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1. Introduction

In western countries diffuse large B cell lymphoma (DLBCL) constitutes 25–30% of adult non-Hodgkin’s lymphoma (NHL) and is the most common subtype of NHL. Its incidence rises from 2 cases per 100,000 at 20–24 years of age, to 45 cases per 100,000 by 60–64 years and 112 per 100,000 by 80–84 years with a marginal male predominance. The disease typically presents ‘de novo’ but may occur as a progression or transformation of a less aggressive, low-grade lymphoma such as CLL or FCL. Significant risk factors for the development of the disease include underlying immune deficiency, often in the setting of HIV-related illness or in the post solid organ transplant setting. Clinical, biological and molecular studies have categorised DLBCL into morphological variants, molecular and immunophenotypic subtypes and distinct clinical entities. However, as the disease remains biologically heterogeneous it is not always possible to ascribe a clear definition for subdivision and these cases are classified as DLBCL not otherwise specified (DLBCL NOS). CHOP-R chemo-immunotherapy has become the gold standard of treatment proven in several large randomised trials, but several discrete clinical entities remain challenging, such as the development of the disease in the elderly with co-morbid illness and patients who are refractory or relapse early after CHOP-R treatment.
2. Early Diagnosis, Prevention and Risk Factors

The development of DLBCL has no clear linked genetic factors which would facilitate screening initiatives. However, patients with a history of immune suppression induced by disease (HIV) or drugs (post renal transplant) are at higher risk of developing high-grade B cell lymphoma.

2.1. Clinical features

Patients may present with a rapidly enlarging tumour mass at single or multiple nodal or extranodal sites. Roughly 30–40% patients present with Stage I or Stage II disease. Patients may present with constitutional symptoms which are often dictated by the organ or anatomical site involvement. Triggers for referral may come from an enlarged lymph node from GPs or from specialist medical or surgical teams.

2.2. Referral pathways

Patients with suspected DLBCL should be referred immediately to a haematologist for assessment on a 2 week wait pathway (see Appendix 1: 2 Week Wait Referral Forms). Patients with worrying features such as hypercalcaemia, severe cytopenia or leucocytosis should be discussed with the local haematology department to arrange direct admission.
3. Investigations and Diagnosis

All patients require full haematological, biochemical, virological, histopathological and staging investigations.

3.1. Haematology
FBC and differential, ESR, CRP.

3.2. Biochemistry
- U&Es, LFTs, uric acid, Ca, PO4, B2M, LDH
- Immunoglobulin profile, serum protein electrophoresis.

3.3. Virology
- Full hepatitis B profile: Hep B S Ab, Hep B S Ag, Hep B c Ab
- Hep C Ab status
- HIV Ab (with counselling and consent) status
- EBV Ab status.

3.4. Imaging
- Contrast enhanced CT scan of neck/chest/abdomen/pelvis
- PET/CT (desirable with IV contrast)
- MRI scan if spinal cord involvement/CNS suspected/may be used in pregnancy/patient allergic to iodine contrast.

The use of PET/CT is more accurate than CT alone in staging DLBCL. Performing PET/CT at staging also increases the accuracy of remission assessment and improves the accuracy of radiotherapy treatment planning. Contrast-enhanced CT is preferable as part of PET/CT at baseline, but repeat scans can be performed without contrast (unless accurate measurements are required or bowel involvement was part of the disease at baseline). If mid-treatment imaging is performed, PET/CT is the preferred method as it is more accurate than CT alone. However there is no conclusive evidence to change treatment on the basis of interim PET/CT scans at present and results from randomised controlled trials are awaited. However all cases should be assessed on a case by case basis in conjunction with the overall prognosis, other clinical results, markers of response and/or biopsy if appropriate. Post-treatment remission assessment is most accurate with PET/CT which should be the standard method in clinical practice.

The 5-point scoring system (known as the Deauville criteria) should be used for reporting response on interim and of treatment scans as per international recommendations. For cases with residual uptake who are considered for escalation/salvage treatment, biopsy confirmation is recommended.

International consensus guidelines have been drawn up to guide clinicians about the role of imaging and response assessment of lymphoma. For more information see International Conference Malignant Lymphoma Imaging Working Group.¹
3.5. **Diagnosis**

All patients require an excision lymph node biopsy by designated surgeons (or in some circumstances an incisional core biopsy of an inaccessible lymph node or extralymphatic organ or in rare cases requiring urgent medical treatment). Fine needle aspiration is **NOT** adequate for the diagnosis. The biopsy should be examined by an expert haematopathologist and tabled for discussion/documentation at the MDT meeting to input into the integrated diagnostic report. Once a recorded histological diagnosis is made each case should be designated an ICD code.

3.6. **Immunophenotype/immunohistochemistry**

The immunophenotype is obtained by immunohistochemistry performed of formalin fixed paraffin embedded material or by flow cytometry of cell suspension or rarely cell blocks from fresh tissues. All DLBCL B cell components should be confirmed by the presence of one or more pan B cell antigens (CD19, CD20, CD22, CD79a). Surface and or cytoplasmic immunoglobulin (IgM >IgG >IgA) can be demonstrated in 50–75% of cases. CD30 maybe expressed especially in the anaplastic morphological variant. Expression of CD10 is found in 30–60% of cases and BCL6 in 60–90% and IRF-4/MUM-1 in 30–65%. The proliferation fraction as detected by Ki67 staining is high (usually >40%) and often maybe >90%.

A cell of origin classification has been proposed with different groups utilising a combination of antibodies to CD10/BCL-6 and IRF-4/MUM-1. Cases with CD10 expression >30% of cells are regarded as GC type as well as cases that are CD10 - , BCL6+, IRF-4/MUM-1 -. All other cases are recognised as non GC type. However, immunophenotyping subdivision does not readily correlate with gene expression based profiling. Currently in routine clinical practice immunophenotypic sub classification does not determine choice of treatment.

3.7. **Chromosomal translocations**

Nearly 30% of cases demonstrate abnormalities of the 3q27 region involving the BCL6 gene. Translocations of the BCL-2 gene the hallmark of follicular lymphoma occurs in 20–30% of DLBCL cases. A MyC rearrangement is present in up to 10% of cases. The break partner is an IG gene in 60% and non IG gene in 40% cases. Twenty per cent of cases with a MyC break have a concurrent IGH-BCL-2 translocation and/or BCL6 break or both. These cases of display high proliferation fractions maybe better categorised as ‘B cell lymphoma unclassified with features intermediate between DLBCL and Burkitt lymphoma’.
3.8. Staging

Staging is according to the Ann Arbor system:

<table>
<thead>
<tr>
<th>Stage</th>
<th>Prognostic groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (I_E)</td>
</tr>
<tr>
<td>Stage II</td>
<td>Involvement of two or more lymph node regions (number to be stated) on the same side of the diaphragm (II) or localised involvement of extralymphatic organ or site and of one or more lymph node regions on the same side of the diaphragm (II_E)</td>
</tr>
<tr>
<td>Stage III</td>
<td>Involvement of lymph node regions on both sides of the diaphragm (III) which may also be accompanied by localised involvement of extralymphatic organ or site (III_E) or by involvement of the spleen (III_S) or both (III_SE)</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node enlargement. Organ should be identified by symbols</td>
</tr>
</tbody>
</table>

A – No symptoms
B – Fever, drenching night sweats, loss of more than 10% of body weight over 6 months
X: Bulky disease: >1/3 mediastinum at the widest point; >10cm maximum diameter of nodal mass
E: Involvement of single, contiguous or proximal, extranodal site

3.9. Further tests and investigations

- Left ventricular ejection fraction estimation prior to anthracycline administration in patients with cardiac history/risk factors (hypertension/DM/IHD), elderly >65 years/frail where anthracyclines being considered.
- Pulmonary function tests.
- Sperm count and cryopreservation if appropriate.
- ENT examination.
- Lumbar puncture if suspected clinical signs of CNS disease, paranasal, breast, paraspinal/epidural or testicular disease. Cytology assessment by cytopsin and flow cytometry performed if suspicious cells seen.
- Bone marrow examination – emerging use of PET/CT is valuable in bone marrow assessment; however, low-volume disease and low-grade disease may be missed, and bone marrow examination may be important in these cases to detect transformed disease where the management approach is different.
4. Prognostic Indices

The International Prognostic Index (IPI) has been used for determining prognosis in DLBCL for over 20 years. Five clinical characteristics – age, lactate dehydrogenase (LDH), number of extranodal sites, Ann Arbor stage and Eastern Co-operative group status – are used to stratify risk and identify 4 risk categories. The age-adjusted IPI for patients <60 years was also developed for younger patients.

4.1. IPI clinical factors

1) Age >60 years
2) Stage III/IV
3) WHO PS ≥2
4) Serum LDH >ULN
5) ≥1 E/N sites of disease.

Table 1: Prognostic IPI

<table>
<thead>
<tr>
<th>International Prognostic Index</th>
<th>Score</th>
<th>Risk group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0–1</td>
<td>Low risk</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Low – Intermediate</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>High – Intermediate</td>
</tr>
<tr>
<td></td>
<td>4–5</td>
<td>High risk</td>
</tr>
</tbody>
</table>

Table 2: Age-adjusted IPI

<table>
<thead>
<tr>
<th>Age-adjusted International Prognostic Index</th>
<th>Score</th>
<th>Risk group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>Low risk</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Low – Intermediate</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>High – Intermediate</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>High risk</td>
</tr>
</tbody>
</table>

Table 3: 5-year OS rates relative to IPI

<table>
<thead>
<tr>
<th>IPI score</th>
<th>5-year OS (%)</th>
<th>Age-adjusted IPI</th>
<th>5-year OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (0–1)</td>
<td>73</td>
<td>Low (0)</td>
<td>83</td>
</tr>
<tr>
<td>Low – Intermediate (2)</td>
<td>51</td>
<td>Low – Intermediate (1)</td>
<td>69</td>
</tr>
<tr>
<td>Intermediate – High (3)</td>
<td>43</td>
<td>Intermediate – High (2)</td>
<td>46</td>
</tr>
<tr>
<td>High (4–5)</td>
<td>26</td>
<td>High (3)</td>
<td>32</td>
</tr>
</tbody>
</table>
The IPI index was developed before incorporation of rituximab, however in the rituximab era, the revised IPI (R-IPI) confirmed the prognostic significance according to the number of risk factors. However in the R-IPI, a convergence of risk between the H-I and high-risk group became apparent, and therefore, more recent efforts have been made to better discriminate between the high-risk groups. The recent established NCCN-IPI\(^2\) better discriminated both high- and low-risk patients and appears to more powerful than the IPI for predicting survival in the rituximab era. Five predictors (age, lactate dehydrogenase (LDH), sites of involvement, Ann Arbor stage, ECOG performance status) were identified and a maximum of 8 points assigned. In the NCCN-IPI, the IPI index has refined categorisation of age and normalised LDH and the identification of disease at specific extranodal sites.

**Table 4: NCCN-IPI**

<table>
<thead>
<tr>
<th>NCCN-IPI</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;40 to ≤ 60</td>
<td>1</td>
</tr>
<tr>
<td>&gt;60 to ≤ 75</td>
<td>2</td>
</tr>
<tr>
<td>&gt; 75</td>
<td>3</td>
</tr>
<tr>
<td><strong>LDH, normalised</strong></td>
<td></td>
</tr>
<tr>
<td>&gt;1 to ≤ 3</td>
<td>1</td>
</tr>
<tr>
<td>&gt;3</td>
<td>2</td>
</tr>
<tr>
<td>Ann Arbor III–IV</td>
<td>1</td>
</tr>
<tr>
<td>*Extranodal disease</td>
<td>1</td>
</tr>
<tr>
<td>Performance status ≥2</td>
<td>1</td>
</tr>
</tbody>
</table>

* Disease in bone marrow, CNS, liver/GI tract, or lung.
5. Service Configuration across the LCA

All new and relapsing cases should be discussed at the local network MDT meeting (see Annex 1). This should ensure consistency and quality of treatment from super specialist expertise and access to the most recent clinical trials. Each MDT meeting should be composed of the recognised quorate membership as dictated by the Improving Outcomes Guidance for haematological malignancies.

All new diagnoses should be centrally reviewed by a specialist haematopathologist. Histopathology laboratories reporting lymphoma should have the facility to carry out immunohistochemistry using a basic panel of antibodies locally, with access within the network to a wider range of antibodies and to molecular techniques should they be required to formulate complex cases. All laboratory methods including immunohistochemistry and molecular technique are subject to standard quality assurance systems. Details of Specialist Integrated Haematological Malignancy Diagnostics services in the LCA are available at Annex 2.

The MDT referral form requires full patient details including NHS number, DOB, clinical history, presence of associated co-morbid illness and performance status. The outcome reported requires the stage of the disease (AA), classification the histological diagnosis, ICD code and prognostic index score if appropriate. Details of the key worker should be recorded. The MDT should recommend a management plan including treatment modality and response assessment details. The final decision should be signed off by the MDT lead or designated cover and communicate to the patients GP within 24 hours.

Treatment facilities to administer induction treatment should at a BSCH level 2 centre or above. Those cases of relapsed disease which require salvage chemotherapy prior to stem cell transplantation should be referred to level 2b or 3 units. Details of JACIE accredited stem cell transplant units in the LCA can be found in Annex 3. In certain instances it may be necessary to refer certain refractory cases to early drug development centres (Phase I) if thought appropriate.
6. Patient Information and Support

If the diagnosis of DLBCL is certain, patients should be informed that DLBCL is a cancer of the blood, bone marrow and immune system. Their prognosis based on the bone marrow cytogenetics (when available) and other co-morbidities should be discussed along with possible treatment options and clinical trials or research studies currently available.

All patients must have access to a key worker. This is usually (but not always) the clinical nurse specialist. The LCA has produced a key worker policy (see Appendix 4: LCA Key Worker Policy) which sets out the definition of a key worker and provides an overview of their role and responsibilities.

The key worker/clinical nurse specialist should ensure that all patients are offered a holistic needs assessment (HNA) (see Appendix 5: LCA Holistic Needs Assessment Tool) at key pathway points, including within 31 days of diagnosis; at the end of each treatment regime; and whenever a person requests one. Following each HNA, every patient should be offered a written care plan. This plan should be developed with the patient and communicated to all appropriate healthcare and allied healthcare professionals.

Written and verbal information is essential and the key worker/clinical nurse specialist plays a key role in ensuring that patients have access to appropriate and relevant written information about their condition.

Patient leaflets are available for all treatment options and are also available for download on the following websites:


www.nhs.uk/ipg/pages/ipstart.aspx
7. Treatment Recommendations

Pre-treatment considerations
All treatment decisions are required to be discussed and validated in the multidisciplinary team meeting (MDT). The backbone of treatment is R-CHOP chemo-immunotherapy. In circumstances where PS is high, a steroid pre-phase should be considered. Pre-treatment men and women of child bearing age should be offered counselling about potential infertility as a result of treatment. In the case of male patients sperm cryopreservation should be offered, but for female patient options may be more limited given the tempo of disease presentation. Please see the LCA Guidance and recommendations for referral to fertility services for more information on referral criteria and contact details for services.

Patients need to be assessed for development of the risk of tumour lysis syndrome, and in cases where high tempo disease is present, the use of rasburicase requires consideration based on clinical risk. Please see Annex 4 and Annex 5 for more information on the management of tumour lysis syndrome and the use of rasburicase.

7.1. Early stage disease

Stage IA non bulky (defined <7.5cm)
In patients with non-bulky limited stage disease 3 cycles of R-CHOP 21 followed by involved site therapy is recommended. This approach is dependent upon the site of the disease, and if side effects of radiotherapy are undesirable, an alternative approach is to administer 6 cycles of R-CHOP 21.

Bulky stage IA/IIA
These patients should be treated with 6 cycles of R-CHOP 21 followed by involved site radiotherapy (ISRT).

7.2. Advanced stage disease

7.2.1. For patients off trial
All patients with advanced disease not on a clinical trial, should receive R-CHOP 21 in line with NICE guidance. Several trials have examined whether R-CHOP 14 is advantageous over R-CHOP 21 and in the large UK series no benefit is derived from R-CHOP 14 leaving R-CHOP 21 as the gold standard. For high IPI patients with extranodal disease, or if tested patients with MyC gene rearrangements, consideration may be given to more intensive approaches with the use of R-CODOX-M/IVAC or R-DA-EPOCH for double hit DLBCL. For patients where cardiac co-morbid illness is problematic, doxorubicin may be substituted by gemcitabine in the R-GCVP regimen or etoposide in R-CEOP. For the very elderly (>80 years) or frail where no overt co-morbid illness exists consideration of dose attenuated R-CHOP (mini R-CHOP) should be considered.

For patients with high-risk disease consideration can be given to higher dose intensified regimens such as R-CODOX-M IVAC. Where a clinical trial exists these patients should be entered. All patients with poor cardiac function should be considered for a non-anthracycline-containing regimen such R-GCVP or R-CEOP. For elderly patients the use of GCSF is mandated as both morbidity and mortality may be minimised by this and maintenance of dense intensity is optimised.
7.2.2. **Clinical trial entry**

All eligible patients where feasible should be considered for entry into clinical trials. There are emerging data from both immunohistochemical and gene expression profiling studies that non GC phenotype conveys a worse prognosis. The recently closed ReMoDL-B trial tested the hypothesis that addition of bortezomib added to the R-CHOP backbone enhances clinical efficacy in DLBCL. For elderly patients considered unsuitable for anthracycline-containing chemo-immunotherapy consideration should be given to patients to enter the INCA trial. New clinical trials trying optimise the R-CHOP backbone are in the progress and may prove beneficial. This most commonly involved strategy is testing with a novel agent in addition to R-CHOP chemo-immunotherapy backbone.

For more details on clinical trials see [section 12: Research and Clinical Trials](#).

1) **REMoDL-B:**

A Randomised Evaluation of Molecular guided therapy for Diffuse Large B Cell Lymphoma with Bortezomib.

2) **INCA:**

A multicentre randomised phase II clinical trial of inotuzumab ozogamicin plus rituximab and CVP (IO-R-CVP) versus gemcitabine plus rituximab and CVP (Gem-R-CVP) for the first-line treatment of patients with diffuse large B cell lymphoma who are not suitable for anthracycline-containing chemotherapy.

7.2.3. **CNS prophylaxis**

The data on CNS prophylaxis are weak but in the following situations is recommended:

- High-risk anatomical sites: orbit, sinus, paraspinal mass
- Testicular lymphoma
- Breast lymphoma
- Bone marrow involvement
- Intravascular B cell lymphoma
- High LDH and extranodal disease (2 or more sites)
- There are no randomised data on the merits of IV versus intrathecal approaches in prophylaxis but 3–4 cycles of IT methotrexate 12.5mg is commonly applied.

For more information, readers should consult the British Society of Haematology Guidelines.

7.3. **Relapsed disease**

The occurrence of relapse after R-CHOP chemo-immunotherapy is poor especially those cases within 1 year of treatment. Where possible all patients should be considered for trial entry if appropriate. In the absence of suitable clinical trials the aim of treatment should be to induce objective clinical response (>50% reduction in disease bulk) with salvage chemo-immunotherapy regimens and in responding patients proceed to consolidation with a BEAM/LEAM autograft. All patients should receive rituximab as part of the salvage regimen if rituximab naïve or the relapse occurs 12 months or more after previous rituximab administration. The choice of salvage therapy is often transplant centre variable but regimens such as R-DHAP, R-ICE, R-IVE, R-GemP, R-Gem-Ox are appropriate. The recent coral trial reported a slight advantage for the use R-DHAP in patients with GC phenotype. For patients not responding to any of the above
salvage therapies consideration should be given to changing to R-Mini–BEAM, or suitable novel agent studies/trials.

When patients present with relapsed disease discussion should be planned at the regional MDT with transplant team representation at the meeting. Close liaison should be maintained with the transplant team so harvesting dates post salvage may be planned appropriately. Failure to respond to first-line salvage treatment carries a very grave prognosis and consideration to entry to trials testing novel agents should be sought. Very occasionally consideration of an allograft may be appropriate in responding patients and should be discussed with the local transplant team.
8. Supportive Care

Supportive care is very important for all patients with haematological malignancies. There are many aspects to consider and they are carefully documented in current clinical trial protocols. These protocols are available for download and should be consulted for precise details of appropriate supportive care, even if patients are not entering the clinical trial.

Patients should ideally be nursed in isolation rooms with appropriate protocols to prevent infections. Clean, neutropenic diets should be instituted and appropriate infection control measures should be undertaken. Prophylaxis and treatment of infection from presentation should be instituted based on local protocols with antibiotic choice largely dependent on local microbiological flora. For patients who will undergo intensive treatment schedules, a central venous access device should be inserted as soon as is safely possible.
9. End of Treatment Information

Once treatment is completed and is successful patients should be aware of long-term follow-up arrangements. Patients should be aware of possible symptoms or relapse/progression and urgent contact details in these occurrences.

An end of treatment consultation should be offered to every patient. This should include an end of treatment HNA (see Appendix 5: LCA Holistic Needs Assessment Tool) and associated written care plan and should also include the discussion and provision of a comprehensive treatment summary. On successful completion of treatment, both the patient and their GP should be made aware of follow-up plans and potential future disease or treatment related issues.

9.1. Treatment summary and care plan

There are two related but distinct documents which patients should be given at the end of their treatment:

- A **treatment summary** provides a summary of the cancer treatments received by the end of the first treatment, planned follow-ups (including mechanisms for these), and signs and symptoms of which to be aware. Their aim is to provide information not only to the patient, but also to the GP about possible consequences of cancer and its treatment, signs of recurrence and other important information. The treatment summary (see Appendix 6: NCSI Treatment Summary) should be completed by the named CNS/key worker with the patient and a copy sent to the GP and the patient.

- A **care plan** is generated as a result of an HNA and is the agreed plan between the patient and healthcare professional about how the identified areas of concern will be addressed. This may cover provision of information (e.g. through an information prescription), onward referral for specialist assessment and intervention (e.g. breathlessness management), or things which the patient themselves can do (e.g. contact their HR department about graduated return to work options).

**Recommendation:** An end of treatment consultation should be offered to every patient. This should include an end of treatment HNA and associated written care plan, and should also include the discussion and provision of a comprehensive treatment summary.

People should be offered access to a health and well-being clinic at the end of treatment. This should provide information to enable to person to self-manage any expected consequences of their cancer and its treatment, as well as general health promotion information, including diet and physical activity.

The MDT outcome form and clinic letters will serve to communicate diagnosis, treatment initiation and new lines of treatment with the GP.
10. Follow-up Arrangements

All patients need clinical assessment, including imaging as dictated by their clinical condition plus additional tests as below. If the patient is in a clinical trial, check if any additional tests are necessary and check follow-up interval. Remember that hormonal failure can occur in various systems after both radiotherapy and chemotherapy. CT scan is routinely performed at 3 months after completion of chemotherapy except for low-grade lymphoma. Discuss with consultant haematologist if symptoms of relapse or refer to study protocol. Surveillance imaging is not recommended. The nature and frequency of follow-up review and investigations for patients will be somewhat tailored by their disease presentation, treatment type, treatment toxicities, disease-related effects, co-morbidities and psycho-social factors.

Standard follow-up outpatient visits should be scheduled as follows:

Year 1: 3 monthly
Year 2: 4 monthly
Years 3–5: 6 monthly

All patients should be made aware of the risks of secondary cancers and participate in national cancer screening programmes, and of the increased risk of cardiovascular disease with the need for periodic monitoring of risk factors in general practice.
11. Rehabilitation and Survivorship

Issues in relation to rehabilitation and the long-term consequences of treatment should be monitored throughout the patient pathway and highlighted to the appropriate allied health professionals if required. Survivorship issues can relate to the effects of the disease process and/or management of long-term adverse effects of treatment. Please refer to LCA Survivorship Guidelines for more information.

Any patient experiencing or reporting reduced mobility and/or ability to perform activities of daily living should be referred for occupational therapy and physiotherapy assessment.

People reporting ongoing consequences such as fatigue, anxiety, pain should be considered for non-pharmacological intervention, including but not limited to, TENS (transcutaneous electrical nerve stimulation), complementary therapy and psychological intervention such as mindfulness.

Referrals include:

- physiotherapist/occupational therapist (fatigue management, rehabilitation)
- dietitian if symptoms impacting on intake/nutritional status especially in cases of GI disturbances and mucositis, weight loss
- speech and language therapist (weight loss, dysphagia or concerns regarding aspiration).

12. Research and Clinical Trials

All patients should if appropriate be offered the opportunity to participate in clinical trials and consideration should be given to referring a patient to a centre where a suitable trial may be open. See the LCA website for details of clinical trials open across the LCA.

For patients with long distances to travel to the trial centre, the option of shared care may be considered:

- If the local hospital has Ethics and R&D approval, care may be transferred to the local unit for the maintenance phase of care.
- If the local hospital does not have the trial open, then bloods may be taken and analysed locally, but all clinical decisions must be taken by the trial centre.

For those centres wishing to participate in shared care, clear documentation of shared care arrangements must be undertaken with communication to both centres, the GP and the patient.

If possible and ideally, all patient diagnostic material should be biobanked in an ethically approved research framework.
13. End-of-life Care

Full integration with palliative care services should be seamless and end-of-life treatment decisions fully discussed with patients and their families where appropriate, fully respecting the dignity of patients and the sensitivities of traumatic difficult situations. For older patients and in those with poor performance status and/or high-risk disease, discussions regarding prognosis and treatment options should also include discussions on end-of-life care. These are to facilitate transitions between active disease-modifying therapy to clinical trials, or supportive care only at the time of disease progression/non-response. The named clinical nurse specialist/key worker, patient, family members and palliative care teams as well as members of the inpatient ward team may be involved. Clear documentation of the discussion with guidance to the treating teams is helpful in communicating these discussions and outputs to the wider team that may care for the individual. Care may be required from specialist palliative care teams which are available in the cancer units and centres affiliated to the LCA (see Appendix 7: LCA Specialist Palliative Care Referral Form for LCA referral form to specialist palliative care). To support consideration of referral to specialist palliative care, please refer to the LCA Referral Criteria for Specialist Palliative Care (see Appendix 8).
14. Further Specific Aggressive B cell NHL Variants

14.1. Mediastinal sclerosing B cell lymphoma

A diffuse large B cell lymphoma arising in the mediastinum from putative thymic B cell origin with distinct clinical, immunohistochemical and genotypic features. Primary mediastinal large B cell lymphoma accounts for 2–4% of non-Hodgkin lymphomas and occurs predominantly in young adults (median age 35 years) with a female preponderance (M:F 1:2). PMBL most likely arises in the thymus with patients with a localised anterior superior mediastinal mass. The mass is often bulky and may invade adjacent structures such as the lungs, pleura or pericardium. The current management recommendation is to treat with R-CHOP chemo-immunotherapy followed by consolidation involved field radiotherapy. However, there are recent data emerging on the utilisation of DA-EPOCH-R without the need to include irradiation. However, the numbers reported in this study were relatively few and these results will require conformation in larger prospective studies.

14.2. Primary DLBCL of the testis

This disease is characterised by a high risk of extranodal, CNS and contralateral testis recurrence. Standard treatment is with R-CHOP chemo-immunotherapy with CNS prophylaxis and contralateral testicular irradiation. Dependent on age and tolerability CNS prophylaxis may include both I/T and intravenous methotrexate.

14.3. Primary CNS lymphoma (PCNSL)

The usual cause of PCNSL is a DLBCL (90% cases). The treatment of primary DLBCL of the CNS should contain high-dose methotrexate of at least a dose of 3g/m$^2$ every 2–3 weeks. The addition of cytarabine improves remission rate and outcome. Chemotherapy treatment should be given in conjunction with rituximab as the gold standard. The combination of R-chemo has been shown to further improve response rates and survival. It is subject to local funding arrangements being in place. Patients and their relatives should be warned about the risk of neurocognitive deterioration during therapy. Patients older than 60 years can be offered consolidative whole brain radiotherapy following a radiological response. In younger patients consideration of a consolidation autologous based stem cell transplant with thiotepa conditioning should be considered if appropriate. Recently the results of the IELSG32 trial confirmed the superiority of the MATRIX regimen, composed of a methotrexate/cytarabine backbone plus thiotepa and rituximab compared with either methotrexate/cytarabine alone or in combination with rituximab. If available, patients should be entered into clinical trials. For patients with relapsed disease whole brain radiotherapy should be administered if feasible to patients who have not previously received radiotherapy.

14.4. DLBCL variant intravascular large B cell lymphoma

Intravascular large B cell lymphoma is rare subtype of extranodal DLBCL characterised by the presence of lymphoma cell only in the lumina of small vessels particularly capillaries. This type of lymphoma is widely disseminated in extranodal sites at presentation (CNS, skin, lung, kidneys, and adrenals). Only a small fraction of patients present with B symptoms. The presentation may be hard to recognise and is often delayed due to the varied clinical presentations which have been described. A distinct clinical variant has been described in Asians with presentation with fever, hepatosplenomegaly and haemophagocytosis.
The disease is rapidly progressive but spares the skin and CNS. Tumour cells are usually positive for B cell associated antigens (CD19, CD20, CD22, and CD79a). CD5 co expression is seen in some cases. The tumour is very aggressive and responds poorly to chemo immunotherapy. The disease is best treated with chemo-immunotherapy with CNS prophylaxis and where appropriate in responding patients strong consideration should be given to consolidation with autologous stem cell transplantation in view of the poor prognosis. In patients with suspected CNS disease higher intensity regimens with CNS penetrating drugs (HD MTX/ARA-C) should be administered if patients are fit enough to tolerate such regimens.4

14.5. HIV-positive DLBCL

HIV DLBCL (along with Burkitt lymphoma) are the two most common subtypes of AIDS-related non-Hodgkin lymphoma and both are AIDS defining illnesses. The diagnosis of HIV DLBCL requires a tissue biopsy and full staging according to the Ann Arbor classification/Cotswolds modification system. All patients require a similar blood work up as for HIV-negative cases. Prognostic factors associated with survival in the post HAART era include the International Prognostic Index and CD4 cell count at diagnosis (CD4 <100 cells/µl predictive of worse outcome).5 All patients should be managed closely with input of both haematono-oncologists and HIV physicians to recognise and deal the potential toxicities of HAART therapy and chemo therapeutic regimens. Current treatment recommendations in first-line treatment for HIV positive DLBCL are similar as for HIV-negative cases with R-CHOP and the inclusion of HAART therapy for all patients. For patients with localised disease an attenuated chemo-immunotherapy course of R-CHOP followed by radiotherapy may be appropriate. For high-risk DLBCL patients (IPI 3–5) there appears little difference in outcome between high-intensity regimens (i.e. R-CODOX-M-IVAC) and R-CHOP and in a retrospective analysis significantly more infections and non-haematological toxicity were noted in the higher intensity regimen arm.6 For a fuller review of systemic HIV-related lymphoma the reader is directed to consult the recently published BHIVA guidelines in HIV Medicine (2014).7

14.6. PTLD – DLBCL

The most common form of post transplant lymphoproliferative disorder (PTLD) is the monomorphic histological subtype. Of these the majority are classified as DLBCL. Pathologically DLBCL PTLD express the B cell antigens (CD20, CD79a, and PAX-5, occasional focal CD30+) and are EBV positive by EBER in situ hybridization. The majority of cases show clonal IGH rearrangement.8 Sometimes there may be histological overlap between DLBCL PTLD and Burkitt type PTLD and cytogenetics is required to separate the subtypes. A biopsy is required preferably excision to categorise the PTLD and all cases of DLBCL PTLD require formal staging. In some forms the bone marrow may be the only site of involvement and a bone marrow aspirate and trephine biopsy should be performed. There have no direct comparative studies of imaging modalities in PTLD and at the least a full body CT is required for staging purposes. The data on the role of FDG PET/CT are limited and requires further prospective evaluation.

Management should be performed by a core MDT with an experienced group of physicians, renal, haematono-oncologists, haematopathologists and radiologists with a particular interest in the treatment of patients undergoing solid organ transplants who develop PTLD. Treatment initially consists of reduction in immune suppression (RIS) usually to 50% of baseline which should be carried out in close conjunction with the renal physicians. Because of the nature of the histology often rituximab plus anthracycline chemotherapy is required with RIS particularly if the disease is clinically aggressive with end organ compromise. Occasionally patients may respond to RIS and single agent rituximab but this is usually for
patients with low-risk disease defined as having none of the following risk factors age >60 years, ECOG PS 2–4, and a raised LDH. For patients with CNS involvement RIS, local radiotherapy +/- steroids is an option but for younger fitter patients HD-MTX should be considered if appropriate.¹¹

For a full description of PTLD please consult the BSCH guideline document published in 2010.⁸
References

1. Sally F, Barrington N, George Mikhaeel et al. Role of Imaging in the Staging and Response Assessment of Lymphoma: Consensus of the International Conference on Malignant Lymphomas Imaging Working Group; American Society of Clinical Oncology


### Annex 1: Multidisciplinary Teams (MDTs) and Constituent Hospital Trusts

<table>
<thead>
<tr>
<th>South East London MDT 1</th>
<th>Guy’s &amp; St Thomas’ NHS Foundation Trust/Lewisham and Greenwich NHS Trust (Lewisham Hospital and Queen Elizabeth Hospital)</th>
</tr>
</thead>
<tbody>
<tr>
<td>South East London MDT 2</td>
<td>King’s College Hospital NHS Foundation Trust (including Princess Royal University Hospital)</td>
</tr>
<tr>
<td>South West London MDT 1</td>
<td>Kingston Hospital NHS Foundation Trust/St George’s University Hospitals NHS Foundation Trust</td>
</tr>
<tr>
<td>South West London MDT 2</td>
<td>Epsom and St Helier University Hospitals NHS Trust/Croydon Health Services NHS Trust</td>
</tr>
<tr>
<td>South West London MDT 3</td>
<td>The Royal Marsden NHS Foundation Trust</td>
</tr>
<tr>
<td>North West London MDT 1</td>
<td>Imperial College Healthcare NHS Trust/The Hillingdon Hospitals NHS Foundation Trust/Chelsea and Westminster Hospital NHS Foundation Trust/West Middlesex University Hospital NHS Trust/Ealing Hospital</td>
</tr>
<tr>
<td>North West London MDT 2</td>
<td>London North West Healthcare NHS Trust (Northwick Park Hospital and Central Middlesex Hospital)</td>
</tr>
</tbody>
</table>
Annex 2: SIHMDS or Current Diagnostic Services and Contacts

Guy’s & St Thomas’ NHS Foundation Trust
Cytogenetics/Flow Lab
ViaPath Pathology
4th Floor, Southwark Wing
Guy’s Hospital
Great Maze Street
London, SE1 9RT

For APML diagnostic and MRD
Dr Yvonne Morgan
Molecular Oncology Diagnostics Unit
GSTT Pathology, 4th Floor, Southwark Wing
Guy’s Hospital
Great Maze Street
London, SE1 9RT

Imperial College Healthcare NHS Trust
Imperial Molecular Pathology Laboratory
G Block, North Corridor
Hammersmith Hospital
Du Cane Road
London, W12 0HS

King’s College Hospital NHS Foundation Trust
KingsPath: Clinical Diagnostic Pathology Service
Haematological Medicine
King’s College Hospital
Denmark Hill
London, SE5 9RS

London North West Healthcare NHS Trust
Processed centrally in TDL laboratories on-site for SIHMDS (in progress), cytogenetics/molecular to:
North West Thames Regional Genetics Service, Haematology Section
Northwick Park Hospital
Watford Road
Harrow, HA1 3UJ

The Royal Marsden Hospital NHS Foundation Trust
The Centre for Molecular Pathology
Downs Road
Sutton, SM2 5PT
Tel: 020 8915 6570
Immunophenotyping Tel: 020 8915 6517 or 020 8915 6518
Cytogenetics Tel: 020 8722 4232
Molecular Genetics Tel: 020 8915 6565
Annex 3: JACIE-accredited Transplant Centres in the LCA

**Imperial College Healthcare NHS Trust**
Dr Eduardo Olavarria  
Consultant Haematologist  
BMT Programme Director  
Haematology Department  
ICHNT  
Hammersmith Hospital  
Du Cane Road  
London, W12 0HS  
Tel: 020 8383 3237  
Fax: 020 8742 9335  
Email: eduardo.olavarria@imperial.nhs.uk

**The Royal Marsden NHS Foundation Trust**
Dr Mike Potter via 020 8661 3670  
katrina.sharpe@rmh.nhs.uk  
Dr Chlo Anthias, contact details as above.  
Dr Mark Ethell, via 020 8661 3794,  
PA: janet.bromell@rmh.nhs.uk

**Department of Haematology-Oncology**
**The Royal Marsden NHS Foundation Trust**
RS11, 2nd Floor, Orchard House,  
Downs Road, Sutton,  
Surrey, SM2 5PT  
Tel: 020 8661 3670  
Fax: 020 8642 9634 (safe haven)  
Alternative email: katrina.sharpe@nhs.net

**St George’s University Hospitals NHS Foundation Trust**
Dr Mickey Koh  
Director: Stem Cell Transplantation  
Consultant Haematologist  
St George’s Hospital and Medical School  
Jenner Wing Corridor 6  
Blackshaw Road  
London, SW17 0QT  
Tel: 020 8725 3545  
Fax: 020 8725 2859  
Email: mickey.koh@stgeorges.nhs.uk

**King’s College Hospital NHS Foundation Trust**
Bone Marrow Transplant Team  
4th Floor, Hambleden Wing  
King’s College Hospital  
Denmark Hill  
London, SE5 9RS  
Tel: 020 3299 4694, 020 3299 5268
Annex 4: Guideline for the Management of Tumour Lysis Syndrome (TLS)

To be read in conjunction with Annex 5: Guidelines for Use of Rasburicase in Adult Haematology and Oncology Patients.

TLS is life-threatening. Rapid lysis of tumour cells leads to the release of cellular contents into circulation resulting in hyperkalaemia, hyperphosphataemia, hyperuricaemia and hypocalcaemia which may lead to acute oliguric renal failure and cardiac arrhythmias. TLS can occur spontaneously in tumours with a very high proliferative rate, and/or during induction treatment. It can be classified as laboratory TLS (no clinical manifestations) or clinical TLS (life-threatening clinical abnormalities). Symptoms during TLS/rasburicase include fever, haemolysis, headaches, vomiting, diarrhoea, rash and hypersensitivity reactions.

Prevention of TLS

1. Standard care is hydration and allopurinol and these help prevent TLS
2. Check urate, renal function and LDH prior to starting chemotherapy and hydrate with 3L/m² over 24 hours
3. For high risk patients rasburicase should be considered

Management (see separate rasburicase protocol): Rasburicase is to be used immediately prior to and during treatment-induction for the indications below and when authorised by a consultant haematologist.

**TLS Screen is to be ordered 1–4 times per day according to patient’s clinical condition until resolves**: urea, creatinine, uric acid, phosphate, potassium, corrected calcium and LDH (FBC if AML/ALL/CML/MPN).

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Diagnosis</th>
<th>Preventative Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High</strong></td>
<td>Burkitt lymphoma</td>
<td>1. IVF (~3L/m²/day, to maintain UOP &gt;100ml/m²/hr) or aggressive hydration as per chemotherapy protocols.</td>
</tr>
<tr>
<td></td>
<td>Burkitt-type ALL</td>
<td>2. Rasburicase* as per rasburicase protocol</td>
</tr>
<tr>
<td></td>
<td>AML or ALL with WBC &gt;100 x 10⁹/L</td>
<td></td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td>AML with WBC &gt; 50 x 10⁹/L</td>
<td>1. IVF (~3L/m³/day, to maintain UOP &gt;100ml/m³/hr) or aggressive hydration as per chemotherapy protocols.</td>
</tr>
<tr>
<td></td>
<td>Other ALL</td>
<td>2. Rasburicase* as per rasburicase protocol</td>
</tr>
<tr>
<td></td>
<td>High-grade NHL with bulky disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CML accelerated/blast phase, or where rapid response to therapy expected</td>
<td></td>
</tr>
<tr>
<td><strong>Minor</strong></td>
<td>Other AML</td>
<td>Use allopurinol.</td>
</tr>
<tr>
<td></td>
<td>Myeloma</td>
<td>Use rasburicase* where clinically indicated (high risk):</td>
</tr>
<tr>
<td></td>
<td>Other lymphoma/CLL</td>
<td>High LDH (&gt;ULN)</td>
</tr>
<tr>
<td></td>
<td>Other CML and MPN</td>
<td>Renal failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High proliferation index</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High uric acid (&gt;420 umol/L or 7mg/ml)</td>
</tr>
</tbody>
</table>

* No dose adjustment in renal/hepatic impairment. Ensure normal G6PD level prior to rasburicase (if low, use aggressive hydration & allopurinol).
References:


Annex 5: Guidelines for Use of Rasburicase in Adult Haematology and Oncology Patients

Criteria for use

Rasburicase may be used only for the following indications, when authorised by a consultant haematologist or oncologist:

- Urate oxidase (rasburicase) is an enzyme which catalyses the oxidation of uric acid to allantoin, which is more easily excreted in the urine.

**Used in the treatment of:**

- hyperuricaemia associated with high grade haematological malignancies
- prevention of complications of tumour lysis syndrome

**Indications (see also separate guideline):**

- Induction or salvage therapy of AML, ALL, high grade lymphoma, high grade multiple myeloma with:
  - High LDH (>ULN)
  - Renal failure
  - High proliferation index (Ki67>80%; consider if Ki67>50%)
  - High uric acid (>420 umol/L or 7mg/ml)

Further to the above, consider using rasburicase in those patients unable to tolerate aggressive hydration.

**Protocol for use:**

1. Ensure patient (male or female) is G6PD negative prior to use (if positive, use aggressive hydration with allopurinol – consider higher doses based on risk of TLS and creat level).
2. Ensure aggressive hydration as per chemotherapy protocols.
3. At initiation of treatment, for uric acid levels of:
   - a) < 420 umol/L (7mg/L), give a single 3mg dose of rasburicase.
   - b) >420 umol/L (7mg/L), give a single 6mg dose of rasburicase.
4. Local policies should be followed with regard to collecting blood samples and laboratory monitoring.
5. Start allopurinol as per protocols the morning after rasburicase given.
6. Measure uric acid levels as per tumour lysis (TLS) protocols and at least daily until TLS resolved.
7. During TLS monitoring, if uric acid levels >20 umol/L (>0.3 mg/L), or renal failure worsens, give another 1.5–6 mg rasburicase, as indicated by level and clinical parameters of TLS.

**References:**


Special warnings and precautions for use

Allergic reactions may occur with this product, patients should be closely monitored and full resuscitation facilities should be at hand. Should any serious allergic or anaphylactic reaction occur treatment should be immediately discontinued and appropriate resuscitation given.

Caution should be exercised in patients with a history of atopic allergies.

Administration of rasburicase decreases serum uric acid to below normal levels, but has no direct effect in reversing hyperphosphataemia, hyperkalaemia and hypocalcaemia. If severe these abnormalities should be corrected following standard treatment guidelines.

There are limited data available to recommend the sequential use of rasburicase and allopurinol.

To ensure accurate measurement of uric acid plasma level during treatment with rasburicase, a strict sample handling procedure must be followed to minimise ex vivo degradation of the analyte. Local policies should be followed with regard to collecting blood samples and laboratory monitoring.
Appendices

Appendix 1: 2 Week Wait Referral Forms
- North West London
- South East London
- South West London

Appendix 2: Treatment of Children

Appendix 3: Treatment of Teenagers and Young Adults
- Teenagers and Young Adults PTC Referrals
- Teenagers and Young Adults MDT Proforma

Appendix 4: LCA Key Worker Policy

Appendix 5: LCA Holistic Needs Assessment Tool

Appendix 6: NCSI Treatment Summary

Appendix 7: LCA Specialist Palliative Care Referral Form

Appendix 8: LCA Referral Criteria to Specialist Palliative Care