Intended for use by Clinicians and Health Care Providers involved in the Management or Referral of patients with Aggressive Lymphoma

Section	Activity	Activity Description	Details	Reference(s)
AA	Cancer Centre Referrals		All patients with a potential or confirmed lymphoproliferative disorder should be referred to the cancer centre.	
A	Diagnosis	Biopsy Type	Excisional biopsy is optimal. Core needle biopsy may be adequate however this should be reviewed on a case by case basis. Pathology review by a lymphoma pathologist recommended.	
B	History and Physical exam		Standard history and physical exam including disease related symptoms, ECOG performance status, palpable lymphadenopathy, organomegaly or masses.	
C	Investigations		Baseline investigations to be obtained prior to therapy: 1. CBC and differential, electrolytes, creatinine, calcium, albumin, total bilirubin, AST/ALT, ALP, LDH, total protein 2. Hepatitis B (Hepatitis B surface antibody, surface antigen and core antibody), hepatitis C and HIV serology for all patients 3. If Hepatitis B surface antigen is positive or hepatitis B surface antigen is negative but hepatitis B core antibody or surface antibody is positive in the absence of vaccination the patient should have HBV DNA PCR performed and prophylaxis/treatment considered in consultation with hepatology. 4. Pregnancy test in women of child bearing age 5. CT scan chest, abdomen and pelvis with or without neck	

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			6. Consider baseline PET CT for diffuse large B cell lymphoma (DLBCL) 7. Bone marrow aspirate and biopsy (1.6cm) with flow cytometry if upstaging would result in a change in management, not required for patients who have undergone baseline PET scan 8. MUGA or echocardiogram for any patient who will receive anthracyclines 9. Consideration of fertility preservation and sperm banking 10. If there is Waldeyer's ring involvement consider upper GI imaging and small bowel follow through	
D	Pathology of Diagnostic Specimen	Synoptic Report	Immunohistochemistry, flow cytometry and fluorescence in situ hybridization (FISH) is performed as per the World Health Organization (WHO) Classification of Tumours of Haematopoietic and Lymphoid Tissues as well as an ancillary testing as indicated (ie. Molecular clonality, EBER, etc.) Specifically, all cases that have the histological appearance of diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL) or B-cell lymphoma, unclassifiable with features intermediate between DLBCL and BL (BCLU) will have the following immunohistochemical (IHC) stains performed: CD20, CD3, CD5, BCL6, CD10, BCL2, MYC, Ki-67 and possibly cyclin D1.	

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			If MYC IHC is positive in >40% of cells and BCL2 IHC is positive in >60% of cells, FISH for MYC and BCL2 rearrangements will be requested stating “double expressing lymphoma, ? double hit” on the FISH requisition. If the age of the patient is >75 years, FISH studies will not be undertaken unless the treating clinician requests them. For such cases, a comment will be included in the pathology report acknowledging the "double-expressing" status of the case and offering to undertake FISH studies upon request. Whether or not FISH is requested, if the case is morphologically an unremarkable DLBCL, the final diagnosis will be DLBCL. Alternatively, if there are morphologically aggressive features such as intermediate-sized cells (instead of large), very numerous mitotic figures and a "starry sky" appearance, FISH for MYC and BCL2 will be requested regardless of MYC and BCL2 IHC results and the final diagnosis will be determined by the morphological and immunophenotypic findings, as follows: a. If neither the morphology nor the immunophenotype are characteristic of BL, then the diagnosis will be DLBCL.	

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			b. If the morphology is imperfect for Burkitt lymphoma but the immunophenotype is typical for this diagnosis (CD10+, BCL6+, BCL2-), or if the morphology is that of Burkitt lymphoma but the immunophenotype is not, then a diagnosis of BCLU will be specified. c. If both the morphology and immunophenotype are typical of Burkitt lymphoma, then the diagnosis will read "aggressive B-cell lymphoma, please see Diagnosis Comment" and the Diagnosis Comment will indicate that the differential diagnosis is between BL and BCLU. The Diagnosis Comment will also indicate that FISH for MYC and BCL2 rearrangements will be carried out on an expedited basis. Regardless of histology, if FISH studies are requested based either on the results of IHC or aggressive morphology, a line in the final diagnosis will be added stating “FISH studies for MYC and BCL2 rearrangements pending”. In cases where FISH is requested, an addendum will be issued based on the final diagnosis in the original report and the results of the FISH studies, as follows: 1. DLBCL with or without MYC rearrangement =	

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			DLBCL 2. BCLU with or without MYC rearrangement = BCLU 3. "Aggressive B-cell lymphoma", as defined above, with MYC rearrangement = BL 4. "Aggressive B-cell lymphoma", as defined above, without MYC rearrangement = BCLU 5. Any morphology with MYC and BCL2 rearrangements = the designation "double hit lymphoma" will be added to the WHO category	
E	Staging		Groups: I Involvement of a single lymphatic site (i.e. nodal region, Waldeyer's ring, thymus or spleen) (I); or localized involvement of a single extralymphatic organ or site in the absence of any lymph node involvement (IE) (rare in Hodgkin lymphoma). II Involvement of two or more lymph node regions on the same side of the diaphragm (II); or localized involvement of a single extralymphatic organ or site in association with regional lymph node involvement with or without involvement of other lymph node regions on the same side of the diaphragm (IIE). The number of regions involved may be indicated by a subscript, as in, for example, II3 III Involvement of lymph node regions on both sides of the diaphragm (III), which also may be accompanied by extralymphatic extension in association with adjacent lymph node involvement (IIIE) or by involvement of the spleen	

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			(IIIS) or both (IIIE,S). Splenic involvement is designated by the letter S. IV Diffuse or disseminated involvement of one or more extralymphatic organs, with or without associated lymph node involvement; or isolated extralymphatic organ involvement in the absence of adjacent regional lymph node involvement, but in conjunction with disease in distant site(s). Stage IV includes any involvement of the liver or bone marrow, lungs (other than by direct extension from another site), or cerebrospinal fluid. Modifiers for Group: E Extranodal S Spleen A & B classification A Asymptomatic B Symptoms: fevers, night sweats, weight loss To guide therapy, patients can be separated into two categories by group: 1. Limited Stage: Group IAE or IIAE, nonbulky and involvement of 3 or less adjacent lymph node regions 2. Advanced Stage: Stage II involving greater than 3 or nonadjacent lymph node regions, stage III or IV, B symptoms or bulky disease (7.5cm or greater)	

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G	Follow Up and Restaging		Prior to each chemotherapy: 1. Brief history and physical examination to evaluate disease status, toxicity and performance status 2. CBC, differential +/- electrolytes, creatinine, ALT/AST, total bilirubin Disease Follow up by CT scanning: 1. After 3 or 4 cycles of chemotherapy to evaluate interim response 2. At the end of treatment if interim scan was abnormal 3. No additional follow up scans are required, as per the discretion of the treating physician Special considerations: 1. Consider repeating bone marrow aspiration and biopsy with flow cytometry at the end of treatment if the bone marrow was involved initially by an aggressive lymphoma 2. If a residual mass is present at the end of therapy, suggest further evaluation with PET/CT when the intent of treatment is curative to establish partial or complete remission 3. If the PET scan is negative, suggest observation 4. If the PET scan is positive options include biopsy, radiation therapy or autologous stem cell transplant and should be discussed at hematology case conference	

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G	Follow up with no evidence of disease		After treatment for aggressive lymphoma, patients should be followed with clinical and laboratory evaluation every 3 months for the first two years then every 6 months for three years. After the initial five years of follow up patients may be discharged to their family physician for ongoing annual surveillance. In addition to monitoring for relapse, follow up includes surveillance for complications of disease and therapy. 1. Patients should be screened annually for hypothyroidism if the thyroid was irradiated as part of treatment. 2. Second malignancy. Patients should undergo all age appropriate screening for malignancy, and women who have had chest or axillary radiation should start breast cancer screening early, at age 40 or ten years after radiation therapy, whichever comes first. Breast MRI should be performed in addition to mammography. 3. Cardiovascular disease. Patients having undergone chest radiation should have annual screening for hypertension, diabetes and hyperlipidemia and *sh*ould have aggressive cardiovascular risk reduction	
H	Treatment of diffuse large B cell lymphoma	Limited stage disease	R-CHOP x 3 cycles plus IFRT, OR R-CHOP x 6 cycles with consideration of radiation if PET scan is positive at the end of treatment	

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			*Both treatment regimens are acceptable and the decision between the two based on patient factors such as age and comorbidities, patient preference and on the radiation field and potential complications of radiation treatment. For example in a young woman in whom the radiation field would include breast tissue it may be preferable to avoid radiation altogether whereas an elderly or frail patient may experience less toxicity from fewer cycles of chemotherapy	
		Advanced stage disease	R-CHOP x 6 cycles Radiation therapy should be administered to sites of initially bulky disease and to areas of PET avidity if scan is positive at the end of treatment	
		Special considerations	1. Include prophylaxis for tumor lysis syndrome 2. A lumbar puncture should be performed in patients with symptoms suggestive of CNS involvement Lumbar puncture and CNS prophylaxis should be provided to those patients who are high risk by the DSHNHL prognostic model for CNS relapse[9], have intravascular or double hit lymphoma, or those with kidney, adrenal or testicular involvement in the form of high dose methotrexate 3gm/m2 x 3 cycles during cycles 2,4 and 6 of R-CHOP (typically planned around day 5-7), provided they are	[9]

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			medically fit. Alternatively, due to issues of scheduling, tolerability or treatment delays, HD MTX can be postponed until chemotherapy is completed and then the three cycles can be performed sequentially every 2 weeks* *DSHNHL prognostic model for CNS relapse: Age >60, LDH>ULN, ECOG>1, Stage III or IV, >1 extranodal site, adrenal/kidney involvement. Each factor gets 1 point and the patient is assigned a score out of 6. Patients with 4-6 risk factors are at high risk of CNS relapse (2y CNS relapse risk 12%) and should receive prophylaxis 3. In elderly patients over the age of 65, prednisone 100mg daily for five days prior to R-CHOP should be considered and routine prophylaxis for febrile neutropenia with Neupogen is recommended 4. In the setting of relapsed/refractory disease multiple salvage chemotherapy options are available through Cancer Care Ontario. If the patient is fit, salvage chemotherapy followed by autologous stem cell transplant is recommended. Some available salvage chemotherapy regimens include GDP, ICE, DHAP, ESHAP and EPOCH. However should the patient not be fit for autologous stem cell transplant	

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			outcomes are poor and options include palliative radiation or chemotherapy. Please refer to the Cancer Care Ontario website for a complete list of funded regimens for both settings https://www.cancercare.on.ca/toolbox/drugformulary/stfmregimens/ 5. Patients with CNS involvement at presentation should be discussed at lymphoma conference. 6. R-CEOP is recommended as an alternative to R-CHOP in patients with poor left ventricular function (EF less than 50%)	
I	Special aggressive B cell lymphoma entities		1.Primary mediastinal large B cell lymphoma -DA-R-EPOCH for most patients x 6 cycles with consideration of IFRT if PET positive after treatment* -R-CHOP x 6 cycles for the less fit with involved field radiation *Note following DA-R-EPOCH and no radiation, FDG-PET has excellent negative predictive value but a low positive predictive value such that a positive PET at the end of treatment requires careful evaluation prior to embarking on further therapy[8] 2.Intermediate between DLBCL and Hodgkin lymphoma (grey zone lymphoma)	[8]

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			-DA-R-EPOCH x 6 cycles with consideration of IFRT to areas of bulky disease or if PET positive after treatment, OR -R-CHOP x 6 cycles for the less fit with consideration of IFRT to areas of bulky disease or if PET positive after treatment 3.Intermediate between DLBCL and Burkitt lymphoma including Double Hit lymphomas -DA-R-EPOCH x 6 cycles with consideration for radiation therapy in patients with bulky disease or if PET positive after treatment AND consider CNS prophylaxis, see section on DLBCL special considerations above 4.Diffuse large B cell lymphoma, leg type should be managed similarly to DLBCL in general. Patients should be staged and those with systemic involvement should receive 6 cycles of R-CHOP followed by IFRT to the area of involvement on the leg. There is paucity of evidence to guide the optimal number of R-CHOP cycles in those with localized disease but they should receive 3-6 cycles of R-CHOP together with IFRT to the leg 5.Patients with testicular lymphoma should receive R-CHOP x 6 cycles and scrotal irradiation in addition to CNS prophylaxis	

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J	Burkitt's lymphoma		*All patients with Burkitt's lymphoma require an LP at the time of diagnosis to rule out CNS involvement. Patients with CNS involvement should be discussed at lymphoma conference *Prophylaxis for tumor lysis syndrome mandatory for all patients	
		Low risk (single extra-abdominal mass <10cm or completely resected abdominal disease and normal LDH)	R-CODOX-M x 3 cycles	
		High risk (all others)	R-CODOX-M followed by R-IVAC x 2 cycles (for a total of four cycles)	
K	Primary CNS lymphoma		*All patients with primary CNS lymphoma require a baseline LP (if not contraindicated from neurologic standpoint), HIV serology, ophthalmologic referral with slit lamp exam and a CT of the chest, abdomen and pelvis for staging purposes. Consider a MRI spine if the patient is symptomatic or has positive CSF Initiate steroids as clinically indicated however hold if possible until after diagnostic procedure	

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			Treatment options include: DeAngelis protocol with the addition of Rituximab Ferreri protocol with the addition of Rituximab *Particularly in patients over the age of 60, WBRT may increase toxicity and can be deferred *Patients can be palliated with WBRT alone, consider for those whose age or performance status would exclude HD MTX based chemotherapy	
		Special considerations	1. If CSF or spinal MRI is positive consider addition of IT chemotherapy 2. If eye exam is positive consider RT to globe	
L	Eye lymphoma		Intra-ocular/optic nerve involvement should be treated as PCNSL and additionally with consideration of RT to the globe Patients with orbital, peri-orbital or conjunctival lymphoma excluding those with intra-ocular or optic nerve involvement should be treated as histology and staging would dictate (see appropriate section within the guidelines) with consideration to RT	
M	Controversies		1. Role of PET scanning 2. CNS prophylaxis in DLBCL 3. Ideal screening, definition and treatment for Double Hit Lymphoma	

Section	Activity	Activity Description	Details	Reference(s)
N	Clinical Trials		Active Clinical Trials	Active Clinical Trials

References

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5. Cheson B, Fisher R, Barringston S, Cavalli F, Schwartz L, Zucca E, Lister TA. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. JCO 2014;32:3059-3068.

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Revisions

1. 2016-01-18 Change in title to Aggressive B non-Hodgkin's Lymphoma
2. 2016-01-19 Addition of clinical trial LY17
3. 2016-08-30 Section C #3, Section paragraph 4, Section N - removed individual trial and added link to Clinical Trials website, added link to clinical trials in references