sc on day 1 from cycle 2 onwards if initial IV dose tolerated well).
- **Cycles:** every 28 days
VI. BURKITT LYMPHOMA 6,7

Modified Magrath Regimen of R-CODOXM/R-IVAC (Blood 2014; 124:2913-2920)

### Regimen A (R-CODOX-M)

| Days: | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 |
|-------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|
|       |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |
| rituximab 375mg/m² IV | x |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |
| cyclophosphamide 800mg/m² IV | x | x |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |
| doxorubicin 50mg/m² IV | x |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |
| vincristine 1.5mg/m² IV cap 2mg | x |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |
| allopurinol 300mg/day po | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| methotrexate 3000mg/m² IV over 2 hour IV** | x |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |
| leucovorin 25mg IV @ 24 hours, then 25mg IV q6h until methotrexate<10⁻⁸ M | xx | xx | xx | xx | xx | xx | xx | xx | xx | xx | xx | xx | xx | xx | xx | xx | xx | xx | xx |
| IT methotrexate 12mg | X |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |
| IT cytarabine 50mg * | X |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |
| Peg-filgrastim 6mg |   | X |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |

*if CNS disease, give extra IT AraC 50mg d5 cycle 1 only

**HDMTX administered once urine pH>7, and diuresis established with hydration including D5-0.2%NS plus 2-3 amps sodium bicarbonate. Continue hydration and alkalinization until MTX cleared.

### Regimen B (R-IVAC)

<table>
<thead>
<tr>
<th>Days:</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
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<tr>
<td>rituximab 375mg/m² IV</td>
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<td>xx</td>
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<tr>
<td>ifosfamide 1500mg/m² IV</td>
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<td>mesna 360mg/m² IV q3 hours</td>
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<tr>
<td>etoposide 60mg/m² IV</td>
<td>X</td>
<td>x</td>
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<td>IT methotrexate 12mg</td>
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<td>Peg-filgrastim 6mg</td>
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*if CNS disease, give extra IT AraC 50mg d3 cycle 1 only

Low risk patients:
- Single extra-abdominal mass <10cm, or completely resected abdominal disease and normal LDH
- Modified regimen A x 3 cycles (cytarabine IT day 1 and methotrexate IT day 3 each cycle)

High risk patients:
- All others
- Alternate regimen A with regimen B for a total of 2 each or 4 cycles total

Start next cycle once ANC>1.0 and platelets>50
### VII. PRIMARY CNS LYMPHOMA PROTOCOL

#### A. Transplant-Eligible Patients: age < 65years, no significant co-morbidities, no immune suppression

<table>
<thead>
<tr>
<th>Week</th>
<th>Step 1</th>
<th><em>Step 2</em></th>
<th>Step 3</th>
<th>Step 4</th>
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<td>14-16</td>
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</tbody>
</table>

**Rituximab 375mg/m² IV d0 and d 4, 14**
- high-dose methotrexate 3.5 g/m² d1&15
- procarbazine 100 mg/m² d1-7

**rituximab 375mg/m² IV d1**
- cytarabine 3 g/m² x d1&2
- G-CSF 5-10 µg/kg d8-13
- Apheresis ~d14 or 15

**Apheresis 3.5 g/m² IV d0**
- high-dose methotrexate 3.5 g/m² d1
- cytarabine 2 g/m² twice daily days 2-3 all q21d for 2 cycles

**thiotepa 300 mg/m² IV days -6,-5**
- busulfan 3.2 mg/kg IV days -4 to -2, ASCT day 0

*Step 2 may begin either week 4 or 5 depending upon patient status and apheresis scheduling*

**Step 1. Induction: High-dose methotrexate/procarbazine q14 days x 2 cycles**

<table>
<thead>
<tr>
<th>Day</th>
<th>Medications</th>
<th>Other Orders</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADMISSION 0</td>
<td>0900hr - Rituximab 375mg/m² (1st infusion protocol) 2000hr – IV D5W + 20meq KCL/L + 2 amps NaHCO3/L @ 200ml/hour x 5d</td>
<td>+ Daily weights  + Daily CBC &amp; Diff, EP, Creat, glucose  + ALT, AlkP, LDH, bilirubin, Alb, Ca, Mg  + LFTs, Ca, lipase, every Monday &amp; Thursday</td>
</tr>
<tr>
<td>1</td>
<td>0800hr - Kytril 1mg IV  0800hr - methotrexate 3500mg/m² IV over 2 hour cycles 1 and 2  0800hr - procarbazine 100mg/m² po daily x 7 days only cycle 1 (round down to nearest 50mg multiple)  0700hr - Urine pH twice daily, call MD if &lt;7.0</td>
<td>0700hr - methotrexate Level daily (expect level &lt; 10 d2, &lt;1 d3)</td>
</tr>
<tr>
<td>2-3</td>
<td>0800hr - folinic acid (leucovorin) 25 mg IV q6 hours until methotrexate level &lt; 0.05  Continue hydration until methotrexate level &lt;0.05</td>
<td>0500-0800hr – methotrexate Level daily</td>
</tr>
<tr>
<td>4</td>
<td>0900hr - Rituximab 375mg/m² IV on cycle 1 only and continue folinic acid</td>
<td>0500-0800hr – methotrexate Level daily</td>
</tr>
<tr>
<td>5</td>
<td><strong>Discharge once methotrexate level &lt;0.05</strong>  <strong>If level 0.01-0.05, discharge on leucovorin 5mg p.o. q6 hours x 2-3 days</strong>  <strong>Discharge meds: septra DS 1 daily or dapsone 50mg daily x 6-9 months; consider dexamethasone taper if on dexamethasone</strong>  <strong>Remember coumarin/LMWH and Dilantin if patient is on these medications</strong></td>
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</tbody>
</table>

*Male IBW = 50kg + 2.3kg x inches > 5ft, Female IBW = 45.5 kg + 2.3kg x inches > 5ft. Adjusted BW = IBW + [40% x (actual – IBW)]

**Step 2. Rituximab/high-dose cytarabine x 1 cycle for stem cell collection after 2 cycles of methotrexate**

<table>
<thead>
<tr>
<th>Day</th>
<th>Medications</th>
<th>Other Orders</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0900hr - Premeds : Hydrocortisone 100mg IV, Benadryl 50mg IV, Zantac 50mg IV, Tylenol 650mg p.o. -rituximab 375mg/m² II</td>
<td>+ Weight  + CBC &amp; Diff, EP, creatinine, glucose  + ALT, AlkP, LDH, bilirubin, Alb, Ca, Mg</td>
</tr>
<tr>
<td>2 &amp; 3</td>
<td>0800hr – Kytril 2mg IV, dexamethasone 10mg IV  0800hr – IV N/S 500mL/hour x 2 hours  1000hr – cytarabine 3g/m² IV over 3 hours (2g/m² if &gt;60yrs or creatinine &gt;100)</td>
<td>Daily CBC &amp; differential starting day 10</td>
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<tr>
<td>9-14</td>
<td>1000hr – G-CSF 480-600 µg subcutaneous daily until apheresis completed (plan for apheresis approximately day 13-15, once ANC&gt;5, Plt&gt;75 and CD34&gt;20)</td>
<td></td>
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</tbody>
</table>
**Step 3. High-dose methotrexate/cytarabine consolidation q21 days x 2 cycles after stem cell collection**

<table>
<thead>
<tr>
<th>Day</th>
<th>Medications</th>
<th>Other Orders</th>
</tr>
</thead>
</table>
| ADMISSION 0 | 16:00hr - Rituximab 375mg/m² IV 2000hr - IV D5W + 20meq KCL/L + 2 amps NaHCO3/L @ 200ml/hour x 5 days | • Daily weights  
• Daily CBC & differential, EP, creatinine, glucose  
• ALT, AlkP, LDH, bilirubin, Alb, Ca, Mg  
• ALT, Alk P, bil, Ca, lipase, every Monday & Thursday |
| 1 | 0800hr - Kytril 1mg IV 0800hr - methotrexate 3500mg/m² IV over 2 hours | 07:00 - Urine pH bid, call MD if <7.0 |
| 2-3 | 0800hr - folinic acid (leucovorin) 25 mg IV q6 hours until methotrexate level < 0.05  
- Continue hydration until methotrexate level <0.05  
0800hr – Kytril 2mg IV, dexamethasone 10mg IV  
1000hr – cytarabine 2g/m² IV over 2 hours twice daily x 2 days  
Reduce to 1.5g/m² if age > 60 years or creatinine > 100 | 0500-08:00 – methotrexate level daily (expect <10 d2, <1 d3, < 0.1 d4, < 0.05 d5) |
| 5 | Discharge once methotrexate level <0.05  
If level 0.01-0.05, discharge on leucovorin 5mg p.o. q6 hours x 2-3 days (other meds as step 1 above) |  |
| 8-12 | 1000hr – G-CSF 480-600 µg subcutaneous daily until post-nadir ANC > 1.5  
Daily CBC & differential starting day 10 |  |

*Male IBW = 50kg + 2.3kg x inches > 5ft, Female IBW = 45.5 kg + 2.3kg x inches > 5ft. Adjusted BW = IBW + [40% x (actual – IBW)]*

**Step 4. TBu/ASCT consolidation after response to methotrexate and high-dose cytarabine**

<table>
<thead>
<tr>
<th>Day</th>
<th>Medications</th>
<th>Other Orders</th>
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</thead>
</table>
| ADMISSION Day -7 | Allopurinol 300 mg p.o. daily until day 0  
2200hr - D5 ½ N/S + 20 mEq KCL/L @ 125 mL/hour until day -1 | • Consult dietician  
• Consult physiotherapy  
• Low bacteria diet  
• 24 hour intake  
• Mouth protocol  
• Record intake and output |
| -6 & -5 | 0800 – thiopeta 300 mg/m² IV over 3 hours x 2 days (use IDEAL BSA) | 0800hr – granisetron 2 mg IV daily x 8 days  
• EP daily x 31days  
• Shower/bath q6 hours x 3 days; avoid skin creams |
| -4 to -2 | 0900 - busulfan 3.2 mg/kg IV daily x 3 days (use ideal weight) | • lorazepam prophylaxis x 4 days  
• CBC & differential daily x 31 days  
• ALT, Alk Phos, bil, alb, Ca, Mg, every Monday & Thursday  
• PT, PTT, every Monday  |
| -1 | Rest day | • mycostatin 500,000 units q2-4 hours  
• septra RS 1 tab p.o. daily  
• acyclovir 5 mg/kg bid IV or 400 mg p.o. four times daily |
| 0 | Autologous Blood Stem Cell INFUSION |  |
| +7 | G-CSF 300µg (if less than 70kg) or 480µg (if over 70kg) subcutaneous daily until post-nadir ANC > 1.5 |  |
### B. Transplant-Ineligible Patients: age ≥65 years, significant co-morbidities, immune suppression

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<tr>
<th>Step 1</th>
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<tbody>
<tr>
<td><strong>Week</strong></td>
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<td>2</td>
</tr>
<tr>
<td>Rituximab 375mg/m² d0, 4</td>
<td>x</td>
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<tr>
<td>high-dose methotrexate 3.5 g/m² d1</td>
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<tr>
<td>procarbazine 100mg/m² x 7 days d1-7</td>
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</tr>
<tr>
<td>Rituximab 375mg/m² d0</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>high-dose methotrexate 3.5 g/m² day 1</td>
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<tr>
<td>cytarabine 2 g/m² twice daily days 2–3</td>
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<tr>
<td>Ifosfamide 2g/m² daily days 1-3</td>
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#### Step 1. Induction: high-dose methotrexate/procarbazine x 1 cycle

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<tr>
<th>Day</th>
<th>Medications</th>
<th>Other Orders</th>
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</table>
| ADMISSION 0 | 0900hr-Rituximab 375mg/m² (1st infusion protocol) 2000hr – IV D5W + 20meq KCL/L + 2 amps NaHCO3/L @ 200ml/hour x 5 days | • Daily weights  
• Daily CBC & differential, EP, creatinine, glucose  
• ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg  
• LFTs, Ca, lipase, every Monday & Thursday |
| 1 | 0800hr - Kytril 1mg IV 0800hr - methotrexate 3500mg/m² IV over 2 hours 0800hr - procarbazine 100mg/m² p.o. daily x 7 days only cycle 1 (round down to nearest 50mg multiple) | 0700hr - Urine pH twice daily, call MD if <7.0 |
| 2-3 | 0800hr - folic acid (leucovorin) 25 mg IV q6hr until MTX level < 0.05 Continue hydration until methotrexate level <0.05 | 0500-0800hr – methotrexate level daily (expect level < 10 d2, <1 d3) |
| 4 | 0900hr- Rituximab 375mg/m² (subsequent infusion protocol)on cycle 1 only and continue folic acid | 0500-0800hr – methotrexate Level daily |
| 5 | • Discharge once methotrexate level <0.05  
• If level 0.01-0.05, discharge on leucovorin 5mg p.o. q6 hours x 2-3 days  
• Discharge meds: septra DS 1 daily or dapsone 50mg daily x 6-9 months; consider dexamethasone taper if on dexamethasone  
• Remember coumadin/LMWH and dilantin if patient is on these medicines |

* Male IBW = 50kg + 2.3kg x inches > 5ft, Female IBW = 45.5 kg + 2.3kg x inches > 5ft. Adjusted BW = IBW + [40% x (actual – IBW)]

#### Step 2. High-dose methotrexate/cytarabine consolidation q21 days x 4 cycles

<table>
<thead>
<tr>
<th>Day</th>
<th>Medications</th>
<th>Other Orders</th>
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</table>
| ADMISSION 0 | 1600hr- Rituximab 375mg/m² (subsequent infusion protocol)on cycle 1 only and continue folic acid) 2000hr – IV D5W + 20meq KCL/L + 2 amps NaHCO3/L @ 200ml/hour x 5 days | • Daily weights  
• Daily CBC & differential, EP, creatinine, glucose  
• ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg  
• LFTs, Ca, lipase, every Monday & Thursday |
| 1 | 0800hr - Kytril 1mg IV 0800hr - methotrexate 3500mg/m² IV over 2 hours | 07:00 - Urine pH bid, call MD if <7.0 |
| 2-3 | 0800hr - folic acid (leucovorin) 25 mg IV q6hrs until methotrexate level < 0.05 -Continue hydration until methotrexate level <0.05 0800hr – Kytril 2mg IV, Decadron 10mg IV 1000hr – cytarabine 2g/m² IV over 2 hours twice daily x 2 days; reduce to 1.5g/m² if age >60 years or creatinine >100 | 0500-08:00 – Methotrexate Level daily (expect <10 d2, <1 d3, <0.1 d4, <0.05 d5) |
| 5 | Discharge once methotrexate level <0.05 If level 0.01-0.05, discharge on leucovorin 5mg p.o. q6 hours x 2-3 days (other meds as step 1 above) | |

* Male IBW = 50kg + 2.3kg x inches > 5ft, Female IBW = 45.5 kg + 2.3kg x inches > 5ft. Adjusted BW = IBW + [40% x (actual – IBW)]

#### Step 3. Ifosfamide consolidation after response to methotrexate and high-dose cytarabine

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<tr>
<th>Day</th>
<th>Medications</th>
<th>Other Orders</th>
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</table>
| 15 or 16 | 0800hr – Kytril 2mg IV, dexamethasone 10mg IV daily x 3d 0800hr – N/S IV 500mL/hour x 1 hour daily x 3d 0900hr – Mesna 400mg/m² IV daily x 3d 0900hr – Ifosfamide 2g/m² with 1g Mesna IV over 3 hours daily x 3d 1200hr – Mesna 400mg/m² IV daily x 3d 1200hr – 1L NS IV 250mL/hour x 4 hours daily x 3d 1600hr – Mesna 400mg/m² IV daily x 3d | • weight (call MD if >2kg above day 1)  
• CBC & differential, EP, creatinine, glucose  
• ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg |
VIII. SECONDARY CNS LYMPHOMA PROTOCOL

A) Transplant-eligible patients (age <65 years, no significant co-morbidities, no immune suppression) with isolated CNS relapse/progression following complete response of systemic lymphoma to RCHOP.

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<th>Step 1</th>
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<tbody>
<tr>
<td></td>
<td>high-dose methotrexate 3.5 g/m² d1</td>
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<td></td>
<td>Rituximab 375 mg/m² d2</td>
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<td>procarbazine 100 mg/m² x 7 days d1-7</td>
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<td></td>
<td>vincristine 1.4 mg/m² d1</td>
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<td>rituximab 1400gsc days 1,4</td>
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<td>dexamethasone 20 mg days 1-4</td>
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<td>cisplatin 35 mg/m² days 1,2</td>
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<td>cytarabine 2 g/m² x 1 dose, days 1,2</td>
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<td>G-CSF 5-10 μg/m² day 8-13</td>
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<td>Apheresis day 13 or 14</td>
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<td>R-1bUM ASCT</td>
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<td>(ritux d-7 + thiopeta 250mg/m² d -6,-5</td>
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<td>busulfan 3.2 mg/kg day -4 to -2,</td>
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<td>melphalan 100 mg/m² d-1, ASCT d 0</td>
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</table>

**Step 1. Induction: high-dose methotrexate/vincristine/procarbazine q14 days x 4 cycles**

**Day** | **Medications** | **Other Orders**
---|---|---
ADMISSION | 2000hr - IV D5W + 20meq KCL/L + 2 amps NaHCO3/L @ 200mL/hour x 5 days | • Daily weights<br>• Daily CBC & differential, EP, creatinine, glucose<br>• ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg<br>• LFTs, Ca, lipase, every Monday & Thursday
1 | 0800hr - Kytril 1mg IV<br>0800hr - methotrexate 3500mg/m² IV over 2 hours cycles 1-4<br>0800hr - procarbazine 100mg/m² p.o. daily x 7 days cycles 1 and 3 (round down to nearest 50mg multiple)<br>1000hr - vincristine 1.4mg/m² IV only cycles 1 and 2 | 0700hr - Urine pH twice daily, call MD if <7.0
2-4 | 0800hr - folinic acid (leucovorin) 25 mg IV q6 hours until methotrexate level < 0.05<br>Continue hydration until methotrexate level <0.05<br>1000hr – Rituximab 375mg/m² IV (first 3 cycles HDMTX) | 0500-0800hr – methotrexate level daily (expect level <10 today)
5 | • Discharge once methotrexate level <0.05<br>• If level 0.01-0.05, discharge on leucovorin 5mg p.o. q6 hours x 2-3 days<br>• Discharge meds: septa DS 1 daily or dapsone 50mg daily x 6-9 months; consider dexamethasone taper if on dexamethasone<br>• Remember coumadin/LMWH and dilantin if patient is on these medications

* Male IBW = 50kg + 2.3kg x inches > 5ft, Female IBW = 45.5 kg + 2.3kg x inches > 5ft.

**Step 2. Rituximab/DHAP x 1 cycle for stem cell collection after 4 cycles of methotrexate**

**Day** | **Medications** | **Other Orders**
---|---|---
1 | 0800hr - hydrocortisone 100mg IV, Benadryl , Zantac, Tylenol<br>0900hr - rituximab 1400mg sc<br>0900hr - IV 1L NS<br>0900hr – dexamethasone 20mg p.o./IV daily x 4 days<br>0900hr – Kytril 1mg IV or 2mg p.o. x 3-4 days<br>0900hr – aperpitent protocol p.o. x 3 days<br>1000hr – cisplatin 35mg/m² IV over 2 hours with mannitol 25g and 500mL NS<br>1200hr – cytarabine 2g/m² IV over 2 hours x 1 doses (1.5g/m² if >60yr) | • Weight<br>• CBC & differential, EP, creatinine, glucose<br>• ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg
2 | 0800hr – dexamethasone Kytril, Aprepitent continued<br>1000hr – cisplatin 35mg/m² IV over 2 hours with mannitol 25g and 500mL NS<br>1200hr – cytarabine 2g/m² IV over 2 hours x 1 doses (1.5g/m² if >60yr) | Daily CBC & differential starting day 10
4 | Rituximab 1400mg sc |
### Step 3. R-TBuM/ASCT consolidation after response to MTX and RDHAP Induction

<table>
<thead>
<tr>
<th>Day</th>
<th>Medications</th>
<th>Other Orders</th>
</tr>
</thead>
</table>
| **ADMISSION** Day -7 | Allopurinol 300 mg p.o. daily until day 0  
Premeds: Hydrocortisone 100mg IV, Benadryl 50mg IV, Zantac 50mg IV, Tylenol 650mg p.o.  
- rituximab 375mg/m² IV (first dose long infusion protocol)  
2200hr - D5½ N/S + 20 mEq KCL/L @ 125 mL/hour until day -1 | • Consult dietician, physiotherapy  
• Low bacteria diet, 24 hour intake  
• Mouth protocol; record intake and output |
| -6 & -5   | 0800hr – thiotepa 250 mg/m² IV over 2 hours x 2 days  
(use ideal BSA)                                                                                                                                                                                                 | • 0800hr – Granisetron 2 mg IV daily x 8 days  
• EP daily x 31 days  
• Shower/Bath q6 hours x 3 days; avoid skin creams |
| -4 to -2  | 0900 - busulfan 3.2 mg/kg IV daily x 3 days  
(use ideal weight)                                                                                                                                                                                                 | • lorazepam prophylaxis x 4 days  
• CBC & differential daily x 31 days  
• ALT, Alk Phos, bilirubin, alb, Ca, Mg, every Monday & Thursday  
• PT, PTT every Monday |
| -1        | 10:00 -melphalan 100mg/m² (actual BSA) IV over 5 minutes  
10:15 – Lasix 20mg IV  
10:30 - mannitol 20% 250 mL IVPB over 1 hour  
11:30 - IV 1L NS @ 500 mL/hour for 3 hours  
14:30 -IV 1L NS with 40 mEq KCl/L @ 125 mL/hour x 18 hours | • Mycostatin 500,000 units q2-4 hours  
• Septra RS 1 tab p.o. daily  
• Acyclovir 5 mg/kg twice daily IV or 400 mg p.o. four times daily |
| 0         | Autologous Blood Stem Cell INFUSION                                                                                                                                                                                                 |
| +7        | G-CSF 300 µg (if less than 70kg) or 480µg (if over 70kg) subcutaneous daily until post-nadir ANC > 1.5 |                                                                 |
B) Transplant-eligible patients (age <65 years, no significant co-morbidities, no immune suppression) with early Systemic and CNS lymphoma (prior to completing RCHOP x6): RCHOP and HDMTX x4 cycles then RDHAP for stem cell mobilization and collection, then R-TBuM/ASCT.

<table>
<thead>
<tr>
<th>Week</th>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Methotrexate 3.5 g/m² q14d</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Rituximab 1400mg sc days 1-4</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dexamethasone 20 mg days 1-4</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cisplatin 35 mg/m² days 1-2</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cytarabine 2 g/m² x1 dose, days 1-2</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>G-CSF 5-10 μg/kg day 8-13</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Apheresis day 13 or 14</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

**HDMTX prior to RCHOP if CNS and systemic lymphoma both identified at time of initial diagnosis.**

**If CNS lymphoma identified after RCHOP initiated but systemic disease responding to RCHOP, then plan for at least 4 doses HDMTX q14d with subsequent cycles RCHOP before proceeding to R-DHAP.

* Male IBW = 50kg + 2.3kg x inches >5ft, Female IBW = 45.5 kg + 2.3kg x inches> 5ft.

### Step 1. Induction: RCHOP q21d as well as high-dose methotrexate q14 days x 4 cycles

<table>
<thead>
<tr>
<th>Day</th>
<th>Medications (HDMTX component)</th>
<th>Other Orders</th>
</tr>
</thead>
</table>
| ADMISSION 0 | 2000hr - IV D5W + 20meg KCL/L + 2 amps NaHCO3/L @ 200mL/hour x 5 days | • Daily weights  
• Daily CBC & differential, EP, creatinine, glucose  
• ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg  
• LFTs, Ca, lipase, every Monday & Thursday  
• Discharge once methotrexate level <0.05  
• If level 0.01-0.05, discharge on leucovorin 5mg p.o. q6 hours x 2-3 days  
• Discharge meds: septra DS 1 daily or dapsone 50mg daily x 6-9 months; consider dexamethasone taper if on dexamethasone  
• Remember coumadin/LMWH and diltiazem if patient is on these medications |
| 1 | 0800hr - Kytril 1mg IV  
0800hr - methotrexate 3500mg/m² IV over 2 hours cycles 1-4 | 0700hr - Urine pH twice daily, call MD if <7.0 |
| 2-4 | 0800hr - folinic acid (leucovorin) 25 mg IV q6 hours until methotrexate level <0.05  
Continue hydration until methotrexate level <0.05  
| 0500-0800hr – methotrexate level daily (expect level < 10 today) |
| 5 | • Discharge once methotrexate level <0.05  
• If level 0.01-0.05, discharge on leucovorin 5mg p.o. q6 hours x 2-3 days  
• Discharge meds: septra DS 1 daily or dapsone 50mg daily x 6-9 months; consider dexamethasone taper if on dexamethasone  
• Remember coumadin/LMWH and diltiazem if patient is on these medications |

### Step 2. Rituximab/DHAP x 1 cycle for stem cell collection after 4 cycles of methotrexate

<table>
<thead>
<tr>
<th>Day</th>
<th>Medications</th>
<th>Other Orders</th>
</tr>
</thead>
</table>
| 1 | 0800hr - hydrocortisone 100mg IV, Benadryl , Zantac, Tylenol  
0900hr - rituximab 1400mg sc  
0900hr - IV 1L NS  
0900hr – dexamethasone 20mg p.o./IV daily x 4 days  
0900hr – Kytril 1mg IV or 2mg p.o. x 3-4 days  
0900hr – apheresis protocol p.o. x 3 days  
1000hr – cisplatin 35mg/m² IV over 2 hours with mannitol 25g and 500mL NS  
1200hr - cytarabine 2g/m² IV over 2 hours x 1 doses (1.5g/m² if >60yr)  
| • Weight  
• CBC & differential, EP, creatinine, glucose  
• ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg |
| 2 | 0800hr – dexamethasone Kytril, Apheresis continued  
1000hr – cisplatin 35mg/m² IV over 2 hours with mannitol 25g and 500mL NS  
1200hr - cytarabine 2g/m² IV over 2 hours x 1 doses (1.5g/m² if >60yr)  
| 4 | Rituximab 1400mg sc  
1000hr – G-CSF 480-600µg subcutaneous daily until apheresis completed (plan for apheresis approximately day 13-15, once ANC>5, Plt>75 and CD34>20)  
| Daily CBC & differential starting day 10 |
### Step 3. R-TBuM/ASCT consolidation after response to MTX and RDHAP Induction

<table>
<thead>
<tr>
<th>Day</th>
<th>Medications</th>
<th>Other Orders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ADMISSION</strong>&lt;br&gt;Day -7</td>
<td>Allopurinol 300 mg p.o. daily until day 0&lt;br&gt;Premeds: Hydrocortisone 100mg IV, Benadryl 50mg IV, Zantac 50mg IV, Tylenol 650mg p.o.&lt;br&gt;<em>-rituximab</em> 375mg/m² IV (first dose long infusion protocol)&lt;br&gt;2200hr - D5½ N/S + 20 mEq KCL/L @ 125 mL/hour until day -1</td>
<td>• Consult dietician, physiotherapy&lt;br&gt;• Low bacteria diet. 24-hour intake&lt;br&gt;• Mouth protocol; record intake and output</td>
</tr>
<tr>
<td>-6 &amp; -5</td>
<td>0800hr – <em>thiotepa</em> 250 mg/m² IV over 2 hours x 2 days&lt;br&gt;(use ideal BSA)</td>
<td>0800hr – Granisetron 2 mg IV daily x 8 days&lt;br&gt;• EP daily x 31 days&lt;br&gt;• Shower/Bath q6 hours x 3 days; avoid skin creams</td>
</tr>
<tr>
<td>-4 to -2</td>
<td>0900 - <em>busulfan</em> 3.2 mg/kg IV daily x 3 days&lt;br&gt;(use ideal weight)</td>
<td>0900 – lorazepam prophylaxis x 4 days&lt;br&gt;• CBC &amp; differential daily x 31 days&lt;br&gt;• ALT, Alk Phos, bilirubin, alb, Ca, Mg, every Monday &amp; Thursday&lt;br&gt;• PT, PTT every Monday</td>
</tr>
<tr>
<td>-1</td>
<td>10:00 - <em>melphalan</em> 100mg/m² (actual BSA) IV over 5 minutes&lt;br&gt;10:15 – Lasix 20mg IV&lt;br&gt;10:30 - mannitol 20% 250 mL IVPB over 1 hour&lt;br&gt;11:30 - IV 1L NS @ 500 mL/hour for 3 hours&lt;br&gt;14:30 - IV 1L NS with 40 mEq KCL/L @ 125 mL/hour x 18 hours</td>
<td>10:00 – Mycostatin 500,000 units q2-4 hours&lt;br&gt;• Septra RS 1 tab p.o. daily&lt;br&gt;• Acyclovir 5 mg/kg twice daily IV or 400 mg p.o. four times daily</td>
</tr>
<tr>
<td>0</td>
<td>Autologous Blood Stem Cell INFUSION</td>
<td></td>
</tr>
<tr>
<td>+7</td>
<td>G-CSF 300 µg (if less than 70kg) or 480µg (if over 70kg) subcutaneous daily until post-nadir ANC &gt; 1.5</td>
<td></td>
</tr>
</tbody>
</table>
C) Transplant-eligible patients (age <65 years, no significant co-morbidities, no immune suppression) with late relapse (prior RCHOP x6) with systemic and CNS lymphoma: HDMTX-Ifosfamide-etopside x2 then RDHAP for stem cell mobilization and collection, then R-TBuM/ASCT

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week</strong></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>high-dose methotrexate 3.5 g/m² d1</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Rituximab 375 mg/m² d2</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Ifosfamide 1.5 g/m² d3-5</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Etoposide 100 mg/m² d3-5</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>rituximab 1400mg sc days 1-4</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>dexamethasone 20 mg days 1-4</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>cisplatin 35 mg/m² days 1-4</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>cytarabine 2 g/m² x1 dose, days 1-2</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>G-CSF 5-10 µg/kg day 8-13</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Apheresis day 13 or 14</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>R-TBuM/ ASCT (ritux d-7 + thiotepa 250mg/m² d -6,-5)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>busulfan 3.2 mg/kg day -4 to -2</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>melphalan 100 mg/m² d -1, ASCT d 0</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

**Step 1. Induction: R-IE and high-dose methotrexate x 2 cycles (HDMTX x3)**

<table>
<thead>
<tr>
<th><strong>Day</strong></th>
<th><strong>Medications</strong></th>
<th><strong>Other Orders</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>ADMISSION</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 0 | 2000hr - IV D5W + 20meq KCL/L + 2 amps NaHCO₃/L @ 200mL/hour x 5 days | • Daily weights  
• Daily CBC & differential, EP, creatinine, |
| | | |
| 1 | 0800hr - Kytril 1mg IV  
0800hr - methotrexate 3500mg/m² IV over 2 hours cycles 1-4 | • ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg  
• LFTs, Ca, lipase, every Monday & Thursday |
| | 0700hr - Urine pH twice daily, call MD if <7.0 |
| 2 | 0800hr - folinic acid (leucovorin) 25 mg IV q6 hours until methotrexate level < 0.05  
Continue hydration until methotrexate level <0.05  
1000hr – Rituximab 375mg/m² IV | 0500-0800hr – methotrexate level daily (expect level < 10 today) |
| 3-5 | 0800hr – Kytril 2mg IV, dexamethasone 10mg IV daily x 3d  
0800hr – NS IV 500mL/hour x 1 hour daily x 3d  
0900hr – Mesna 0.5 g IV daily x 3d  
0900hr – Ifosfamide 1.5g/m² with 1g Mesna IV over 3 hours daily x 3d  
1200hr – Mesna 0.5 g IV daily x 3d  
1200hr – 1/2NS IV 250mL/hour x 4 hours daily x 3d  
1200hr – Etoposide 100 mg/m² IV daily x 3d  
1600hr – Mesna 1.0 g IV daily x 3d  
1000hr | • Discharge once methotrexate level <0.05  
• If level 0.01-0.05, discharge on leucovorin 5mg p.o. q6 hours x 2-3 days  
• Discharge meds: septran DS 1 daily or dapsone 50mg daily x 6-9 months; consider dexamethasone taper if on dexamethasone  
• Remember coumadin/LMWH and dilantin if patient is on these medications |

* Male IBW = 50kg + 2.3kg x inches > 5ft, Female IBW = 45.5 kg + 2.3kg x inches> 5ft.
# Step 2. Rituximab/DHAP x 1 cycle for stem cell collection after 4 cycles of methotrexate

<table>
<thead>
<tr>
<th>Day</th>
<th>Medications</th>
<th>Other Orders</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0800hr – hydrocortisone 100mg IV, Benadryl, Zantac, Tylenol 0900hr – rituximab 1400mg sc 0900hr – IV 1L NS 0900hr – dexamethasone 20mg p.o./IV daily x 4 days 0900hr – Kytril 1mg IV or 2mg p.o. x 3-4 days 0900hr – aprepitent protocol p.o. x 3 days 1000hr – cisplatin 35mg/m² IV over 2 hours with mannitol 25g and 500mL NS 1200hr – cytarabine 2g/m² IV over 2 hours x 1 doses (1.5g/m² if &gt;60yr)</td>
<td>• Weight  • CBC &amp; differential, EP, creatinine, glucose  • ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg</td>
</tr>
<tr>
<td>2</td>
<td>0800hr – dexamethasone Kytril, Aprepitent continued 1000hr – cisplatin 35mg/m² IV over 2 hours with mannitol 25g and 500mL NS 1200hr – cytarabine 2g/m² IV over 2 hours x 1 doses (1.5g/m² if &gt;60yr)</td>
<td>Daily CBC &amp; differential starting day 10</td>
</tr>
<tr>
<td>4</td>
<td>Rituximab 1400mg sc</td>
<td></td>
</tr>
<tr>
<td>8-13</td>
<td>1000hr – G-CSF 480-600µg subcutaneous daily until apheresis completed (plan for apheresis approximately day 13-15, once ANC&gt;5, Plt&gt;75 and CD34&gt;20)</td>
<td></td>
</tr>
</tbody>
</table>

**Note:**
- All medications should be administered under medical supervision.
- Monitor vital signs and observe for adverse reactions.
- Regular laboratory tests should be conducted as per protocol.
- Ensure proper hydration and electrolyte balance.
- Use appropriate infection control measures.
- Monitor platelet counts and manage bleeding as required.

---

### Day 1

**Admission Day -7**
- Allopurinol 300 mg p.o. daily until day 0
- Premeds: Hydrocortisone 100mg IV, Benadryl 50mg IV, Zantac 50mg IV, Tylenol 650mg p.o.
  - **Rituximab** 375mg/m² IV (first dose long infusion protocol)
- 2200hr - D5½ N/S + 20 mEq KCL/L @ 125 mL/hour until day -1

**Day -6 & -5**
- 0800hr – **Thiotepa** 250 mg/m² IV over 2 hours x 2 days
  - (use ideal BSA)
- 0900 – **Busulfan** 3.2 mg/kg IV daily x 3 days
  - (use ideal weight)

**Day -4 to -2**
- 0900 – **Thiotepa** 250 mg/m² IV over 2 hours x 2 days
- 0900 – **Busulfan** 3.2 mg/kg IV daily x 3 days
- 1000hr – **G-CSF** 480 µg subcutaneous daily until apheresis completed (plan for apheresis approximately day 13-15, once ANC>5, Plt>75 and CD34>20)

**Day 0**
- **Autologous Blood Stem Cell Infusion**
- **G-CSF** 300 µg (if less than 70kg) or 480µg (if over 70kg) subcutaneous daily until post-nadir ANC > 1.5

---

### Day 1

- **Consult dietician, physiotherapy**
- **Low bacteria diet, 24hour intake**
- **Mouth protocol; record intake and output**

**Day -6 & -5**
- 0800hr – **Granisetron** 2 mg IV daily x 8 days
- **EP** daily x 31days
- **Shower/Bath** q6 hours x 3 days; avoid skin creams

**Day -4 to -2**
- **Lorazepam prophylaxis** x 4 days
- **CBC & differential daily x 31 days**
- **ALT, Alk Phos, bilirubin, Alb, Ca, Mg, every Monday & Thursday**
- **PT, PTT every Monday**

**Day 0**
- **Mycostatin 500,000 units q2-4 hours**
- **Septra RS 1 tab p.o. daily**
- **Acyclovir 5 mg/kg twice daily IV or 400 mg p.o. four times daily**
VIII. SECONDARY CNS LYMPHOMA PROTOCOL

D) Transplant-ineligible patients (age >65 years, significant co-morbidities, or immune suppression) with isolated CNS relapse/progression following complete response of systemic lymphoma to RCHOP. (consider only for highly motivated patients who wish curative intent therapy. Otherwise palliation with IT chemotherapy, radiotherapy, or supportive care).

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Rituximab 375mg/m² d0, 4</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>high-dose methotrexate 3.5 g/m² d1</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>procarbazine 100mg/m² x 7 days d1-7</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Rituximab 375mg/m² d0</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>high-dose methotrexate 3.5 g/m² day 1</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>cytarabine 1.5-2 g/m² bid days 2-3</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Ifosfamide 2g/m² daily days 1-3</td>
<td>x</td>
<td></td>
</tr>
</tbody>
</table>

**Step 1. Induction: high-dose methotrexate/procarbazine x 1 cycle**

<table>
<thead>
<tr>
<th>Day</th>
<th>Medications</th>
<th>Other Orders</th>
</tr>
</thead>
</table>
| ADMISSION 0 | 0900hr-Rituximab 375mg/m² (1st infusion protocol) 2000hr – IV D5W + 20meq KCL/L + 2 amps NaHCO3/L @ 200mL/hour x 5 days | • Daily weights  
• Daily CBC & differential, EP, creatinine, glucose  
• ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg  
• LFTs, Ca, lipase, every Monday & Thursday  |
| 1       | 0800hr - Kytril 1mg IV 0800hr - methotrexate 3500mg/m² IV over 2 hours 0800hr - procarbazine 100mg/m² p.o. daily x 7 days only cycle 1 | 0700hr - Urine pH twice daily, call MD if <7.0 |
| 2-3     | 0800hr - folinic acid (leucovorin) 25 mg IV q6hr until MTX level < 0.05 Continue hydration until methotrexate level <0.05 | 0500-0800hr – methotrexate level daily (expect level < 10 d2, <1 d3) |
| 4       | 0900hr- Rituximab 375mg/m² (subsequent infusion protocol) on cycle 1 only and continue folinic acid | 0500-0800hr – methotrexate Level daily |
| 5       | • Discharge once methotrexate level <0.05  
• If level 0.01-0.05, discharge on leucovorin 5mg p.o. q6 hours x 2-3 days  
• Discharge meds: septra DS 1 daily or dapsone 50mg daily x 6-9 months; consider dexamethasone taper if on dexamethasone  
• Remember coumadin/LMWH and dilantin if patient is on these medications | |

* Male IBW = 50kg + 2.3kg x inches > 5ft, Female IBW = 45.5 kg + 2.3kg x inches > 5ft. Adjusted BW = IBW + [40% x (actual – IBW)]

**Step 2. High-dose methotrexate/cytarabine consolidation q21 days x 4 cycles**

<table>
<thead>
<tr>
<th>Day</th>
<th>Medications</th>
<th>Other Orders</th>
</tr>
</thead>
</table>
| ADMISSION 0 | 1600hr- Rituximab 375mg/m² (subsequent infusion protocol) on cycle 1 only and continue folinic acid 2000hr – IV D5W + 20meq KCL/L + 2 amps NaHCO3/L @ 200mL/hour x 5 days | • Daily weights  
• Daily CBC & differential, EP, creatinine, glucose  
• ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg  
• ALT, Alk P, bilirubin, Ca, lipase, every Monday & Thursday  |
| 1       | 0800hr - Kytril 1mg IV 0800hr - methotrexate 3500mg/m² IV over 2 hours | 07:00 - Urine pH bid, call MD if <7.0 |
| 2-3     | 0800hr- folinic acid (leucovorin) 25 mg IV q6hrs until methotrexate level < 0.05 Continue hydration until methotrexate level <0.05 | 0500-0800hr – methotrexate Level daily (expect <10 d2, <1 d3) |
| 5       | Discharge once methotrexate level <0.05  
• If level 0.01-0.05, discharge on leucovorin 5mg p.o. q6 hours x 2-3 days (other meds as step 1 above) | |
| 8-12    | 10:00 – G-CSF 480-500 μg subcutaneous daily until post-nadir ANC >1.5 | Daily CBC & diff starting d10 |

* Male IBW = 50kg + 2.3kg x inches > 5ft, Female IBW = 45.5 kg + 2.3kg x inches > 5ft. Adjusted BW = IBW + [40% x (actual – IBW)]
### Step 3. Ifosfamide consolidation after response to methotrexate and high-dose cytarabine

<table>
<thead>
<tr>
<th>Day</th>
<th>Medications</th>
<th>Other Orders</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 or 16</td>
<td>0800hr – Kytril 2mg IV, dexamethasone 10mg IV daily x 3d</td>
<td>• weight (call MD if &gt;2kg above day 1)</td>
</tr>
<tr>
<td></td>
<td>0800hr – N/S IV 500mL/hour x 1 hour daily x 3d</td>
<td>• CBC &amp; differential, EP, creatinine, glucose</td>
</tr>
<tr>
<td></td>
<td>0900hr – Mesna 1.0 g IV daily x 3d</td>
<td>• ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg</td>
</tr>
<tr>
<td></td>
<td>0900hr – Ifosfamide 2g/m² with 1g Mesna IV over 3 hours daily x 3d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1200hr – Mesna 0.5 g IV daily x 3d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1200hr – 1/2NS IV 250mL/hour x 4 hours daily x 3d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1600hr – Mesna 1.0 g IV daily x 3d</td>
<td></td>
</tr>
</tbody>
</table>
E) Transplant-ineligible patients (age >65 years, significant co-morbidities, or immune suppression) with early Systemic and CNS lymphoma prior to completing initial RCHOP x6. (consider only for highly motivated patients who wish curative intent therapy. Otherwise palliation).

**If CNS lymphoma identified after RCHOP initiated but systemic disease responding to RCHOP, then plan for at least 4 doses HDMTX**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Days</th>
<th>Concentration</th>
<th>Dosage</th>
<th>Repeat</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ifosfamide</td>
<td>1-3</td>
<td>2g/m²</td>
<td>2g/m²</td>
<td></td>
<td>Q Day</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>1-3</td>
<td>2g/m²</td>
<td>2g/m²</td>
<td></td>
<td>Q Day</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>1-3</td>
<td>20mg</td>
<td>20mg</td>
<td></td>
<td>Q Day</td>
</tr>
<tr>
<td>Rituximab</td>
<td>1-3</td>
<td>2g/m²</td>
<td>2g/m²</td>
<td></td>
<td>Q Day</td>
</tr>
<tr>
<td>G-CSF 5-10µg/kg</td>
<td>8-13</td>
<td></td>
<td></td>
<td></td>
<td>Q Day</td>
</tr>
</tbody>
</table>

*HDMTX prior to RCHOP*#1 if CNS and systemic lymphoma both identified at time of initial diagnosis.

**If CNS lymphoma identified after RCHOP initiated but systemic disease responding to RCHOP, then plan for at least 4 doses HDMTX q14d with subsequent cycles RCHOP before proceeding to R-AraC.

**Male IBW = 50kg + 2.3kg x inches > 5ft, Female IBW = 45.5 kg + 2.3kg x inches > 5ft.**

---

**Step 1. Induction: RCHOP q21d as well as high-dose methotrexate q14 days x 4 cycles**

<table>
<thead>
<tr>
<th>Day</th>
<th>Medications (HDMTX component)</th>
<th>Other Orders</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADMISSION 0</td>
<td>2000hr - IV D5W + 20meq KCl/L + 2 amps NaHCO₃/L @ 200mL/hour x 5 days</td>
<td>- Daily weights - Daily CBC &amp; differential, EP, creatinine, glucose ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg - LFTs, Ca, lipase, every Monday &amp; Thursday</td>
</tr>
<tr>
<td>1</td>
<td>0800hr - Kytril 1mg IV 0800hr - methotrexate 3500mg/m² IV over 2 hours cycles 1-4</td>
<td>0700hr - Urine pH twice daily, call MD if &lt;7.0</td>
</tr>
<tr>
<td>2-4</td>
<td>0800hr - folinic acid (leucovorin) 25 mg IV q8 hours until methotrexate level &lt; 0.05 Continue hydration until methotrexate level &lt;0.05</td>
<td>0500-0800hr – methotrexate level daily (expect level &lt; 10 today)</td>
</tr>
<tr>
<td>5</td>
<td>- Discharge once methotrexate level &lt;0.05 - If level 0.01-0.05, discharge on leucovorin 5mg p.o. q6 hours x 2-3 days - Discharge meds: septra DS 1 daily or dapsone 50mg daily x 6-9 months; consider dexamethasone taper if on dexamethasone - Remember coumadin/LMWH and dilantin if patient is on these medications</td>
<td></td>
</tr>
</tbody>
</table>

**Step 2. Rituximab/DHAP x 1 cycle for stem cell collection after 4 cycles of methotrexate**

<table>
<thead>
<tr>
<th>Day</th>
<th>Medications</th>
<th>Other Orders</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0800hr - hydrocortisone 100mg IV, Benadryl , Zantac, Tylenol 0900hr - rituximab 1400mg sc 0900hr - IV 1L NS 0900hr – dexamethasone 20mg p.o./IV daily x 4 days 0900hr – Kytril 1mg IV or 2mg p.o. x 3-4 days 0900hr – aprepitant protocol p.o. x 3 days 1000hr – cisplatin 35mg/m² IV over 2 hours with mannitol 25g and 500mL NS 1200hr- cytarabine 2g/m² IV over 2 hours x 1 doses (1.5g/m² if &gt;60yr)</td>
<td>- Weight - CBC &amp; differential, EP, creatinine, glucose ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg</td>
</tr>
<tr>
<td>2</td>
<td>0800hr – dexamethasone Kytril, Aprepitent continued 1000hr – cisplatin 35mg/m² IV over 2 hours with mannitol 25g and 500mL NS 1200hr- cytarabine 2g/m² IV over 2 hours x 1 doses (1.5g/m² if &gt;60yr)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Rituximab 1400mg sc</td>
<td></td>
</tr>
<tr>
<td>8-13</td>
<td>1000hr – G-CSF 480-600µg subcutaneous daily until apheresis completed (plan for apheresis approximately day 13-15, once ANC&gt;5, Plt&gt;75 and CD34&gt;20)</td>
<td>Daily CBC &amp; differential starting day 10</td>
</tr>
</tbody>
</table>

**Step 3. Ilosfamide consolidation after response to methotrexate and high-dose cytarabine**

<table>
<thead>
<tr>
<th>Day</th>
<th>Medications</th>
<th>Other Orders</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 or 16</td>
<td>0800hr – Kytril 2mg IV, dexamethasone 10mg IV daily x 3d 0800hr – N/S IV 500mL/hour x 1 hour daily x 3d 0900hr – Mesna 1.0 g IV daily x 3d 0900hr – Ilosfamide 2gm with 1g Mesna IV over 3 hours daily x 3d 1200hr – Mesna 0.5 g IV daily x 3d 1200hr – 1/2NS IV 250mL/hour x 4 hours daily x 3d 1600hr – Mesna 1.0 g IV daily x 3d</td>
<td>- weight (call MD if &gt;2kg above day 1) - CBC &amp; differential, EP, creatinine, glucose ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg</td>
</tr>
</tbody>
</table>
F) Transplant-ineligible patients (age >65 years, significant co-morbidities, or immune suppression) with late relapse (prior RCHOP x6) with relapsed systemic and CNS lymphoma.

This situation is unfortunately associated with extremely poor prognosis, and generally should be treated with palliative intent. Treatments could include IT chemotherapy, radiotherapy, decadron, or best supportive care.
APPENDIX B: GENERAL RADIOTHERAPY GUIDELINES

Aggressive Non-Hodgkin Lymphomas

30Gy/15-35Gy/20 is recommended in lymphoma subtypes and situations except:
1. Nasal NK/T cell lymphomas: 30Gy/10 or 40-50Gy +/- concurrent cisplatin
3. Primary or secondary CNS lymphoma: Whole brain radiotherapy
   - Palliative: 20Gy/5 - 35Gy/20 +/- 10Gy/5 boost depending on age, KPS, anticipated life expectancy, status of extracranial disease?
   - Curative, post-methotrexate: 23.4Gy/13 fractions if in CR, or 45Gy/25 fractions
     (?alternative 30Gy/15 + boost 15Gy/8 or 35 Gy/20 + boost 10 Gy/5?) in PR

Indolent Lymphoma

24Gy/12 - 30Gy/20 fractions is generally recommended for most subtypes and situations except:
1. Palliation: lower doses may be used for palliation such as 4Gy/2 fractions
2. Contiguous stage II disease, curative intent: higher doses up to 40Gy may be used
3. Gastric MALT 30Gy/20

Hodgkin Lymphoma

20Gy/10 for early stage favorable, 30Gy/15 early stage unfavorable and advanced stage is recommended in lymphoma subtypes and situations except for nodular lymphocyte-predominant Hodgkin disease (NLPHD):
- IFRT alone to 30Gy/15-35Gy/20 fractions

What is INRT/ISRT? 8-10

- definitions are per ILROG guidelines and depends of whether radiation is sole treatment or part of combined modality regimen

Role of IMRT/VMAT/TOMO 11,12

- role of IMRT/VMAT/TOMO over 3DCRT is at discretion of treating radiation oncologist - this is determined on a case by case basis
- the low dose bath is a consideration when using IMRT as it relates to potential long term risk of second malignancies

Role of PET in Planning 13-16

- this is outlined in the ILROG guidelines for HL, nodal HL and extranodal HL
APPENDIX C: PROGNOSTIC MODELS

ECOG Performance Status

<table>
<thead>
<tr>
<th>Status</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease activities without restriction.</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g. light housework, office work).</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care. Confined to bed or chair more than 50% of waking hours.</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.</td>
</tr>
</tbody>
</table>

International Prognostic Index (IPI) for DLBCL Following CHOP-Type Chemotherapy\(^17\)

<table>
<thead>
<tr>
<th>Factors</th>
<th># of Factors</th>
<th>5 year PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 60 years</td>
<td>0-1</td>
<td>60%</td>
</tr>
<tr>
<td>ECOG 2-4</td>
<td>2-3</td>
<td>30%</td>
</tr>
<tr>
<td>Stage III/IV</td>
<td>4-5</td>
<td>15%</td>
</tr>
<tr>
<td>ENS &gt; 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased LDH</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Revised IPI for DLBCL Following R-CHOP Chemotherapy\(^18\)

<table>
<thead>
<tr>
<th>Factors</th>
<th># of Factors</th>
<th>% of Patients</th>
<th>4 year PFS</th>
<th>4 year DSS</th>
<th>4 year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 60 years</td>
<td>0</td>
<td>11</td>
<td>96%</td>
<td>95%</td>
<td>95%</td>
</tr>
<tr>
<td>ECOG 2-4</td>
<td>1-2</td>
<td>48</td>
<td>81%</td>
<td>83%</td>
<td>79%</td>
</tr>
<tr>
<td>Stage III/IV</td>
<td>3-5</td>
<td>41</td>
<td>55%</td>
<td>56%</td>
<td>55%</td>
</tr>
<tr>
<td>ENS &gt; 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased LDH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

R-CHOP for DLBCL by Elevated LDH and Stage 3-4\(^18\)

<table>
<thead>
<tr>
<th># of Factors</th>
<th>% of Patients</th>
<th>4 year PFS</th>
<th>4 year DSS</th>
<th>4 year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>27</td>
<td>92%</td>
<td>90%</td>
<td>84%</td>
</tr>
<tr>
<td>1</td>
<td>38</td>
<td>78%</td>
<td>79%</td>
<td>77%</td>
</tr>
<tr>
<td>2</td>
<td>35</td>
<td>53%</td>
<td>56%</td>
<td>55%</td>
</tr>
</tbody>
</table>

An online prognostic calculator is available at: http://www.qxmd.com/calculate-online/hematology/prognosis-large-b-cell-lymphoma-r-ipi

Modified IPI for Non-Bulky Stage I-IIA DLBCL Treated with CHOP x 3 cycles and IFRT

<table>
<thead>
<tr>
<th>Factors</th>
<th># of Factors</th>
<th>5 year PFS</th>
<th>10 year PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 60 yrs</td>
<td>0</td>
<td>94%</td>
<td>89%</td>
</tr>
<tr>
<td>ECOG 2-4</td>
<td>1-2</td>
<td>79%</td>
<td>73%</td>
</tr>
<tr>
<td>Stage II</td>
<td>3-4</td>
<td>60%</td>
<td>50%</td>
</tr>
<tr>
<td>Increased LDH</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Salvage Age-Adjusted IPI for Relapsed DLBCL\textsuperscript{19}

<table>
<thead>
<tr>
<th>Factors</th>
<th># of Factors</th>
<th>~ PFS for HDCT/ASCT Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage III/IV</td>
<td>0</td>
<td>70%</td>
</tr>
<tr>
<td>Elevated LDH</td>
<td>1</td>
<td>50%</td>
</tr>
<tr>
<td>ECOG 2-4</td>
<td>2</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>10%</td>
</tr>
</tbody>
</table>

Primary CNS Lymphoma (Memorial Sloan Kettering Cancer Center Model)\textsuperscript{20}

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>mOS</th>
<th>5 year OS</th>
<th>mFFS</th>
<th>5 year FFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 50 years</td>
<td>5-8 years</td>
<td>50-60%</td>
<td>2-5 years</td>
<td>35-40%</td>
</tr>
<tr>
<td>Age &gt;50 years, KPS &gt; 70%</td>
<td>2-3 years</td>
<td>15-35%</td>
<td>1.5 years</td>
<td>10-20%</td>
</tr>
<tr>
<td>Age &gt;50 years, KPS &lt; 70%</td>
<td>1 year</td>
<td>10%</td>
<td>0.5-1 year</td>
<td>5-10%</td>
</tr>
</tbody>
</table>

Simplified IELSG Primary CNS Lymphoma (Leon Berard Cancer Centre Model)\textsuperscript{21}

<table>
<thead>
<tr>
<th>Factors</th>
<th># of Factors</th>
<th>mOS</th>
<th>5 year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 60 years</td>
<td>0</td>
<td>6 years</td>
<td>60%</td>
</tr>
<tr>
<td>Elevated LDH</td>
<td>1</td>
<td>4 years</td>
<td>40%</td>
</tr>
<tr>
<td>Deep Tumour</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>o Cerebellum</td>
<td>2</td>
<td>1 year</td>
<td>23%</td>
</tr>
<tr>
<td>o Periventricular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>o Basal ganglion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>o Brainstem</td>
<td>3</td>
<td>0.5 years</td>
<td>0%</td>
</tr>
</tbody>
</table>

Follicular Lymphoma Internacional Prognostic Index (FLIPI) Pre-dated Rituximab-Chemotherapy (Survival with Non-Rituximab Containing Therapy)\textsuperscript{22}

<table>
<thead>
<tr>
<th>Factors</th>
<th>Prognosis</th>
<th># Factors</th>
<th>% Patients</th>
<th>5 year OS</th>
<th>10 year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 60 years</td>
<td>Good</td>
<td>0-1</td>
<td>36</td>
<td>90%</td>
<td>70%</td>
</tr>
<tr>
<td>Stage III-IV</td>
<td>Intermediate</td>
<td>2</td>
<td>37</td>
<td>78%</td>
<td>50%</td>
</tr>
<tr>
<td>Increased LDH</td>
<td>Poor</td>
<td>3-5</td>
<td>27</td>
<td>53%</td>
<td>35%</td>
</tr>
</tbody>
</table>

An online prognostic calculator is available at:  

FLIPI 2\textsuperscript{23}

<table>
<thead>
<tr>
<th>Factors</th>
<th>Prognosis</th>
<th># Factors</th>
<th>% Patients</th>
<th>3 year PFS</th>
<th>5 year PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 60 years</td>
<td>Good</td>
<td>0</td>
<td>20</td>
<td>91%</td>
<td>80%</td>
</tr>
<tr>
<td>Marrow involvement</td>
<td>Intermediate</td>
<td>1-2</td>
<td>53</td>
<td>69%</td>
<td>51%</td>
</tr>
<tr>
<td>Increased B2M</td>
<td>Poor</td>
<td>3-5</td>
<td>27</td>
<td>51%</td>
<td>19%</td>
</tr>
<tr>
<td>Hb &lt; 120 g/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5+ nodal sites</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

www.albertahealthservices.ca
Hodgkin Lymphoma International Prognostic Score (IPS) for Advanced Disease

<table>
<thead>
<tr>
<th>Factors</th>
<th># of Factors</th>
<th>5 year FFS with ABVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥45 years</td>
<td>0-1</td>
<td>80%</td>
</tr>
<tr>
<td>Male</td>
<td>2</td>
<td>70%</td>
</tr>
<tr>
<td>Stage IV</td>
<td>3</td>
<td>60%</td>
</tr>
<tr>
<td>Albumin &lt;40 g/L</td>
<td>4-7</td>
<td>50%</td>
</tr>
<tr>
<td>Hb&lt;105 g/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC&gt;15 x 10^9/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocyte &lt; 0.6 x 10^9/L or &lt; 8% WBC</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

An online prognostic calculator is available at: [http://www.qxmd.com/calculate-online/hematology/hasenclever-hodgkins-prognosis-score-ips](http://www.qxmd.com/calculate-online/hematology/hasenclever-hodgkins-prognosis-score-ips)

Prognosis of Hodgkin Lymphoma Relapsed After Prior Chemotherapy

<table>
<thead>
<tr>
<th>Factors</th>
<th># of Factors</th>
<th>2nd Line Chemo</th>
<th>HDCT/ASCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to relapse &lt;1 year</td>
<td>0</td>
<td>70%</td>
<td>100%</td>
</tr>
<tr>
<td>Relapse stage III-IV</td>
<td>1</td>
<td>60%</td>
<td>70%</td>
</tr>
<tr>
<td>Hb&lt;105 female, 120 male</td>
<td>2</td>
<td>30%</td>
<td>50%</td>
</tr>
<tr>
<td>3</td>
<td>0%</td>
<td>50%</td>
<td></td>
</tr>
</tbody>
</table>

* 5yr OS by second line therapy.  
* Freedom from second failure was 50% for 0-1 factor, 35% for 2 factors, and 15% for 3 factors.

Mantle Cell Lymphoma (MIPI)

<table>
<thead>
<tr>
<th>Points</th>
<th>Age</th>
<th>ECOG</th>
<th>LDH (ULN 235)</th>
<th>WBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;50</td>
<td>0-1</td>
<td>&lt;0.67 ULN</td>
<td>&lt;6.7</td>
</tr>
<tr>
<td>1</td>
<td>50-59</td>
<td>-</td>
<td>0.67-0.99 ULN</td>
<td>6.7-9.99</td>
</tr>
<tr>
<td>2</td>
<td>60-69</td>
<td>2-4</td>
<td>1-1.49 ULN</td>
<td>10.0-14.99</td>
</tr>
<tr>
<td>3</td>
<td>70+</td>
<td>-</td>
<td>≥1.5 ULN</td>
<td>≥15.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Points</th>
<th>Age</th>
<th>ECOG</th>
<th>LDH (ULN 235)</th>
<th>WBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;50</td>
<td>0-1</td>
<td>&lt;157</td>
<td>&lt;6.7</td>
</tr>
<tr>
<td>2</td>
<td>60-69</td>
<td>2-4</td>
<td>235-352</td>
<td>10.0-14.99</td>
</tr>
<tr>
<td>3</td>
<td>70+</td>
<td>-</td>
<td>≥352</td>
<td>≥15.0</td>
</tr>
</tbody>
</table>

Risk | # Points | ~Median OS | ~5 year OS |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0-3</td>
<td>6 years</td>
<td>60%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>4-5</td>
<td>4 years</td>
<td>40%</td>
</tr>
<tr>
<td>High</td>
<td>6-11</td>
<td>2 years</td>
<td>20%</td>
</tr>
</tbody>
</table>


Post-Transplantation Lymphoproliferative Disease (PTLD) Prognostic Scoring Systems

1. Evens et al., 2010

Score 1 point for each: hypoalbumenia, bone marrow involvement, CNS involvement

<table>
<thead>
<tr>
<th># of Factors</th>
<th>Overall 3 year PFS</th>
<th>Overall 3 year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>84%</td>
<td>93%</td>
</tr>
<tr>
<td>1</td>
<td>66%</td>
<td>68%</td>
</tr>
<tr>
<td>2-3</td>
<td>7%</td>
<td>11%</td>
</tr>
</tbody>
</table>
Patients who received rituximab-based therapy as part of their initial treatment had a 3-year PFS of 70% and an OS of 73% compared with a 3-year PFS of 21% (p<0.0001) and an OS of 33% (p=0.0001) for patients who did not receive rituximab.

2. Leblond et al., 2001

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>PS</th>
<th>and/or</th>
<th># of Sites</th>
<th>mOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>low-risk</td>
<td>PS &lt; 2</td>
<td>and</td>
<td>1</td>
<td>&gt;5 years</td>
</tr>
<tr>
<td>intermediate risk</td>
<td>PS &gt; 2</td>
<td>or</td>
<td>2 or more</td>
<td>3 years</td>
</tr>
<tr>
<td>high risk</td>
<td>PS &gt; 2</td>
<td>and</td>
<td>2 or more</td>
<td>1 month</td>
</tr>
</tbody>
</table>
Waldenström Macroglobulinemia

<table>
<thead>
<tr>
<th>Study</th>
<th>Prognostic Factors</th>
<th>Stratification</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gobbi et al, 1994</td>
<td>Hb &lt;9 g/dL</td>
<td>0-1 factor</td>
<td>mOS 80 months</td>
</tr>
<tr>
<td></td>
<td>Age &gt;70 years</td>
<td>0-2 2-4 factors</td>
<td>mOS 48 months</td>
</tr>
<tr>
<td></td>
<td>Weight loss</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cryoglobulinaemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morel et al, 2000</td>
<td>Age ≥ 65 years</td>
<td>0-1 factor</td>
<td>5 year survival 87%</td>
</tr>
<tr>
<td></td>
<td>Albumin &lt;40 g/L</td>
<td>2 factors</td>
<td>5 year survival 62%</td>
</tr>
<tr>
<td></td>
<td>1 cytopenia (1-point)</td>
<td>3-4 factors</td>
<td>5 year survival 25%</td>
</tr>
<tr>
<td></td>
<td>&gt;1 cytopenia (2-points)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dhodapkar et al, 2001</td>
<td>β2M &gt;3 mg/L</td>
<td>β2M&lt;3 mg/L + Hb&gt;12 g/dL</td>
<td>5 year survival 87%</td>
</tr>
<tr>
<td></td>
<td>Hb &lt;12 g/dL</td>
<td>β2M&lt;3 mg/L + Hb&lt;12 g/dL</td>
<td>5 year survival 63%</td>
</tr>
<tr>
<td></td>
<td>IgM &gt;40 g/L</td>
<td>β2M&gt;3 mg/L + IgM&lt;40 g/L</td>
<td>5 year survival 53%</td>
</tr>
<tr>
<td></td>
<td>Other combinations</td>
<td>β2M&gt;3 mg/L + IgM&gt;40 g/L</td>
<td>5 year survival 21%</td>
</tr>
<tr>
<td>Merlini et al, 2003</td>
<td>Age≥60 years</td>
<td>&lt;60 years, Hb&gt;100, Alb≥35</td>
<td>mOS 178 months</td>
</tr>
<tr>
<td></td>
<td>Hb&lt;100 g/L</td>
<td>&gt;60 years, Hb &lt;100, Alb&lt;35</td>
<td>mOS 33 months</td>
</tr>
<tr>
<td></td>
<td>Albumin &lt;35 g/L</td>
<td>Other combinations</td>
<td>mOS 84 months</td>
</tr>
</tbody>
</table>

CLL Prognostic Score from MD Anderson Cancer Center

<table>
<thead>
<tr>
<th>Factors</th>
<th># of Factors</th>
<th># of Patients</th>
<th>5 year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;60 years</td>
<td>0</td>
<td>364</td>
<td>96%</td>
</tr>
<tr>
<td>B2M &gt;2 mg/L</td>
<td>1</td>
<td>623</td>
<td>79%</td>
</tr>
<tr>
<td>Alb &lt; 35</td>
<td>2</td>
<td>497</td>
<td>69%</td>
</tr>
<tr>
<td>Creatinine &gt; 1.6</td>
<td>3</td>
<td>70</td>
<td>30%</td>
</tr>
<tr>
<td>17p mutations</td>
<td>4-5</td>
<td>10</td>
<td>16%</td>
</tr>
</tbody>
</table>

CLL Internation Prognostic Score: Bahlo 2015ASCO, J Clin Oncol 33, 2015 (suppl; abstr 7002)

<table>
<thead>
<tr>
<th>Factors</th>
<th>Points</th>
<th>Risk Group</th>
<th>5 year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;65 years</td>
<td>1</td>
<td>Low (0-1 points)</td>
<td>93% (~90%)</td>
</tr>
<tr>
<td>Clinical Stage &gt;1</td>
<td>1</td>
<td>Intermediate (2-3 points)</td>
<td>79% (~80%)</td>
</tr>
<tr>
<td>IGHV unmutated</td>
<td>2</td>
<td>High (4-6 points)</td>
<td>64% (~60%)</td>
</tr>
<tr>
<td>B2M &gt;3.5 mg/L</td>
<td>2</td>
<td>Very high risk (7-10 points)</td>
<td>23% (~25%)</td>
</tr>
<tr>
<td>17p deletion or TP53 mutations</td>
<td>4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The full analysis set was collected from eight phase 3 trials in France, Germany, the United Kingdom, the United States, and Poland (n=3,472 patients, median age 61 years (27-86 yrs)). 89% of patients had received treatment for CLL and median overall survival (OS) was 95 months. The model was externally validated in a third dataset comprising 845 patients with newly diagnosed CLL from the Mayo Clinic; 39% had received treatment for CLL. The final model of multivariate analysis identified 5 independent predictors for OS: **TP53** (17p) mutation (deleted and/or mutated; hazard ratio [HR]: 4.2); **IGHV** mutation status (unmutated, HR: 2.6); B2M (>3.5 mg/L; HR: 2.0); clinical stage (Binet B/C or Rai I-IV, HR: 1.6); and age (≥65 years, HR: 1.7). Using weighted grading, a prognostic score from 0 to 10 was derived that separated the patients into four different groups: low risk (score 0-1), intermediate risk (score 2-3), high risk (score 4-6), and very high risk (score 7-10). At 5 years, significantly different rates of OS were observed for the low to the very high risk group, 93%, 79%, 64%, and 23%, respectively (P<0.001; C-statistic c=0.72 [95% CI: 0.69, 0.76]). The multivariable model was confirmed on the internal validation datasets; in addition, the four risk groups were reproduced with on the Mayo dataset, with 5-year OS rates of 97%, 91%, 68% and 21%, respectively (P<0.001; C-statistic c=0.79 [95% CI: 0.74, 0.85]).
# APPENDIX D: LYMPHOMA RESPONSE CRITERIA

<table>
<thead>
<tr>
<th>Response</th>
<th>Definition</th>
<th>Nodal Masses</th>
<th>Spleen, Liver</th>
<th>Bone Marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>Disappearance of all evidence of disease</td>
<td>(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative</td>
<td>not palpable, nodule disappeared</td>
<td>Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immuno-histochemistry should be negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(b) Varibly FDG-avid or PET negative; regression to normal size on CT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>Regression of measurable disease and no new sites</td>
<td>≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Varibly FDG-avid or PET negative; regression on CT</td>
<td>≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen</td>
<td>Irrelevant if positive prior to therapy; cell type should be specified</td>
</tr>
<tr>
<td>SD</td>
<td>Failure to attain CR/PR or PD</td>
<td>(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Varibly FDG-avid or PET negative; no change in size of previous lesions on CT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapsed Disease or PD</td>
<td>Any new lesion or increase by ≥50% of previously involved sites from nadir</td>
<td>Appearance of a new lesion(s) &gt; 1.5 cm in any axis, ≥50% increase in SPD of more than one node, or ≥50% increase in longest diameter of a previously identified node &gt; 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy</td>
<td>&gt; 50% increase from nadir in the SPD of any previous lesions</td>
<td>New or recurrent involvement</td>
</tr>
</tbody>
</table>

**Abbreviations:** CR=complete response, FDG-PET=(18)F-fluorodeoxyglucose positron emission tomography, CT=computed tomography, PR=partial response, SPD=sum of the product of the diameters, SD=stable disease, PD=progressive disease.

# LYMPHOMA RESPONSE CRITERIA

## Complete Response (CR)

The designation of CR requires the following:

1. Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy.

2a. Typically FDG-avid lymphoma: in patients with no pretreatment PET scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.

2b. Varibly FDG-avid lymphomas/FDG avidity unknown: in patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, all lymph nodes and nodal masses must have regressed on CT to normal size (<1.5 cm in their greatest transverse diameter for nodes >1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and more than 1.0 cm in their short axis before treatment must have decreased to ≤1.0 cm in their short axis after treatment.

3. The spleen and/or liver, if considered enlarged before therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by...
imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.

4. If the bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of >20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but that demonstrates a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.

Partial Response (PR)

The designation of PR requires all of the following:

1. At least a 50% decrease in sum of the product of the diameters (SPD) of up to six of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following: they should be clearly measurable in at least 2 perpendicular dimensions; if possible they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

2. No increase should be observed in the size of other nodes, liver, or spleen.

3. Splenic and hepatic nodules must regress by ≥50% in their SPD or, for single nodules, in the greatest transverse diameter.

4. With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.

5. Bone marrow assessment is irrelevant for determination of a PR if the sample was positive before treatment. However, if positive, the cell type should be specified (e.g., large-cell lymphoma or small neoplastic B cells). Patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders. When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders.

6. No new sites of disease should be observed.

7. Typically FDG-avid lymphoma: for patients with no pre-treatment PET scan or if the PET scan was positive before therapy, the post-treatment PET should be positive in at least one previously involved site.

8. Variably FDG-avid lymphomas/ FDG-avidity unknown: for patients without a pre-treatment PET scan, or if a pre-treatment PET scan was negative, CT criteria should be used.
9. In patients with follicular lymphoma or mantle-cell lymphoma, a PET scan is only indicated with one or at most two residual masses that have regressed by more than 50% on CT; those with more than two residual lesions are unlikely to be PET negative and should be considered partial responders.

**Stable Disease (SD)**

Stable disease is defined as the following:

1. A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR, but does not fulfill those for progressive disease (see Relapsed Disease [after CR]/Progressive Disease [after PR, SD]).

2. Typically FGD-avid lymphomas: the PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET.

3. Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pre-treatment PET scan or if the pre-treatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

**Relapsed Disease (after CR)/ Progressive Disease (after PR or SD)**

1. Lymph nodes should be considered abnormal if the long axis is more than 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is more than 1.0. Lymph nodes $<1.0 \times <1.0$ cm will not be considered as abnormal for relapse or progressive disease.

2. Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.

3. At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (e.g., splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by $>50\%$ and to a size of $1.5 \times 1.5$ cm or more than 1.5 cm in the long axis.

4. At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.

5. Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems ($<1.5$ cm in its long axis by CT).

6. Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable (e.g., pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an
abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative.

7. In clinical trials where PET is unavailable to the vast majority of participants, or where PET is not deemed necessary or appropriate for use (e.g., a trial in patients with MALT lymphoma), response should be assessed as above, but only using CT scans. However, residual masses should not be assigned CRu status, but should be considered partial responses.
### Table 3. Revised Criteria for Response Assessment

<table>
<thead>
<tr>
<th>Response and Site</th>
<th>PET-CT-Based Response</th>
<th>CT-Based Response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete</strong></td>
<td>Complete metabolic response</td>
<td>Complete radiologic response (all of the following)</td>
</tr>
<tr>
<td>Lymph nodes and extranodal sites</td>
<td>Score 1, 2, or 3* with or without a residual mass on 5FST It is recognized that in Waldenström's disease, extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.</td>
<td>Target nodes/nodal masses must regress to ≤ 1.5 cm in LDI No extranodal sites of disease</td>
</tr>
<tr>
<td>Nonmeasured lesion</td>
<td>Not applicable</td>
<td>Absent</td>
</tr>
<tr>
<td>Organ enlargement</td>
<td>Not applicable</td>
<td>Regress to normal</td>
</tr>
<tr>
<td>New lesions</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>No evidence of FDG-avid disease in marrow</td>
<td>Normal by morphology; if indeterminate, IHC negative</td>
</tr>
<tr>
<td><strong>Partial</strong></td>
<td>Partial metabolic response</td>
<td>Partial remission (all of the following)</td>
</tr>
<tr>
<td>Lymph nodes and extranodal sites</td>
<td>Score 4 or 5† with reduced uptake compared with baseline and residual masses of any size</td>
<td>&gt; 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites</td>
</tr>
<tr>
<td></td>
<td>At interim, these findings suggest responding disease</td>
<td>When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value</td>
</tr>
<tr>
<td></td>
<td>At end of treatment, these findings indicate residual disease</td>
<td>When no longer visible, 0 × 0 mm</td>
</tr>
<tr>
<td>Nonmeasured lesions</td>
<td>Not applicable</td>
<td>For a node &gt; 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation</td>
</tr>
<tr>
<td>Organ enlargement</td>
<td>Not applicable</td>
<td>Absent/normal, regressed, but no increase</td>
</tr>
<tr>
<td>New lesions</td>
<td>None</td>
<td>Spleen must have regressed by &gt; 50% in length beyond normal</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan</td>
<td>None</td>
</tr>
<tr>
<td><strong>No response or stable disease</strong></td>
<td>No metabolic response</td>
<td>Stable disease</td>
</tr>
<tr>
<td>Target nodes/nodal masses, extranodal lesions</td>
<td>Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment</td>
<td>&lt; 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met</td>
</tr>
<tr>
<td>Nonmeasured lesions</td>
<td>Not applicable</td>
<td>No increase consistent with progression</td>
</tr>
<tr>
<td>Organ enlargement</td>
<td>Not applicable</td>
<td>No increase consistent with progression</td>
</tr>
<tr>
<td>New lesions</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>No change from baseline</td>
<td>Not applicable</td>
</tr>
<tr>
<td><strong>Progressive disease</strong></td>
<td>Progressive metabolic disease</td>
<td>Progressive disease requires at least 1 of the following</td>
</tr>
<tr>
<td>Individual target nodes/nodal masses</td>
<td>Score 4 or 5 with an increase in intensity of uptake from baseline and/or New FDG-avid node consistent with lymphoma at interim or end-of-treatment assessment</td>
<td>PPD progression:</td>
</tr>
<tr>
<td>Extranodal lesions</td>
<td></td>
<td>An individual node/lesion must be abnormal with:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LDI &gt; 1.5 cm and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increase by ≥ 50% from PPD nadir and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>An increase in LDI or SDI from nadir</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.5 cm for lesions ≤ 2 cm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.0 cm for lesions &gt; 2 cm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>In the setting of splenomegaly, the splenic length must increase by ≥ 50% of the extent of its prior increase beyond baseline (eg, ≥ 1.5 cm spleen must increase to &gt; 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline</td>
</tr>
<tr>
<td></td>
<td></td>
<td>New or recurrent splenomegaly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>New or clear progression of preexisting nonmeasured lesions</td>
</tr>
<tr>
<td>Nonmeasured lesions</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

*Note: 5FST = 5-fluorouracil, doxorubicin, cyclophosphamide, vincristine, and prednisone; LDI = lymphocytosis differential index; PPD = purified protein derivative; SDI = standard deviation index.
<table>
<thead>
<tr>
<th>Response and Site</th>
<th>PET-CT-Based Response</th>
<th>CT-Based Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>New lesions</td>
<td>New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or repeat scan may be considered</td>
<td>Regrowth of previously resolved lesions</td>
</tr>
<tr>
<td></td>
<td>A new node &gt; 1.5 cm in any axis</td>
<td>A new extranodal site &gt; 1.0 cm in any axis; if &lt; 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma</td>
</tr>
<tr>
<td></td>
<td>A new extranodal site &gt; 1.0 cm in any axis; if &lt; 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma</td>
<td>Assessable disease of any size unequivocally attributable to lymphoma</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>New or recurrent FDG-avid foci</td>
<td>New or recurrent involvement</td>
</tr>
</tbody>
</table>

**Abbreviations:** 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDI, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDI and perpendicular diameter; Sdi, shortest axis perpendicular to the LDI; SSD, sum of the product of the perpendicular diameters for multiple lesions.

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (e.g., GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).

**PET 5PS:** 1, no uptake above background; 2, uptake < mediastinum; 3, uptake > mediastinum but < liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.
APPENDIX E: New Lymphoma Patient Data Sheet

Identification:

Name ___________________________ DOB (d/m/y) ________________
AHN ______________________________ ACB# ________________
Gender: male female Age at Diagnosis ________________

Diagnostic Information:

Date Diagnosis (d/m/y) __________________ Surgical accession # ________________
Biopsy type: open surgical/core needle fine needle bone marrow blood
Diagnosis: ________________
Stage: I II III IV B sx: yes no Bulk>10cm: yes no
Marrow +ve: yes no Other Extranodal Sites: ________________
LDH elevated: yes no ECOG Status: 0 1 2 3 4

Prognosis Score by Histology:

Large Cell Lymphoma: #IPI Factors: 0 1 2 3 4 5
 Circle if present: Age > 60yr Stage III/IV LDH>ULN ECOG 2-4 >2 Extranodal Sites

Follicular: # FLIPI Factors: 0 1 2 3 4 5
 Circle if present: Age > 60yr Stage III/IV LDH>ULN Hb<120g/L >5 Nodal Sites

Hodgkin: # IPS Factors: 0 1 2 3 4 5 6 7
 Circle if present: Age > 45 yr Stage IV Male Lymphocyte<0.6 (or < 8%WBC) Albumin < 40 g/L
Hb < 105g/L WBC > 15

Initial Treatment:

<table>
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<tr>
<th>Therapy</th>
<th>Plan</th>
<th>Regimen / Radiation Site</th>
<th>Start Date d/m/y</th>
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</thead>
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<tr>
<td>Chemotherapy</td>
<td>yes</td>
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<tr>
<td>Maintenance Rituximab</td>
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<td>no</td>
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<tr>
<td>Radiotherapy</td>
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<td>no</td>
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<tr>
<td>Stem Cell Transplant</td>
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<td>no</td>
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First Relapse Information:

Relapse/progression after treatment 1: yes no Date relapse (d/m/y) ________________
2nd Treatment: Regimen __________________ Radiation yes no HDCT/ASCT yes no

Survival Information:

Dead: yes no Date death or last follow-up (d/m/y) ________________
Cause of death: lymphoma other (specify) ________________
Ann Arbor Staging Nodal Sites

FLIPI Nodal Sites

Revised-International Prognostic Index for Diffuse Large B-Cell Lymphoma Following R-CHOP Chemotherapy

Factors:
- Age > 60yr
- ECOG 2-4
- Stage III/IV
- ENS > 1
- ↑ LDH

FLIPI (Follicular Lymphoma International Prognostic Index)

Factors
- Survival with Non-Rituximab Containing Therapy
- Age > 60yrs
- Prognosis
- Stage 3-4
- Increased LDH
- Hb < 120g/l
- 5+ nodal sites

Primary CNS lymphoma Prognostic Index

Adverse Factors
- Overall Survival mOS 5yr OS
- Failure-Free Survival mFFS 5yr FFS
- Age < 50 yrs 5-8 yrs 50-60% 2.5yrs 35-40%
- Age > 50 yrs KPS > 70% 2-3 yrs 15-35% 1.5 yrs 10-20%
- Age > 50 yrs KPS < 70% 1 yr 10% 0.5-1yr 5-10%

Hodgkin Lymphoma International Prognostic Score for Advanced Stage Disease

Factors
- # Factors 5yr FFS with ABVD
- Age > 45 yrs 0-1 80%
- Male 2 70%
- Stage 4 3 60%
- Albumin < 40 g/L 4-7 50%
- Hb < 105g/L 10.0-14.99
- WBC ≥ 15 x 10⁹/L
- Lymphocyte < 0.6 x 10⁹/L or < 8% WBC

Mantle Cell Lymphoma (MIPI)

Points
- Age ECOG LDH(ULN 235) WBC
- 0 <50 0-1 < 157 <6.7
- 2 60-69 2-4 225-352 10.0-14.99
- 3 70+ - ≥ 352 ≥15.0

Risk # points ~Median OS ~5yr OS
- Low 0-3 6yr 60%
- Intermediate 4-5 4yr 40%
- High 6-11 2yr 20%

Ann Arbor Staging System

<table>
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<tr>
<th>Stage</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>I</td>
<td>Single lymph node region (I) or one extralymphatic organ (IE)</td>
</tr>
<tr>
<td>II</td>
<td>≥2 lymph node regions (II) or local extralymphatic extension plus lymph nodes (IE), same side of diaphragm.</td>
</tr>
<tr>
<td>III</td>
<td>Lymph node regions both sides of diaphragm, either alone (III) or with local extralymphatic extension (IIIE)</td>
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<tr>
<td>IV</td>
<td>Diffuse involvement of one or more extralymphatic organs or sites.</td>
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ECOG Performance Status

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<th>Number</th>
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<td>0</td>
<td>Fully active, able to carry on all pre-disease activities without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature.</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory, capable of all self-care but unable to carry out any work activities. Up and about &gt;50% waking hours.</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care. Confined to bed or chair more than 50% of waking hours.</td>
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<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.</td>
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## APPENDIX F: Ideal Body Weight

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