Primary Mediastinal Large B-Cell Lymphoma

This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson’s specific patient population; MD Anderson’s services and structure; and MD Anderson’s clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers. 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: CD45 (LCA), CD3, CD5, CD10, CD19, CD20, CD22, kappa and lambda light chains
- Additional immunohistochemical studies to determine subgroup: CD5, CD10, CD15, CD23, CD54, CD79a, CD95, BCL-2, BCL-6, MUM-1, MIB1 (Ki67), TRAF1 and nuclear REL

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 (fever, sweats, weight loss)
- CBC with differential and platelets, 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 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, greater than or equal to 2 extranodal sites, or if IPI score greater than or equal to 3
- Consider thoracentesis if clinically indicated

1 Typical immunophenotype: diffuse positivity for CD20 or another pan B-cell marker
2 See Appendix A: International Prognostic Index (IPI) on Page 5
3 For young patients receiving limited anthracycline, this can be omitted
4 See Physical Activity, Nutrition, and Tobacco Cessation Algorithms; ongoing reassessment of lifestyle risks should be a part of routine clinical practice

See Page 2, Induction Therapy
Note: Consider Clinical Trials as treatment options for eligible patients.

INDUCTION THERAPY

1 DAEPOCH-R: dose adjusted EPOCH-R: etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab (see Appendix C). Administration of R-EPOCH is based on age and performance status of the patient.

2 See Appendix B: Response Criteria for Malignant Lymphoma on Pages 6-8
Note: Consider Clinical Trials as treatment options for eligible patients.

**POST-TREATMENT RESPONSE EVALUATION**

**RESULTS**

Complete response¹ Deauville 1-3

- Multidisciplinary conference and/or follow-up evaluation if previous bulky mass² or large residual non-fluorodeoxyglucose (FDG) avid mass
- Complete treatment

Partial response¹ Deauville 4 PET – equivocal³

- Repeat PET scans in 6-8 weeks until normalization or stabilization
- Consider biopsy of residual mass only if high clinical suspicion or close imaging follow-up not feasible
- Consider Radiation Oncology evaluation
- PET normalized?
  - Yes
    - Complete treatment
  - No
    - Biopsy positive?
      - Yes
        - See Page 4, Relapse
      - No
        - History and physical with CT and labs as clinically indicated:
          - Every 3 months for 1 year, then
          - Every 4 months for 2 years, then
          - Every 6 months for 2 years, then
          - Annually

No response or progressive disease¹ Deauville 5

- Biopsy
- Biopsy positive?
  - Yes
    - See Page 4, Relapse
  - No
    - History and physical with CT and labs as clinically indicated:
      - Every 3 months for 1 year, then
      - Every 4 months for 2 years, then
      - Every 6 months for 2 years, then
      - Annually

¹ See Appendix B: Response Criteria for Malignant Lymphoma on Pages 6-8
² Bulky disease: mass 7.5 cm or greater on CT imaging
³ PET equivocal: maximum standardized uptake value (SUV) greater than mediastinal blood pool in the residual mediastinal mass

Department of Clinical Effectiveness V3
Approved by the Executive Committee of the Medical Staff on 12/12/2017
Primary Mediastinal Large B-Cell Lymphoma

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

**CONSOLIDATION / ADDITIONAL THERAPY**

Relapse or refractory

- Patient candidate for high dose therapy
  - Patient has greater than or equal to partial response²?
    - Yes: High dose therapy plus autologous or allogeneic stem cell transplant (in the context of a clinical trial)
    - No: Patient not a candidate for high dose therapy
      - Individual approach including: clinical trial², palliative chemotherapy or palliative radiation therapy

- Patient not a candidate for high dose therapy
  - Patient candidate for high dose therapy
    - Clinical trial
    - New non-cross-resistant regimen, chemotherapeutic agents (e.g., rituximab with one of the following regimens: ICE, ESHAP, MINE, DHAP)
    - Consider radiation therapy for consolidation with involved site approach

---

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 on Page 6
² Clinical trials or individual regimens: patients who progress after three successive regimens are unlikely to derive additional benefit from currently utilized combination chemotherapy regimens, except for patients with disease-free interval
APPENDIX A: International Prognostic Index (IPI)

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

International Index, ALL PATIENTS:
Number of characteristics
- Low 0 or 1
- Low intermediate 2
- High intermediate 3
- High 4 or 5

Age-Adjusted International Prognostic Index

Pre-Treatment Characteristics, ALL PATIENTS LESS THAN OR EQUAL TO 60 YEARS:
- Serum LDH greater than one times upper limit of normal
- ECOG performance status 2-4
- Extranodal involvement greater than 1 site

International Index, ALL PATIENTS LESS THAN OR EQUAL TO 60 YEARS:
Number of characteristics
- Low 0
- Low intermediate 1
- High intermediate 2
- High 3
## APPENDIX B: 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 extralymphatic sites</td>
<td>Score 1, 2, or 3 with or without a residual on 5PS</td>
<td>Target nodes/nodal masses must regress to less than or equal to 1.5 cm in LDi</td>
</tr>
<tr>
<td>No Uptake</td>
<td>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 mediastinum and/or liver. In this circumstance, complete metabolic response may 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>No extralymphatic sites of disease</td>
</tr>
<tr>
<td>Deauville 1-3</td>
<td></td>
<td></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>Partial metabolic response</td>
<td>Partial remission (all of the following)</td>
</tr>
<tr>
<td>Lymph nodes and extralymphatic sites</td>
<td>Score 4 or 5 with reduced uptake compared with baseline and residual mass(es) of any size</td>
<td>Greater than or equal to 50% decrease in sum of product diameter (SPD) of up to 6 target measurable nodes and extranodal sites</td>
</tr>
<tr>
<td>Deauville 5</td>
<td>At interim, these findings suggest responding disease</td>
<td>When a lesion is too small to measure on CT, assign 5 mm x 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 x 0 mm. For a node greater than 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 greater than 50% in length beyond normal</td>
</tr>
<tr>
<td>Deauville 4</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>New lesion</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>


Continued on next page

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### APPENDIX B: Response Criteria for Response Assessment - continued

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<th>CT-Based Response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Partial</strong></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>
<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>Less than 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>
<tr>
<td><strong>Progressive disease</strong></td>
<td>Progressive metabolic response</td>
<td>Progressive disease requires at least 1 of the following PPD progression</td>
</tr>
<tr>
<td>Individual target nodes/ nodal masses Extranodal lesions</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: LDi greater than 1.5 cm and Increase by greater than or equal to 50% from PPD nadir and An increase in LDi or SDi from nadir: 0.5 cm for lesions less than or equal to 2 cm 1 cm for lesions greater than 2 cm In the setting of splenomegaly, the splenic length must increase by greater than 50% of the extent of its prior increase beyond baseline (e.g., a 15 cm spleen must increase to greater than 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline. New or recurrent splenomegaly</td>
</tr>
</tbody>
</table>

### APPENDIX B: 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</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 C: Dose Adjusted EPOCH-R

<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 a day days 1-5</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>5 mcg/kg/day subcutaneously daily starting on day 6 until ANC greater than 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 is at least 1 K/microliter and the platelet count was at least 100 K/microliter

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

² Measurements of ANC and platelet nadir are based on twice weekly CBC only

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


This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson's specific patient population; MD Anderson's services and structure; and MD Anderson's clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers. This algorithm should not be used to treat pregnant women.
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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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