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Diffuse Large B Cell Lymphoma (includes Grade 3b Follicular Lymphoma)

Pathological Diagnosis
- Review by member of regional lymphoma pathology group
- Immunophenotyping / Immunohistochemistry
- MYC re-arrangement testing (by FISH)
- FISH for relevant cytogenetic/molecular abnormalities

Initial Evaluation
- Physical examination
- Performance status
- B symptoms
- FBC, U&E, LFT, Ca, urate
- LDH, B2 microglobulin
- Hepatitis B, C and HIV
- ECG-- if indicated
- CXR if pulmonary involvement at diagnosis
- CT scan of neck, chest, abdomen & pelvis
- Depending on site of disease imaging of head and neck or MRI may be appropriate
- Bone marrow aspirate & trephine (could omit if baseline PET undertaken)
- Cardiac echo or MUGA scan (consider if >60 years, history of cardiac disease, hypertension, diabetes, heavy smoker)
- Lumbar puncture (LP) only if symptoms of CNS disease

Management
- All patients should be discussed at an MDT

Special consideration for those patients <18y
Effective treatment of DLBCL and Burkitt /Burkitt-like lymphoma in this age group is available with a paediatric approach. Consideration for following a paediatric treatment protocol (FAB/LMB96 type approach using low dose anthracycline, ref 1) should be given to those <18y.
Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>Localised, one nodal area</td>
</tr>
<tr>
<td>II</td>
<td>Two or more nodal areas on the same side of the diaphragm</td>
</tr>
<tr>
<td>III</td>
<td>Nodal disease on both sides of diaphragm (including spleen)</td>
</tr>
<tr>
<td>IV</td>
<td>Extranodal disease (including bone marrow involvement)</td>
</tr>
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Stage is suffixed with A or B depending on the absence or presence of B symptoms (fevers, drenching night sweats, weight loss of 10% body mass)

International Prognostic Index (IPI) and Revised IPI (R-IPI)

This should be recorded for all patients.

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>IPI</th>
<th>Risk factors (n)</th>
<th>Risk category</th>
<th>DLBCL 3yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 60 years</td>
<td>Low</td>
<td>0 - 1</td>
<td>91%</td>
<td></td>
</tr>
<tr>
<td>Raised LDH</td>
<td>Low-intermediate</td>
<td>2</td>
<td>81%</td>
<td></td>
</tr>
<tr>
<td>Performance status ≥ 2</td>
<td>High-intermediate</td>
<td>3</td>
<td>65%</td>
<td></td>
</tr>
<tr>
<td>Ann Arbor stage ≥ 3</td>
<td>High</td>
<td>4 - 5</td>
<td>59%</td>
<td></td>
</tr>
<tr>
<td>Two or more extranodal sites of disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<thead>
<tr>
<th>R-IPI</th>
<th>Risk factors</th>
<th>Prognostic group</th>
<th>4 year PFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>0</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>1 or 2</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>3, 4 or 5</td>
<td>53</td>
<td></td>
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Induction therapy

CNS prophylaxis recommended if:
- raised LDH + > 1 extranodal site
- involvement of following sites: testes, breast, epidural space, paraspinal mass, paranasal sinuses (see ref 2)
- intravascular B cell lymphoma (see ref 3)
- MYC +ve (ref 4)
- HIV +ve
(Refer to separate CNS prophylaxis policy)

Consider primary PEG GCSF prophylaxis (day 2) for patients >70yrs

MYC +ve patients
Consider R CODOX-M/IVAC regimen in view of poor outcome with R-CHOP and high risk of CNS relapse (ref 4). If concerns re tolerability of this regimen, due to age/comorbidity Dose adjusted R-EPOCH is a reasonable alternative (ref 8).

Radiotherapy

In patients undergoing RT, this may be with either involved site or involved field RT

In patients with stage IA disease receiving 6 cycles of chemotherapy, local radiotherapy may be considered in >60s with prior bulk disease, patients in whom salvage chemotherapy may not be feasible, patients receiving attenuated systemic chemotherapy
Interim restaging (post 3rd or 4th cycle)

- CT imaging

**Complete Response (CR) or Partial Response (PR)**

Continue R-CHOP to total of 6 cycles
(8 cycles no longer recommended, RICOVER study, ref 7)

**No Response (NR) or Progressive Disease (PD)**

Change to salvage regimen (see below)

Restaging at completion of treatment

- CT imaging
- Repeat other positive baseline studies
- Consider PET-CT if residual mass

**CR (including residual PET neg mass)**

Follow up as per separate policy

**PR with single PET positive mass**

Consider radiotherapy

**NR, PD or PR with multiple PET positive masses**

Salvage therapy or palliation

In patients with a single PET +ve lesion, biopsy may be considered
Relapsed/refractory disease

In patients with a single site of disease at relapse, radiotherapy may used as consolidation treatment after autologous stem cell transplant.

*Rituximab should be omitted if primary refractory disease or progression within 6 months of Rituximab containing regimen.

In selected cases there may still be a place for a GIANNI type approach in patients with true primary refractory disease.
Systemic Anti-Cancer Therapy Definitions

1. **R-CHOP**
   - Rituximab 375mg/m² IV infusion Day 1
   - Doxorubicin 50mg/m² IV Bolus Day 1
   - Vincristine 1.5mg/m² (max 2mg) IV Bolus Day 1
   - Cyclophosphamide 750mg/m² Bolus Day 1
   - Prednisolone 50mg daily days 1-5
   - Repeated every 21 days

2. **R-CEOP**
   - Rituximab 375mg/m² IV infusion Day 1
   - Epirubicin 50mg/m² IV Bolus Day 1
   - Vincristine 1.5mg/m² (max 2mg) IV Bolus Day 1
   - Cyclophosphamide 750mg/m² Bolus Day 1
   - Prednisolone 50mg daily days 1-5
   - Repeated every 21 days

3. **R-miniCHOP**
   - Rituximab 375mg/m² IV infusion Day 1
   - Doxorubicin 50mg/m² IV Bolus Day 1
   - Vincristine 1.5mg/m² (max 2mg) IV Bolus Day 1
   - Cyclophosphamide 750mg/m² Bolus Day 1
   - Prednisolone 50mg daily days 1-5
   - Repeated every 21 days

4. **CODOX-M IVAC including CNS prophylaxis**
   - Cyclophosphamide 800mg/m² IV infusion on day 1 and 200mg/m² infusion on Days 2 to 5 inclusive (4 doses)
   - Cytarabine 70mg/m² intrathecal injection days 2 and 4
   - Doxorubicin 40mg/m² IV bolus on day 1
   - Vincristine 1.5mg/m² (max 2mg) IV bolus on days 1 and 8 (2 doses) (cycle 3 days 1, 8 and 15 – 3 doses)
   - Methotrexate 3000mg/m² infusion over 24 hours on day 10
   - Leucovorin 15mg/m² IV starting 36 hours after the start of IV Methotrexate
   - 6 hourly (if after 24 hours of completing methotrexate the patient is not being sick to an oral dose)
   - G-CSF – from Day 13 until neutrophil count >1.0 × 10⁹/l
   - Methotrexate 12.5mg/m² intrathecal injection day 15

Continue with this next stage when the patient’s neutrophil count >1.0 × 10⁹/l
Day 1 = day of initiating this IVAC stage of the treatment – should be completed as a separate protocol on CEPAS – see next page
Clinical Management Guideline for Diffuse Large B Cell Lymphoma

5. **R-EPOCH**
   - Rituximab 375mg/m² IV infusion Day 1 then
   - Etoposide 50mg/m² IV infusion on days 1-4 (4 doses)
   - Prednisolone 60mg/m² orally days 1-5 (5 Days)
   - Vincristine 0.4mg/m² IV continuous infusion days 1-4
   - Doxorubicin 10mg/m² IV continuous infusion days 1-4
   - Cyclophosphamide 750mg/m² IV infusions on day 5
   - Repeat every 21 days

   The instructions for dose adjustment are available at:

6. **R-IVE**
   - Rituximab 375mg/m² IV infusion Day 1 then
   - Epirubicin 50mg/m² IV bolus Day 1
   - Etoposide 200mg/m² IV infusion day 1-3 (3 doses)
   - Ifosphamide 3gm/m² IV infusion days 1-3 (3 doses)
   - Repeated for up to three cycles

7. **R-ESHAP**
   - Rituximab 375mg/m² IV infusion Day 1 then
   - Etoposide 40mg/m² IV infusion on days 1-4 (4 doses)
   - Methylprednisolone 500mg/m² IV infusion on days 1-4 (4 doses)
   - Cisplatin 25mg/m² IV continuous infusion over 24 hours on days 1-4 (4 doses)
   - Cytarabine 2g/m² IV infusion over 3 hours Day 5.
   - Repeat after 21 days max three cycles

8. **BEAM**
   - Carmustine (BCNU) 300mg/m² IV infusion on Day 1
   - Cytarabine 200mg/m² IV infusion twice daily Days 2-5 (8 doses)
   - Etoposide Phosphate 200mg/m² IV infusion Days 2-5 (4 doses)
   - Melphalan 140mg/m² IV infusion Day 6
   - Stem Cell Return Day 7

9. **PECC**
   - Prednisolone 40mg/m² orally daily Days 1-7 (7 doses)
   - Etoposide 200mg/m² orally daily Days 1-3 (3 doses)
   - Lomustine (~CCNU) 100mg/m² orally daily Day 1
   - Chlorambucil 20mg/m² orally daily Day 1-4 (4 doses)

10. **CEPP**
    - Cyclophosphamide 600mg/m² IV infusion Day 1 and Day 8 (2 doses)
    - Etoposide 70mg/m² IV infusion Day 1
    - Etoposide 140mg/m² orally days 2 and 3 (2 doses)
Procarbazine 60mg/m² orally Days 1 to 10 (10 doses)
Prednisolone 60mg/m² orally Days 1 to 10 (10 doses)
References


4. MYC Gene Rearrangements are Associated with a Poor Prognosis in Diffuse Large B-Cell Lymphoma Patients treated with R-CHOP Chemotherapy. Savage K et al. Blood, 2009, 114: 3533-3537

5. R-CHOP with Etoposide Substituted for Doxorubicin (R-CEOP): Excellent Outcome in Diffuse Large B Cell Lymphoma for Patients with a Contraindication to Anthracyclines. Moccia A et al, Blood, 2009, 114 (22): abstract 408

