Primary Mediastinal Large B-Cell Lymphoma

Disclaimer: This algorithm has been developed for MD Anderson using a multidisciplinary approach considering circumstances particular to MD Anderson’s specific patient population, services and structure, and clinical information. This is not intended to replace the independent medical or professional judgment of physicians or other health care providers in the context of individual clinical circumstances to determine a patient’s care. This algorithm should not be used to treat pregnant women.

Note: Consider Clinical Trials as treatment options for eligible patients.

PATHOLOGIC DIAGNOSIS

ESSENTIAL:
• Hematopathology review of all slides with at least one paraffin block or 15 unstained slides representative of the tumor. Rebiopsy if consult material is nondiagnostic.
• Adequate morphology and immunophenotyping to establish diagnosis
  ○ Paraffin Panel: CD3, CD20 and/or another pan-B-cell marker (CD19, Pax-5, CD79a) or
  ○ Flow cytometry immunophenotypic studies: CD54 (LCA), CD3, CD5, CD10, CD19, CD20, CD22, kappa and lambda light chains
• Additional immunohistochemical studies to determine subgroup: PD-L1/L2, CD5, CD10, CD15, CD23, CD54, CD79a, BCL-2, BCL-6, MUM-1/IRF4, and MIB1 (Ki67).

OF USE IN CERTAIN CIRCUMSTANCES:
• EBER in situ hybridization, LMP-1, HHV-8, CD138, CD30, TdT and ALK1
• FISH studies to detect gene rearrangements; involving: MYC, BCL-2 and/or BCL-6
• Molecular studies to detect clonality of the IgH gene

STRONGLY RECOMMENDED:
• FNA or core biopsy for tissue array/banking by protocol

INITIAL EVALUATION

ESSENTIAL:
• Physical exam: attention to node-bearing areas, including Waldeyer's ring, and to size of liver and spleen
• ECOG performance status
• B symptoms (Unexplained fever >38°C during the previous month; Recurrent drenching night sweats during the previous month; Weight loss >10 percent of body weight ≤ 6 months of diagnosis)
• CBC with differential, LDH, BUN, creatinine, albumin, AST, ALT; total bilirubin, alkaline phosphatase, serum calcium, uric acid
• Beta 2 microglobulin
• Screening for HIV 1 and 2, hepatitis B and C (HBcAb, HBsAg, HCV Ab)
• Chest x-ray, PA and LAT
• CT with contrast of neck, chest, abdomen and pelvis
• Unilateral or bilateral bone marrow biopsy with or without aspirate
• Calculation of IPI
• Muga scan or echocardiogram
• PET/CT
• Discuss fertility issues and sperm banking for patients of child bearing potential
• Lifestyle risk assessment

OF USE IN SELECTED CASES:
• CT or MRI of head
• Pregnancy test
• Consider lumbar puncture and intrathecal chemotherapy if paranasal sinus, testicular, epidural, ≥ 2 extranodal sites, or if IPI score ≥ 3
• Consider thoracentesis if clinically indicated

See Page 2, Induction Therapy
Primary Mediastinal Large B-Cell Lymphoma

INDUCTION THERAPY

All stages → DAEPOCH-R for 6 cycles → Evaluate response after 2 cycles by PET scan → Patient has greater than or equal to partial response? → Yes → Continue planned treatment → See Page 3, Post-treatment Response Evaluation → No → Core needle or excisional biopsy → Biopsy positive? → Yes → See Page 4, Relapse or Refractory Treatment → No → Continue planned treatment

1 DAEPOCH-R: dose adjusted EPOCH-R: etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab (see Appendix B); administration is based on age and performance status of the patient
2 See Appendix C: Response Criteria for Malignant Lymphoma

Note: Consider Clinical Trials as treatment options for eligible patients.
Primary Mediastinal Large B-Cell Lymphoma

RESPONSE EVALUATION

Complete response¹
Deauville 1-3

History and physical with CT neck, chest, abdomen, and pelvis with contrast and labs as clinically indicated:
- Every 3 to 4 months for 1 year, then
- Every 6 months for 2 years, then
- Annual PA and LAT CXR

Multidisciplinary conference and/or follow-up evaluation if previous bulky mass³ or large residual non-fluorodeoxyglucose (FDG) avid mass

Complete treatment

Partial response¹
Deauville 4²
PET – equivocal⁴

PET normalized?

Yes

Multidisciplinary conference and/or consider Radiation Oncology evaluation if previous bulky mass² or large residual non-FDG avid mass

Complete treatment

No

Biopsy positive?

Yes

See Page 4, Relapse or Refractory Treatment

No

Biopsy

Yes

See Page 4, Relapse or Refractory Treatment

Biopsy positive?

No

Multidisciplinary conference and/or consider Radiation Oncology evaluation if:
- Biopsy or residual mass negative though high clinical/radiographic suspicion
- Biopsy of residual mass is not possible due to location/patient refusal with high clinical/radiographic suspicion

No response or progressive disease¹
Deauville 5¹

¹ See Appendix C: Response Criteria for Malignant Lymphoma
² See Appendix D: Deauville Criteria
³ Bulky disease: mass ≥ 7.5 cm on CT imaging
⁴ PET equivocal: maximum standardized uptake value (SUV) greater than mediastinal blood pool in the residual mediastinal mass
CONSOLIDATION / ADDITIONAL THERAPY

Patient has greater than or equal to partial response? 

- Yes
  - High dose therapy plus autologous or allogeneic stem cell transplant (in the context of a clinical trial)

- No
  - Patient candidate for intensive therapy?
    - Yes
      - Clinical trial
      - Standard of care chimeric antigen receptor (CAR) T-cell therapy
    - No
      - Individual approach including: clinical trial*, palliative chemotherapy or palliative radiation therapy

RELAPSE or REFRACTORY #1

- Clinical trial
- New non cross-resistant regimen, chemo-immunotherapy (e.g., rituximab with one of the following regimens: ICE, ESHAP, MINE, DHAP)
- Consider radiation therapy for consolidation with involved site approach

ADDITIONAL THERAPY

ICE = ifosfamide, carboplatin, etoposide
ESHAP = etoposide, methylprednisolone, high-dose cytarabine, cisplatin
MINE = mesna, ifosfamide, mitoxantrone, etoposide
DHAP = dexamethasone, cytarabine, cisplatin

1 See Appendix B: Response Criteria for Malignant Lymphoma
2 Clinical trials or individual regimens; except for patients with disease-free interval, those who progress after three successive regimens are unlikely to derive additional benefit from currently utilized combination chemotherapy regimens

Note: Consider Clinical Trials as treatment options for eligible patients.
### APPENDIX A: International Prognostic Index (IPI)

#### Pre-Treatment Characteristics, ALL PATIENTS:
- Age > 60 years old
- Serum LDH greater than upper limit of normal
- ECOG performance status 2-4
- Stage III or IV
- Extranodal involvement > 1 site

#### International Index, ALL PATIENTS:
<table>
<thead>
<tr>
<th>Number of characteristics</th>
<th>Low</th>
<th>Low intermediate</th>
<th>High intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>4 or 5</td>
</tr>
</tbody>
</table>

#### Age-Adjusted IPI

#### Pre-Treatment Characteristics, ALL PATIENTS ≤ 60 YEARS:
- Serum LDH greater than one times upper limit of normal
- ECOG performance status 2-4
- Extranodal involvement > 1 site

#### International Index, ALL PATIENTS ≤ 60 YEARS:
<table>
<thead>
<tr>
<th>Number of characteristics</th>
<th>Low</th>
<th>Low intermediate</th>
<th>High intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
APPENDIX B: Dose Adjusted EPOCH-R

### Table 1. EPOCH-R starting dose level

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose, route, treatment days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>375 mg/m² IV day 1</td>
</tr>
<tr>
<td>Etoposide</td>
<td>50 mg/m²/day continuous IV days 1-4</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>10 mg/m²/day continuous IV days 1-4</td>
</tr>
<tr>
<td>Vincristine</td>
<td>0.4 mg/m²/day continuous IV days 1-4</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>750 mg/m²/day IV day 5</td>
</tr>
<tr>
<td>Prednisone</td>
<td>60 mg/m² PO twice daily days 1-5</td>
</tr>
<tr>
<td>Filgrastim product</td>
<td>5 mcg/kg subcutaneously daily starting on day 6 until ANC &gt; 5 K/microliter</td>
</tr>
<tr>
<td>Next Cycle¹</td>
<td>Day 21</td>
</tr>
</tbody>
</table>

1. Begin on day 21 if the ANC ≥ 1 K/microliter and the platelet count ≥ 100 K/microliter

### Table 2. EPOCH dose-adjustment paradigm

<table>
<thead>
<tr>
<th>Nadir measurements²</th>
<th>Dose-adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>If nadir ANC ≥ 0.5 K/microliter</td>
<td>20% increase in etoposide, doxorubicin and cyclophosphamide above last cycle</td>
</tr>
<tr>
<td>If nadir ANC &lt; 0.5 K/microliter on 1 or 2 measurements</td>
<td>Same doses as last cycle</td>
</tr>
<tr>
<td>If nadir ANC &lt; 0.5 K/microliter on at least 3 measurements or If nadir platelet count &lt; 25 K/microliter on 1 measurement</td>
<td>20% decrease in etoposide, doxorubicin and cyclophosphamide below last cycle</td>
</tr>
</tbody>
</table>

Note: Dose adjustments above starting dose level apply to etoposide, doxorubicin and cyclophosphamide. Dose adjustments below starting dose level apply to cyclophosphamide only.

² Measurements of ANC and platelet nadir are based on twice weekly CBC only.
APPENDIX C: 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></td>
<td></td>
</tr>
<tr>
<td>Lymph nodes and extralymphatic sites No Uptake Deauville 1-3</td>
<td>Score 1, 2, or 3 with or without a residual on 5PS It is recognized that in Waldeyer’s ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal in the 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 ≤ to 1.5 cm in LDi No extralymphatic 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 lesion</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</td>
</tr>
<tr>
<td><strong>Partial</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymph nodes and extralymphatic sites Deauville 5</td>
<td>Score 4 or 5 with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease</td>
<td>Decrease of ≥ 50% in sum of product diameter (SPD) of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default value When no longer visible, 0 x 0 mm For a node &gt; 5 mm x 5 mm, but smaller than normal, use actual measurement for calculation</td>
</tr>
<tr>
<td>Nonmeasured lesion</td>
<td>Not applicable</td>
<td>Absent, normal, regressed, but no increase</td>
</tr>
<tr>
<td>Organ enlargement</td>
<td>Not applicable</td>
<td>Spleen must be regressed by &gt; 50% in length beyond normal</td>
</tr>
<tr>
<td>New lesion</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>


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Department of Clinical Effectiveness V4
Approved by the Executive Committee of the Medical Staff on 11/19/2019

Continued on next page
### APPENDIX C: Response Criteria for Response Assessment - continued

<table>
<thead>
<tr>
<th>Response and Site</th>
<th>PET-CT-Based Response</th>
<th>CT-Based Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial</td>
<td>Partial metabolic response</td>
<td>Partial remission (all of the following)</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>Not applicable</td>
</tr>
</tbody>
</table>

#### No response or stable disease

<table>
<thead>
<tr>
<th></th>
<th>No metabolic response</th>
<th>Stable disease</th>
</tr>
</thead>
<tbody>
<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 lesion</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 lesion</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>No change from baseline</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

#### Progressive disease

<table>
<thead>
<tr>
<th></th>
<th>Progressive metabolic response</th>
<th>Progressive disease requires at least 1 of the following PPD progression</th>
</tr>
</thead>
<tbody>
<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 foci consistent with lymphoma at interim or end-of-treatment assessment</td>
<td>An individual node/lesion must be abnormal with:</td>
</tr>
<tr>
<td>Extranodal lesions</td>
<td></td>
<td>• &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 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 &gt; 50% of the extent of its prior increase beyond baseline (e.g., a 15 cm spleen must increase to &gt; 16 cm). If no prior splenomegaly, must increase by ≥ 2 cm from baseline.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• New or recurrent splenomegaly</td>
</tr>
</tbody>
</table>

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Continued on next page
**APPENDIX C: Revised Criteria for Response Assessment - continued**

<table>
<thead>
<tr>
<th>Response and Site</th>
<th>PET/CT-Based Response</th>
<th>CT-Based Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive disease</td>
<td>Progressive metabolic response</td>
<td>Progressive disease requires at least 1 of the following PPD progression</td>
</tr>
<tr>
<td>Nonmeasured lesions</td>
<td>None</td>
<td>New or clear progression of preexisting nonmeasured lesions</td>
</tr>
<tr>
<td>New lesion</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 interval scan may be considered.</td>
<td>Regrowth of previously resolved lesions A new node &gt; 1.5 cm in any axis A new extranodal site &gt; 1 cm in any axis; if &lt; 1 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma 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>

APPENDIX D: Deauville Criteria

- Score 1: no uptake
- Score 2: uptake less than or equal to mediastinum
- Score 3: uptake greater than mediastinum but less than or equal to liver
- Score 4: uptake greater than liver at any site
- Score 5: uptake greater than liver and new sites of disease
- Score X: new areas of uptake unlikely to be related to lymphoma

A score of 1-3 is regarded as negative and 4 or 5 as positive.
SUGGESTED READINGS


Continued on next page
SUGGESTED READINGS - continued


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DEVELOPMENT CREDITS

This practice algorithm is based on majority expert opinion of the Lymphoma Center Faculty at the University of Texas MD Anderson Cancer Center. It was developed using a multidisciplinary approach that included input from the following:

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