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 diagnosis¹
  - 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 size of liver and spleen
- ECOG Performance status
- B symptoms (fever, sweats, weight loss)
- CBC, differential, 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, HBaAg, HCVAb)
- Chest x-ray, PA and LAT
- Chest and abdominopelvic CT
- Neck CT
- Unilateral or bilateral bone marrow biopsy with or without aspirate
- Calculation of International Prognostic Index (IPI)²
- Muga scan³ or echocardiogram
- PET/CT
- Discuss fertility issues and sperm banking for patients of child bearing potential

OF USE IN SELECTED CASES:
- Head CT or MRI
- Pregnancy test
- Consider lumbar puncture and intrathecal chemotherapy if paranasal sinus, testicular, epidural, greater than or equal to 2 extranodal sites, IPI³ 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.
INDUCTION THERAPY

All Stages → DAEPOCH-R\(^1\) for 6 cycles

Evaluate response after 2 cycles by PET scan

Patient responding?

Complete or Partial Response\(^1\)

Continue planned treatment

Core needle or excisional biopsy

Biopsy positive?

Yes

No

Core needle or excisional biopsy

Yes

No

See relapse or refractory treatment on Page 4

See Page 3 – Post Treatment Evaluation

Continue planned treatment

See Page 4 – Post Treatment Evaluation

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 Page 6
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POST-TREATMENT RESPONSE EVALUATION

RESULTS

Complete Response\(^1,4\)
Deauville 1-3

- Multidisciplinary conference and/or f/u evaluation if previous bulky mass\(^2\) or large residual non-FDG avid mass

Deauville 4 Partial
Response\(^3\)
PET – equivocal\(^3,4\)

- 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

No response or
Progressive
disease\(^1,4\)
Deauville 5

- 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

Yes

PET normalized?

Complete treatment

No

Biopsy

Yes

See relapse page 4

No

Biopsy positive?

Yes

See relapse page 4

No

Biopsy negative?

Complete treatment

Complete treatment

Multidisciplinary conference and/or consider Radiation Oncology evaluation if previous bulky mass\(^2\) or large residual non-FDG avid mass

Yes

Biopsy positive?

See relapse page 4

No

Multidisciplinary conference and/or consider Radiation Oncology evaluation if previous bulky mass\(^2\) or large residual non-FDG avid mass

\(^1\) See Appendix B: Response Criteria for Malignant Lymphoma on Page 6
\(^2\) Bulky disease: mass 7.5 cm or greater on CT imaging.
\(^3\) PET equivocal: maximum SUV greater than mediastinal blood pool in the residual mediastinal mass

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Department of Clinical Effectiveness V2
Approved by the Executive Committee of the Medical Staff on 12/15/2015
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Note: Consider Clinical Trials as treatment options for eligible patients.

**RELAPSE or REFRACTORY #1**

- Clinical Trial
- New non-cross-resistant resistant regimen, chemo-immunotherapy e.g. Rituximab with one of the following regimens ICE, ESHAP, MINE, DHAP
- Consider radiotherapy for consolidation

**ADDITIONAL THERAPY**

- Patient candidate for high dose therapy
- Relapse or Refractory
- Patient not a candidate for high dose therapy

**CONSOLIDATION / ADDITIONAL THERAPY**

- High dose therapy plus autologous or allogeneic stem cell transplant (in the context of a clinical trial)
- Individual approach including: Clinical trial, palliative chemotherapy or palliative radiation

ICE: Ifosfamide, Carboplatin, Etoposide
ESHAP: Etoposide, Methyprednisolone (Solumedrol), high-dose Cytarabine (Ara-C), 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.
Note: Consider Clinical Trials as treatment options for eligible patients.

APPENDIX A: INTERNATIONAL PROGNOSTIC INDEX\(^1\) (IPI)

<table>
<thead>
<tr>
<th>Pre-Treatment Characteristics ALL PATIENTS:</th>
<th>INTERNATIONAL INDEX, ALL PATIENTS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age greater than 60 years</td>
<td>Number of Characteristics</td>
</tr>
<tr>
<td>Serum LDH greater than one times normal</td>
<td>Low</td>
</tr>
<tr>
<td>Performance status 2-4</td>
<td>0 or 1</td>
</tr>
<tr>
<td>Stage III or IV</td>
<td>Low intermediate</td>
</tr>
<tr>
<td>Extranodal involvement greater than 1 site</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>High intermediate</td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>4 or 5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pre-Treatment Characteristics ALL PATIENTS LESS THAN OR EQUAL TO 60 YEARS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum LDH greater than one times normal</td>
</tr>
<tr>
<td>Performance status 2-4</td>
</tr>
<tr>
<td>Extranodal involvement greater than 1 site</td>
</tr>
</tbody>
</table>

| 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>Complete</td>
<td>Complete metabolic response</td>
<td>Complete radiologic response (all of the following)</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 (eg, with chemo 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>Target nodes/nodal masses must regress to less than or equal 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 FGD-avid disease in marrow</td>
<td>Normal by morphology</td>
</tr>
<tr>
<td>Partial</td>
<td>Partial metabolic response</td>
<td>Partial remission (all of the following)</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>Greater than or equal to 50% decrease in 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 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 Deauville 4</td>
<td>Not applicable</td>
<td>Spleen must be regressed by greater than 50% in length beyond normal</td>
</tr>
<tr>
<td>New lesion</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>


Continued on next page
## APPENDIX B: RESPONSE 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>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 1.0 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 15cm 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

<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 (eg. 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></td>
<td></td>
<td>A new node greater than 1.5 cm in any axis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A new extranodal site greater than 1.0 cm in any axis; if less than 1.0 cm in any axis, its presence must be unequivocally and must be attributable to lymphoma</td>
</tr>
<tr>
<td></td>
<td></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>

APPENDIX C: 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 CIV Days 1-4</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>10 mg/m²/day CIV Days 1-4</td>
</tr>
<tr>
<td>Vincristine</td>
<td>0.4 mg/m²/day CIV 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 BID Days 1-5</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>5 mcg/kg/day subcutaneously Day 6 till ANC greater than 5x10⁹/L</td>
</tr>
<tr>
<td>Next Cycle²</td>
<td>Day 21</td>
</tr>
</tbody>
</table>

Table 2. EPOCH dose-adjustment paradigm

<table>
<thead>
<tr>
<th>Nadir Measurements³</th>
<th>Dose-Adjustment⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>If Nadir ANC at least 0.5 K/microL</td>
<td>20% increase in etoposide, doxorubicin and cyclophosphamide above last cycle</td>
</tr>
<tr>
<td>If Nadir ANC less than 0.5 K/microL on 1 or 2 measurements</td>
<td>Same dose(s) as last cycle</td>
</tr>
<tr>
<td>If Nadir ANC less than 0.5 K/microL on at least 3 measurements</td>
<td>20% decrease in etoposide, doxorubicin and cyclophosphamide below last cycle</td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>If Nadir platelet count less than 25 K/microL on 1 measurement</td>
<td>20% decrease in etoposide, doxorubicin and cyclophosphamide below last cycle</td>
</tr>
</tbody>
</table>

1 DAEPCH-R: dose adjusted EPOCH-R: Etoposide, Prednisone, Vincristine, Cyclophosphamide, Doxorubicin and Rituximab (See Appendix C)
2 Began on day 21 if the ANC is at least 1 k/microL and the platelet count was at least 100 k/microL.
3 Measurements of ANC and platelet nadir are based on twice weekly CBC only.
4 Dose adjustments above starting dose level apply to etoposide, doxorubicin, and cyclophosphamide. Dose adjustments below starting dose level apply to cyclophosphamide only.
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SUGGESTED READINGS

First-Line Therapy


Second-Line Therapy


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**SUGGESTED READINGS**


Barrington, S.F., Mikhaeel, N.G. (2013). When should FDG-PET be used in the modern management of lymphoma? British Journal of Haematology


Primary Mediastinal Large B-Cell Lymphoma

This practice guideline 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 medical oncologists, radiation oncologists, surgical oncologists, and hematopathologists:

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DEVELOPMENT CREDITS

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Approved by the Executive Committee of the Medical Staff on 12/15/2015