Diffuse Large B Cell Lymphoma Overview

Review Histology, Present at lymphoma MDT, enrol in clinical trial if available, complete staging and prognostic score – refer below

<table>
<thead>
<tr>
<th>R-IPI</th>
<th>Factors</th>
<th>Risk Group</th>
<th>Number of factors</th>
<th>4 year PFS (%)</th>
<th>4 year OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very good</td>
<td>Age &gt;60 PS &gt;2 Elevated LDH &gt;1 extranodal site Stage III/IV</td>
<td>0</td>
<td>94</td>
<td>94</td>
<td></td>
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<tr>
<td>Good</td>
<td>1,2</td>
<td>80</td>
<td>79</td>
<td></td>
<td></td>
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<tr>
<td>Poor</td>
<td>3,4,5</td>
<td>53</td>
<td>55</td>
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</table>

Limited Stage Disease

Includes;
- IA/IE including bulk
- IIA/IIE excluding bulk >10cm
- Cases with bulk of 7-10cm or multiple sites should be considered on a case by case basis and potentially treated as for advanced stage disease

Options;
- 3xRCHOP + IF RT
- 4xRCHOP (low risk elderly)
- Full course RCHOP +/- RT

Advanced Stage Disease

Includes;
- Stage I/IIB
- Stage II bulk (>10cm)
- Stage III/IV

Options;
- 6-8x RCHOP + consider RT to sites of original bulk ≥7.5cm, extranodal sites and if failure to obtain CR (consider PET)

CNS Prophylaxis

Possible indications include;
- ≥2 extranodal* sites of involvement with increased LDH
- Paranasal sinus
- Paraspinal
- Testicular
- Breast

*Concordant Bone marrow involvement is considered an extranodal site

Treatment
3g/m² methotrexate IV with folinic acid rescue for 2-4 cycles
<table>
<thead>
<tr>
<th>Sub Topics</th>
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<td>Primary CNS lymphoma</td>
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<td>CNS involvement with systemic disease</td>
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<tr>
<td>Elderly patients</td>
</tr>
<tr>
<td>Treatment when anthracyclines are contraindicated</td>
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<tr>
<td>Primary Mediastinal B Cell lymphoma</td>
</tr>
<tr>
<td>Testicular Lymphoma</td>
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<tr>
<td>HIV positive patients</td>
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<tr>
<td>Relapsed Disease</td>
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</tbody>
</table>
Diagnosis

Requires an adequate biopsy, usually an excision lymph node biopsy where possible or, where not, possibly a core biopsy.

Overlap can exist between DLBCL and Burkitt Lymphoma as per the WHO provisional entity of **B cell lymphoma, unclassifiable, with features intermediate between diffuse large B cell lymphoma and Burkitt lymphoma**. These are aggressive lymphomas for which the most appropriate therapeutic approach is not established. The “double hit” lymphomas (MYC/8q24 breakpoint in combination with a BCL2/18q21 and/or BCL6/3q27 breakpoint) are associated with a very poor prognosis.

All cases should be reviewed at lymphoma conference, if possible.

**Initial Investigations**

- Full blood count, Na, K, Ca, PO₄, renal function, urate, liver function tests, LDH, immunoglobulins
- Hepatitis B testing (HbsAg and HbcAb) and consider HIV and hepatitis C testing.
- Bone marrow biopsy obtaining 20 mm of haematopoietic tissue (may not be needed if stage IA or IIA)
- CT scan chest, abdomen, pelvis +/- neck if lymph node palpable in the neck.
- Consider cardiac echocardiogram/gated heart scan for patients who are to receive an anthracycline.
- PET Scanning is not part of routine initial assessment but should be considered where upstaging would lead to a change in management
- Lumbar puncture with cytology and flow cytometry should be considered for those at high risk of CNS involvement, these include: testicular, breast, epidural, sinus, bone marrow involvement, ≥2 extranodal sites
- Fertility discussions

**Staging** Ann Arbor (Cotswold modification) staging system

<table>
<thead>
<tr>
<th>I</th>
<th>Involvement of a single lymph node or lymphoid structure (spleen, thymus, Waldeyer’s ring)</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>Two or more regions on the same side of the diaphragm</td>
</tr>
<tr>
<td>III</td>
<td>Two or more regions on both sides of the diaphragm</td>
</tr>
<tr>
<td>IV</td>
<td>Involvement of extranodal sites (such as liver, lung or marrow) not due to direct extension from a nodal site</td>
</tr>
<tr>
<td>X</td>
<td>Bulky Disease</td>
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<tr>
<td></td>
<td>- 10 cm maximal dimension of a nodal mass, or</td>
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<td></td>
<td>- Mediastinal mass &gt; 1/3 internal transverse diameter of the thorax measured at the level of T5/6 intercostal space on PA CXR.</td>
</tr>
<tr>
<td>E</td>
<td>Involvement of a single extranodal site, adjacent to a known nodal site.</td>
</tr>
<tr>
<td>B</td>
<td>- Recurrent unexplained fever &gt; 38º, or</td>
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<tr>
<td></td>
<td>- Recurrent unexplained drenching night sweats or unexplained weight loss (&gt;10% from baseline in the previous six months).</td>
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</table>
Limited Stage Management

Includes:
- IA/IE including bulk
- IIA/IIE excluding bulk >10cm
- Cases with bulk of 7-10cm or multiple sites should be considered on a case by case basis and potentially treated as for advanced stage disease

Options:
- 3xRCHOP + IF RT
- 4xRCHOP (with IPI 0)
- Full course RCHOP +/- Radiotherapy if bulky disease

Rationale

Previous studies in the pre-rituximab era have identified a group “very limited disease” (stage 1, 1E without bulk or IPI 0) that do well with limited systemic chemotherapy - 3 cycles CHOP combined with IF XRT. Patients with more “advanced” localised disease (stage 1 with IPI RFs/bulk or stage II ) do not fare as well because of higher systemic relapse risk whether treated by limited cycles of CHOP + IF XRT or extended cycles of CHOP chemotherapy.

The optimal management of patients with “advanced” localised disease in the rituximab era is unknown. Cases should be considered on a case by case basis – options include RCHOPx3 + IFR or extended course RCHOP +/- IF RT

Where significant toxicities of radiotherapy are expected, consideration can be given to full course chemotherapy. In the pre rituximab era there was a lower PFS and OS with chemotherapy alone compared to combined modality.
therapy (5yr PFS, 5yr OS 64% vs 72%, 77% vs 82% respectively). Whether this continues to hold true with the addition of rituximab is unknown. For young women less than 30 years of age, the increased risk of breast cancer from radiotherapy to the breast tissue must be entered into the equation and discussed with the patient.

Bonnet et al (J Clin Oncol. 2007;25(7):787) demonstrated no difference in PFS, OS in patients (>60yrs) with Stage I and II with IPI 0 between 4 cycles of CHOP and 4 cycles of CHOP + IF RT.

The role of PET in limiting radiotherapy has been investigated by some groups and warrants further study.

### Advanced Stage Management

**Includes;**
- Stage I/IIB
- Stage II bulk (>10cm)
- Stage III/IV

**Options;**
- 6-8x RCHOP + Consolidative radiotherapy (36Gy) should be considered to sites of initial bulk ≥7.5cm and to sites of residual disease with consideration to patient age and site specific toxicities. PET to guide the role of consolidative radiotherapy can be considered but results of prospective studies confirming this strategy are still awaited.

### Advanced Stage Management Rationale

#### Choice of Chemotherapy
- RCHOP remains accepted first line treatment with no consistent superiority of second or third line regimen demonstrated.

#### Number of Cycles of Chemotherapy
- The Ricover Study showed 6 CHOP-14 + 8R to be equivalent and less toxic compared to 8RCHOP-14.
- There are no large studies comparing number of cycles of RCHOP-21 and the majority of studies have used eight cycles.
- options include;
  - Six to eight cycles of RCHOP chemotherapy (to maximum response + 2 cycles)
  - Eight cycles of RCHOP
  - 6CHOP + 8R
- Restaging should be undertaken after 4 cycles
- Those with a poor response, less than PR, to four cycles of RCHOP should be reviewed and consideration given to altering therapy.
- Those with a residual mass after cycle 4 should be considered for a PET CT after cycle 6

#### The Role of Radiotherapy

In state III/IV the presence of bulk is an adverse factor however majority of patients with stage III/IV disease with bulk will relapse at distant sites rather than at the site of bulk. Whilst ASH 2008 abstract 584 demonstrated patients in CR/CRU after completion of chemotherapy did not appear to benefit from additional radiotherapy, Held et Al JCO 32(11)2014 demonstrated an improved PFS/OS on treatment received analysis and trend to improved PFS/OS on intention to treat analysis for patients receiving 36Gy to any extranodal site of involvement and any sites with an initial bulk of ≥ 7.5cm.
CNS prophylaxis

Possible indications include:
- ≥2 extranodal* sites of involvement with increased LDH
- Paranasal sinus
- Paraspinal
- Testicular
- Breast

*Concordant Bone marrow involvement is considered an extranodal site

Treatment:
3g/m² methotrexate IV for 2-4 cycles

Primary CNS Lymphoma

This is an extranodal lymphoma that arises from the brain, eye, meninges or spinal cord in the absence of systemic disease.

Prognostic factors (IELSG)
- Age >60yrs
- ECOG PS >1
- Raised LDH
- Raised CSF protein
- Deep brain sites involved

There is no general consensus on optimal management of this condition. Various strategies have been employed in studies. Taking these studies together, the following conclusions can be drawn:

- There is no role for surgical debulking.
- Doses of systemic methotrexate have varied (3-8g/m2) but a minimum of 3g/m2 is required to achieve CNS penetration.
- Systemic methotrexate together with cytarabine has shown improved PFS compared to methotrexate alone (Ferrari et al IELSG group). However haematological toxicity was significant with 92% experiencing grade 3-4 haematological toxicity.
- The addition of rituximab to methotrexate-based chemotherapy has shown promising results. It is presumed that dose intensification would provide higher levels of rituximab in the CSF which presumably could translate to better efficacy.
- The role of intrathecal chemotherapy is controversial with conflicting results.
- Whole brain radiotherapy is associated with significant toxicities (see neurocognitive sequelae below).
WBRT, in addition to methotrexate, has been shown to increase the number of patients obtaining a CR (30-65% with MTX alone vs 82-88% with MTX+WBRT) and to improve PFS (13-17 months vs 32-40 months). Some authors suggest use of WBRT as consolidation for those <60yrs while others suggest delaying WBRT until time of relapse.

### Neurocognitive Sequelae

Neurocognitive effects are common and are multifactorial:

a. CNS lymphoma – whilst imaging shows solitary lesions, autopsy studies have shown widespread infiltrative disease.

b. Age-related co-morbidities can be common in this age group (median age for PCNSL 60yrs).

c. Treatment related – both methotrexate and WBRT+/- chemotherapy have neurological sequelae. However, the effects are more pronounced with whole brain radiotherapy especially in those >60yrs of age.

The cumulative incidence of neurotoxicity at five years has been reported at 24% but is higher in those >60years of age and in those treated with WBRT.
Neurotoxicity is progressive with all patients eventually requiring nursing care and the majority dying from causes related to neurotoxicity. The onset is variable and increases with time but occurs in some within months of therapy. The pattern of neurocognitive effects is of a subcortical dementia characterised by psychomotor slowing, executive and memory dysfunction, behavioural changes, gait ataxia and incontinence. The cognitive dysfunction occurs early and is followed by motor and eventually autonomic dysfunction. Imaging studies show diffuse white matter disease and cortical/subcortical atrophy.

Treatment Regimen for PCNSL

The following treatment strategy is suggested taking into account the above observations.

- **Rituximab 375mg/m² IV day 1**
- **High dose Methotrexate (HDMTX) 8g/m² IV day 2**
- **4 x 2 weekly cycles then restage with MRI**

If CR obtained:

- Cytarabine 2g/m² BD days 1 and 2 – 1 cycle only
- and if age <60 years, proceed with whole brain radiotherapy, reduced dose 23-30gy rather than 40 Gy (with consolidation to the residual masses) to minimise toxicity

If PR obtained:

- 2 more cycles of HDMTX chemotherapy
- Cytarabine 2g/m² BD days 1 and 2 – 1 cycle only
- If CR and if age <60 years, you may proceed with reduced dose whole brain radiotherapy, 23-30gy (Note that some authors have suggested delaying whole brain radiotherapy until relapse
- If only PR achieved, then proceed to full dose WBRT 36 Gy (with consolidation to the residual masses)

If no or poor response on restaging, proceed with salvage chemotherapy followed by an autologous bone marrow transplant in suitable candidate (Soussain et al, JCO, VOLUME 26 _ NUMBER 15 _ MAY 20, 2008) or whole brain radiotherapy 36 Gy.

For those not candidates for systemic therapy options include, whole brain radiotherapy can be considered as first line treatment, PFS 12-16 months.
CNS Involvement in Patients with Systemic DLBCL

There is little published data in this area and much in this area is extrapolated from management of primary CNS lymphoma.

The treatment recommendation is for:

- RCHOP 6-8 cycles with 3-8g/m² methotrexate IV administered prior to or on day 3 of the RCHOP cycle
- G-CSF use is suggested with this protocol
- Whole brain radiotherapy is reserved until relapse (see neurocognitive sequelae above).

The role of intrathecal chemotherapy is uncertain.

Elderly Patients

- 70% of DLBCL occurs in patients >60yrs of age.
- Response rates to therapy are similar in the elderly and those <60yrs.
- Response rates decline with reduction in dose intensity.
- Efforts should, therefore, be made to treat the elderly with good performance status with standard therapy.
- The Ricover 60 Trial treated patients aged between 61-80 with WHO PS <3 and absence of marked organ impairment (with 13% of patients aged 76-80) and demonstrated the tolerability of RCHOP-14 in this age group. Additional supportive therapy in this trial included:
  - Prephase chemotherapy (100mg prednisone days 1-7) prior to cycle 1
  - Patients complaining of fatigue after tapering prednisone, hydrocortisone 20mg mane and 10mg midday was used.
- In the very elderly (>75yrs) giving 75% of the dose of cyclophosphamide, doxorubicin can be undertaken to assess tolerability with an aim to escalate to 100% of the dose if tolerated.
- R mini CHOP as per the GELA LNH03-7B study (ASH 2010 Abstract 853) administered in those >80years has shown good tolerability with 2yr PFS and OS of 47.4% and 58.8% respectively at a median of 20 months follow up. This protocol gave rituximab 375mg/m² day 1, cyclophosphamide 400mg/m² day 1, doxorubicin 25mg/m² day 1, vincristine maximum dose 1mg day1 and prednisone 40mg/m² days 1-5.

Treatment Where Anthracyclines are Contraindicated

Etoposide can be substituted for doxorubicin (Moccia et al ASH 2009 Abstract 408) “CEOP”
Etoposide 50mg/m² IV day 1 and etoposide 100mg/m² orally days 2-3 of each cycle.

Primary Mediastinal B Cell Lymphoma

Clinical features:

- Represents <3% of DLBCL
- The clinical features, pathology, genetics and transcriptional profile distinguishes this disease from other types of DLBCL
- Appears to arise from B cells within the thymus and presents as a bulky tumour in the anterior mediastinum that can cause compressive effects
- Tumour extension is local, invading lungs, chest wall, pleura and pericardium often resulting in effusions
- Extranodal sites may be involved – kidneys, adrenals, liver, ovaries, CNS
- The disease affects females more than males and peak incidence is in the third and fourth decades
- Neuroimaging and CSF examination should be considered for those with extranodal involvement or a raised LDH

Prognosis

- The IPI is of limited utility due to the age distribution and usual confinement to the mediastinum
- Negative predictors of survival in this disease include:
  - Age >40yrs
  - Male sex
  - LDH >2xULN
PS≥2  
- Advanced disease

**Management**
- Initial therapy is critical as there are poor response rates to salvage chemotherapy
- Responses to Dose Adjusted EPOCH + R in a small study look very promising
- RCHOP appears equivalent to 3rd generation regimes but has not been directly compared to R-DA-EPOCH
- The role of IF RT is uncertain. Whilst reports show increased rates of converting PR to CR with RT, other reports show excellent results with chemotherapy alone. The majority of cases are young females in whom mediastinal radiotherapy can carry significant late toxicities and needs to be reviewed carefully. PET to guide the use of radiotherapy can be considered.

**Primary Testicular DLBCL**

Represents 1-2% of NHL. Median age of presentation 66 years.

**Diagnosis and Staging**
- A unilateral orchidectomy is usually performed initially to obtain diagnostic tissue
- Staging must involve CT chest, abdo, pelvis, bone marrow biopsy with 20cm of haematopoietic tissue obtained for assessment
- CSF for cytology and cell markers is required at diagnosis and those with involvement should be treated as per the DLBCL with CNS involvement section of this protocol.

**Prognosis**
- Outcome is worse than would be predicted by the IPI and stage.
- Whilst 80% present with stage I-II disease with a low or low-intermediate IPI, the five year OS is 48% and 10 year OS 27%.
- Relapse is common and frequently involves the CNS (frequently with parenchymal disease), contralateral testis or other extranodal sites (hence prophylaxis to these sites).

**Treatment**
- Systemic therapy with an anthracycline containing regime is required due to high rates of systemic relapse even in those presenting with localized disease treated with orchidectomy alone or orchidectomy + loco-regional radiotherapy.
- The high relapse rates in sites protected from the effects of systemic chemotherapy has led to recommendations for prophylactic therapy directed at the testes and CNS.

**CNS Prophylaxis**
- Intrathecal chemotherapy has only been studied in limited numbers. It has been shown to prolong PFS and reduce but not eliminate CNS relapse. The actuarial risk of CNS relapse considering competitive risk of death in patients treated with IT MTX is estimated at 2%.
- Whole brain radiotherapy has not been studied and DLBCL is predominantly a disease of older men who would be a risk of significant neurotoxicity with WBRT.
- Systemic methotrexate 6g/m² (four cycles every 28 days given after completion of chemotherapy and radiotherapy to the contralateral) has been trialled in a small prospective study and no cases of CNS relapse occurred but two patients died of sepsis. Systemic Methotrexate is currently being studied by the IESLG.
- Overall CNS prophylaxis with systemic methotrexate or four doses of 15mg IT MTX is recommended (systemic treatment is preferred)

**Radiotherapy**
- Contralateral scrotal irradiation (30Gy) has been evaluated in small trials and appears to be of benefit with low morbidity (infertility, but normal or near normal production of testosterone)
**Treatment Recommendation**
- Systemic therapy with RCHOP
- Scrotal irradiation.
- CNS prophylaxis is recommended with systemic methotrexate or intrathecal methotrexate (systemic treatment is preferred).

**Relapsed Disease**

- Relapsed disease requires confirmation with FNA or formal biopsy
- Repeat formal staging investigations required

Good prognosis features in relapsed disease are:
- Remission duration >12 months (Coral study 3 year EFS for relapse <12 months from prior rituximab 20% vs 45%)
- Absence of bulk
- Chemosensitivity to salvage chemotherapy

The aIPI (age adjusted IPI) at relapse has been shown to be predictive in those going forward for autologous stem cell transplant.

<table>
<thead>
<tr>
<th>Number of Factors</th>
<th>aIPI</th>
<th>4yr PFS</th>
<th>4yr OS</th>
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<tbody>
<tr>
<td>0</td>
<td></td>
<td>70%</td>
<td>74%</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>39%</td>
<td>49%</td>
</tr>
<tr>
<td>2-3</td>
<td></td>
<td>16%</td>
<td>18%</td>
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**Transplant Eligible**

Early relapse (<12 months) post RCHOP portends a poor prognosis and the optimal treatment strategy for this group is yet to be defined. Consider enrolment in a clinical trial if available. Cases require discussion at transplant meeting to consider suitability for transplant.

The role of autologous stem cell transplant in relapsed disease has only been demonstrated in those obtaining at least a PR to salvage chemotherapy (Coral Study).

There is no data suggesting superiority of 1 salvage regimen over another (commonly used include RICE and RDHAP).

**Transplant Ineligible**

Palliative options include:
- Radiotherapy for localized disease
- CNOP
- CEPP
- PEP
- Oral etoposide

**Relapse post autologus stem cell transplant**

EBMT registry data (JCO 29(10) 2011 demonstrate a 3yr PFS 41.7% and OS 3.8% in patients receiving RIC allo following relapse post autograft. Patients with relapse >12 months post autograft and chemosensitive disease had superior outcomes. Cases should be considered on a case by case basis.