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# Pan-London Haemato-Oncology Clinical Guidelines

Lymphoid Malignancies

Part 2: Diffuse Large B-Cell Lymphoma

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## Disclaimer

These guidelines should be read in conjunction with the latest NICE guidance, and all applicable national/international guidance. The prescribing information in these guidelines is for health professionals only. It is not intended to replace consultation with the Haematology Consultant at the patient's specialist centre. For information on cautions, contra-indications and side effects, refer to the up-to-date prescribing information. While great care has been taken to see that the information in these guidelines is accurate, the user is advised to check the doses and regimens carefully and if there is any uncertainty about the guidance provided, you should discuss your queries with a Haematology Consultant or Senior Pharmacist. No set of guidelines can cover all variations required for specific patient circumstances. It is the responsibility of the healthcare practitioners using them to adapt them for safe use within their institutions and for the individual needs of patients.

## Contact us

The writing cycle for the guidelines will be from May-July each year. If you wish to be part of the writing group, please contact us through the following link: [Pan London Blood Cancer](https://panlondonbloodcancer@nhs.net) (or via [uclh.panlondonbloodcancer@nhs.net](mailto:uclh.panlondonbloodcancer@nhs.net)).

If you wish to report errors or omissions that require urgent attention please contact us via the same email addresses.



# 1 Introduction

In western countries diffuse large B-cell lymphoma (DLBCL) constitutes 25–30% of adult non-Hodgkin 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 follicular lymphoma (FL) or chronic lymphocytic leukaemia (CLL). Significant risk factors for the development of the disease include underlying immune deficiency, such as HIV-related or in the post-solid organ transplant setting.

Clinical, biological and molecular studies have categorised DLBCL into morphological, 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). R-CHOP 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 R-CHOP treatment.

## 2 Early Diagnosis, Prevention and Risk Factors

The development of DLBCL has no clear linked genetic factors that would facilitate screening initiatives. However, patients with a history of immune suppression, inherited, viral (HIV) or iatrogenic (post-solid organ 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.

### 2.2 Referral pathways

Patients with suspected DLBCL should be referred immediately to a diagnostic team (i.e. ENT/haematologist etc.) for assessment on a 2 week wait pathway. Patients with worrying features such as hypercalcaemia, severe cytopenia or leucocytosis should be discussed with the local haematology department to consider direct admission.

### 3 Investigations and Diagnosis

Diagnosis and management of non-Hodgkin lymphoma is covered in the 2016 NICE guidance (NG52). All patients require full haematological, biochemical, virological, histopathological and staging investigations.

#### 3.1 Haematology

- FBC and differential.

#### 3.2 Biochemistry

- U&Es, LFTs, uric acid, Ca, PO<sub>4</sub>, LDH
- Immunoglobulin profile, serum protein electrophoresis
- Consider screening for diabetes with a random glucose and HBA1c as patients will require steroids.

#### 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 status (with appropriate counselling and consent)
- EBV DNA in patients' post-solid organ transplant.

#### 3.4 Imaging

- Contrast enhanced CT scan of neck/chest/abdomen/pelvis
- PET/CT
- MRI or CT scan of the brain, spine, orbits and sinuses, if central nervous system (CNS) or craniofacial disease is present or suspected
- MRI scanning may be used in pregnancy or in patients allergic to iodine contrast.

The use of PET/CT is more accurate than CT alone in staging DLBCL (i.e. potentially identifying extranodal sites that may direct CNS prophylaxis). Performing PET/CT at staging also increases the accuracy of remission assessment and improves the accuracy of radiotherapy treatment planning.

Mid-treatment imaging (after cycle 3 or 4 by CT scan) may be performed if there is nothing to indicate that the patient is responding (such as improvement in palpable disease, resolution of symptoms or normalisation of blood counts) to assess response. Otherwise no interim scan is required. The positive predictive value of an interim PET scan is variable and there is no conclusive evidence (i.e. PETAL study, Dührsen U *et al*, 2018)<sup>1</sup> that changing treatment on the basis of interim PET/CT scans at present alters outcome. A routine interim PET scan is therefore not recommended.

Post-treatment remission assessment is most accurate with PET/CT (6 weeks post-completion of chemotherapy or 12 weeks post-radiotherapy), 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 scans as per international recommendations. For cases with residual uptake that 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.<sup>2</sup>

### 3.5 Diagnosis

All patients require an excision lymph node biopsy (by designated surgeons) or incisional core biopsy (by interventional radiologists). Fine needle aspiration is not adequate for the diagnosis.

The biopsy should be examined by an expert haematopathologist who is based at a SIHMDS and tabled for discussion/documentation at the multidisciplinary team (MDT) meeting. The expert haematopathologist should integrate all investigations performed on the biopsy and produce an integrated diagnostic report as per the 2017 World Health Organization (WHO) classification of tumours of haematopoietic and lymphoid tissues with corresponding ICD-O code.

### 3.6 Immunohistochemistry & In-situ hybridisation

Appropriate immunohistochemistry is used to make the diagnosis as described in the WHO classification of lymphoid neoplasms and to differentiate from other entities that need to be considered and excluded.<sup>3</sup> The immunophenotype separates DLBCL into two subtypes: germinal centre (GC) B-cell type and non-GC type, which provides prognostic information and should be documented in reports. Hans algorithm (using expression of CD10, BCL6 and MUM1) is the most frequently used system for this designation.

MYC protein expression is detected in around 30–50% of cases, with simultaneous expression of BCL2 in 20–35% of cases. These cases have been termed ‘double-expressor lymphoma’ and in some studies have a worse prognosis than DLBCL NOS<sup>4</sup> and this has been recognised by the WHO classification. Cut-off values of 40% for MYC and 50% for BCL2 are generally used for DLBCLs as high expressors of these proteins. A cut-off of 70% has provided improved inter-observer reproducibility for MYC expression<sup>5</sup>. Antibodies to CD19, CD30 and CD22 should be available given the potential therapeutic applicability of these markers. All samples should be evaluated for EBV association by EBER in-situ hybridisation (additional work-up for EBNA1, EBNA2 and LMP-1 are optional). EBV-positive DLBCL, not otherwise specified (NOS) is a distinct entity in the 2017 WHO classification. Evaluation of ALK expression may be required in rare cases (ALK-positive large B cell lymphoma). Documentation of EBV association is essential also to identify other entities such as lymphomatoid granulomatosis, EBV-positive mucocutaneous ulcer, fibrin associated large B cell lymphoma, plasmablastic lymphoma and primary effusion lymphoma. Samples suspected to be of primary mediastinal large B cell lymphoma would need additional evaluation for expression of CD23, CD30, CD15, and possibly PDL1.

### 3.7 Chromosomal translocations

Nearly 30% of cases demonstrate abnormalities of the 3q27 region involving the *BCL6* gene. Translocation of the *BCL2* gene, the hallmark of FL, occurs in 20–30% of DLBCL cases. A *MYC* rearrangement is present in up to 10% of cases. The break partner is an immunoglobulin (IG) gene in 60% and a non-IG gene in 40% of cases. Twenty per cent of cases with an *MYC* translocation have a concurrent *IGH-BCL2* translocation and/or *BCL6* break or both. These cases (approximately 8%) have been referred to as High grade B cell lymphoma (HGBCL) with *MYC* and

*BCL2* and/or *BCL6* rearrangements ('double-hit' or 'triple-hit' lymphoma) in the 2017 WHO classification (except for cases that fulfil criteria for FL or lymphoblastic lymphoma). These patients have a particularly poor outcome and also a higher incidence of central nervous system (CNS) involvement/relapse.

It is recommended that all cases of HGBCL should be tested for *MYC* rearrangement by FISH, and further testing, either concurrently or sequentially, should be performed for *BCL2* and *BCL6* rearrangements.<sup>6</sup> Alternatively, DLBCLs could be initially screened for *MYC* expression by immunohistochemistry, and cases with *MYC* expression in >40% cells can be selected for FISH studies<sup>7</sup>.

Molecular subtypes of DLBCL with distinct genotypic, epigenetic and clinical characteristics have been more recently described, but yet to translate into trials and clinical practice<sup>8,9</sup>.

### 3.8 Staging

Table 1: **Lugano classification<sup>10</sup> for staging of lymphomas (derived from Ann Arbor staging with Cotswolds modifications)**

Stage	Involvement	Extranodal (E) status
<b>Stage I</b>	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
<b>Stage II</b>	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
<b>Stage II bulky</b>	II as above with "bulky" disease	Not applicable
<b>Stage III</b>	Nodes on both sides of the diaphragm Nodes above the diaphragm with spleen involvement	Not applicable
<b>Stage IV</b>	Additional non-contiguous extralymphatic involvement	Not applicable
Bulky disease: >7.5cm maximum diameter of nodal mass		

### 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 are being considered.
- Sperm cryopreservation in male patients and referral to a fertility unit for female patients, if appropriate.
- ENT examination if appropriate.
- Lumbar puncture if suspected clinical signs of CNS disease. Cytology assessment by cytopsin and flow cytometry performed if suspicious cells seen.<sup>11</sup> A dose of intrathecal methotrexate can be administered at the same time.
- Bone marrow (BM) examination – emerging use of PET/CT is valuable in bone marrow assessment and in some centres has replaced routine BM assessment (where it's reserved



for specific situations). Low-volume disease or concurrent low-grade disease may be missed, and BM examination may be important in these cases where the management approach may be different (i.e. influencing decision for CNS prophylaxis, abbreviated chemo and RT if stage 1 disease or subsequent follow-up).<sup>12</sup>

- Additional tests, including testicular ultrasound scan and slit lamp examination, are required for those presenting with CNS disease.

## 4 Prognostic Indices

The International Prognostic Index (IPI) has been used for determining prognosis in DLBCL for over 20 years.<sup>13</sup> Five clinical characteristics – age, LDH, number of extranodal sites, Ann Arbor stage and Eastern Co-operative Group (ECOG) performance status (PS)– are used to stratify risk and identify four 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) ECOG PS  $\geq 2$
- (4) Serum LDH >upper limit of normal (ULN)
- (5)  $\geq 1$  E/N sites of disease.

**Table 2: Prognostic IPI**

International Prognostic Index	
Score	Risk group
0–1	Low risk
2	Low – Intermediate
3	High – Intermediate
4–5	High risk

**Table 3: Age-adjusted IPI for patients  $\leq 60$  years (Stage III/IV, LDH >ULN, ECOG PS  $\geq 2$ )**

Age-adjusted International Prognostic Index	
Score	Risk group
0	Low risk
1	Low – Intermediate
2	High – Intermediate
3	High risk

**Table 4: 5-year OS rates relative to IPI**

IPI score	5-year OS (%)	Age-adjusted IPI	5-year OS (%)
Low (0–1)	73	Low (0)	83
Low – Intermediate (2)	51	Low – Intermediate (1)	69
Intermediate – High (3)	43	Intermediate – High (2)	46
High (4–5)	26	High (3)	32

The prognostic impact of the IPI index has been confirmed in the rituximab era (Ziepert JCO 2010)<sup>14</sup> The NCCN-IPI<sup>15</sup> has refined categorisation of age and normalised LDH and the identification of disease at specific extranodal sites and can better discriminate both high- and low-risk patients. It appears to be more powerful than the IPI for predicting survival in the rituximab era but is not widely used.

**Table 5: NCCN-IPI**

NCCN-IPI	Score
<b>Age</b>	
>40 to ≤60	1
>60 to ≤75	2
>75	3
<b>LDH ratio (Patient LDH/LDH ULN)</b>	
>1 to ≤3	1
>3	2
Ann Arbor III–IV	1
*Extranodal disease	1
Performance status ≥2	1

\* Disease in bone marrow, CNS, liver/GI tract, or lung. ULN, upper limit of normal.

## 5 Delivery of care

Patients should be managed within the guidance and recommendations set out by NICE 2016 (NG47) Haematological cancers: improving outcomes (<https://www.nice.org.uk/guidance/ng47>).

## 6 Patient Information and Support

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

[www.macmillan.org.uk/information-and-support/lymphoma/lymphoma-non-hodgkin/understanding-cancer](http://www.macmillan.org.uk/information-and-support/lymphoma/lymphoma-non-hodgkin/understanding-cancer)

[www.lymphomas.org.uk/about-lymphoma/types/non-hodgkin-lymphoma/diffuse-large-b-cell-lymphoma](http://www.lymphomas.org.uk/about-lymphoma/types/non-hodgkin-lymphoma/diffuse-large-b-cell-lymphoma)

<https://bloodwise.org.uk/info-support/high-grade-non-hodgkin-lymphoma>

## 7 Treatment Recommendations

### 7.1 Pre-treatment considerations

All treatment decisions are required to be discussed and validated in the MDT. The backbone of treatment is R-CHOP chemo-immunotherapy. In circumstances where performance status 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 patients options may be more limited given the tempo of disease presentation.

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.<sup>16</sup>

Clarity regarding CNS prophylaxis (indications and mode) should take place in the MDT at presentation.

### 7.2 Early stage disease

#### *Stage IA non-bulky (defined <7.5cm)*

*3-4 cycles of R-CHOP 21 and involved site radiotherapy (ISRT).*

In patients with non-bulky stage IA 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. Abbreviation of chemotherapy to 4 cycles can be considered in a subgroup of stage I low-risk patients (< 60y, normal LDH and ECOG PS 0), who achieve a PET-ve remission after 4 cycles of R-CHOP (Lamy *et al*, Blood 2018)<sup>17</sup>.

#### *Stage IIA non-bulky (defined <7.5cm)*

*6 cycles of R-CHOP 21*

Patients with non-bulky stage IIA DLBCL are treated with 6 cycles of R-CHOP21, but can be considered for a combined modality approach (3-4 cycles of R-CHOP 21 and ISRT) if the disease is amenable for radiotherapy.

#### *Bulky stage IA/IIA (≥7.5cm)*

*6 cycles of R-CHOP 21 followed by (ISRT).*

## 7.3 Advanced stage disease

### 7.3.1 For patients not enrolled on a clinical trial

*6 cycles of R-CHOP 21 and consider ISRT radiotherapy to sites of bulk.*

All patients with advanced disease should receive R-CHOP 21. Several trials have examined whether R-CHOP 14 is advantageous over R-CHOP 21 and in the large UK randomised trial no benefit was derived from R-CHOP 14, leaving R-CHOP 21 as the gold standard.<sup>18</sup> The prospective randomised phase 3 study of RCHOP versus DA-EPOCH-R and molecular analysis of DLBCL (CALGB/Alliance 50303 study) suggested no difference in outcomes but increased toxicity with the DA-EPOCH-R regimen. The delivery of DA-EPOCH-R is also more complex in terms of pharmacy support and a requirement for dynamic blood count monitoring and dose-adjustment.<sup>19</sup>

For poor risk patients such as those with high-risk IPI or 'double/triple-hit' lymphoma, there is no established standard of care and alternatives to R-CHOP (with or without high-dose methotrexate [HD-MXT]) include R-CODOX-M/R-IVAC, DA-EPOCH-R or R-CHOEP.<sup>20</sup>

It is not recommended (and not commissioned) that patients are autografted in first remission outside a clinical trial.

For patients where cardiac co-morbid illness is problematic, doxorubicin may be substituted by gemcitabine in the R-GCVP regimen<sup>21</sup> or etoposide in R-CEOP<sup>22</sup>. 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.<sup>23</sup>

As per NICE guidance (NG52), ISRT should be considered at the end of chemotherapy to sites of initial bulk ( $\geq 7.5$ cm).

Primary G-CSF prophylaxis is recommended for patients aged >65 years, frail patients and those with significant co-morbidities.

### 7.3.2 Clinical trial entry

All eligible patients, where feasible, should be considered for entry into clinical trials. Data from both immunohistochemical and gene expression profiling studies suggest that a non-GC phenotype conveys a worse prognosis, although this was not confirmed when prospectively assessed in the UK ReMoDL-B trial. The ReMoDL-B<sup>24</sup> and Pyramid trials<sup>25</sup> assessed the addition of bortezomib to the R-CHOP backbone but no difference in clinical outcome was observed. Similarly, the addition of lenalidomide or ibrutinib to the R-CHOP backbone did not demonstrate a significant survival benefit in the whole trial populations in large phase 3 randomised studies. However in the Phoenix study (Younes *et al*, JCO 2019<sup>26</sup>) a significant interaction between treatment and age was identified. In patients < 60 years, ibrutinib+R-CHOP improved EFS (HR, 0.579), PFS (HR, 0.556), and OS (HR, 0.330) and slightly increased serious adverse events (35.7% v 28.6%), but the proportion of patients receiving at least 6 cycles of R-CHOP was similar between treatment arms (92.9% v 93.0%). In contrast patients  $\geq 60$  years, ibrutinib plus R-CHOP worsened EFS, PFS, and OS, increased serious adverse events (63.4% v 38.2%), and decreased the proportion of patients receiving at least 6 cycles of R-CHOP (73.7% v 88.8%). Results from further prospective trials investigating different combinations or sequences of novel agents are underway

For elderly patients considered unsuitable for anthracycline-containing chemo-immunotherapy, consideration should be given to patients to enter into suitable trials.

An up-to-date list of clinical trials can be found here: <https://lymphoma-action.org.uk/welcome-lymphoma-trialslink>.

### 7.3.3 CNS prophylaxis

CNS prophylaxis should be offered to patients with any of these factors:

1. High (4-6) CNS-IPI
2. Involvement of  $\geq 3$  extranodal sites irrespective of CNS-IPI.
3. Anatomical sites: testicular, renal/adrenal, intravascular.

Consider CNS prophylaxis in patients with any of the following risk factors:

1. Anatomical sites: breast, uterus

Where CNS prophylaxis is indicated:

- a. High dose intravenous methotrexate is preferred.
- b. Patients' physiological fitness for HD-MTX should be considered (including cardiac and renal function). Regarding renal function, we consider CrCl  $\geq 50$  ml/min to be acceptable.
- c. 2-3 cycles of at least 3 g/m<sup>2</sup> with an infusion time of 2–4 hours is recommended.
- d. HD-MTX should be administered as early as possible as part of first line therapy without compromising dose and time intensity of RCHOP-like treatment.
- e. HD-MTX may be intercalated with RCHOP-21; the optimum scheduling of which is unclear, but day 8-14 is common practice.
2. If HD-MTX is successfully delivered then additional IT prophylaxis is not recommended.
3. If unable to deliver HD-MTX, IT prophylaxis may be considered, however there is a paucity of data to support this approach.

A high IPI also identifies patients at increased risk of CNS disease and the German High-Grade Lymphoma Study Group (DSHNHL) developed the 'CNS-IPI score' as a tool to estimate the risk of CNS relapse/progression in patients (n=2164) with DLBCL treated with R-CHOP (Schmitz, *et al* 2016)<sup>27</sup>. The model consists of the 5 established IPI factors plus involvement of kidney and/or adrenal glands. The 2-year rates of CNS relapse were 0.6%, 3.4% and 10.2% in those identified as low risk (0-1 factors), intermediate risk (2-3 factors) or high risk (4-6 factors) respectively.

The number of extranodal sites identified by PET/CT imaging has also been shown to have an impact on CNS relapse rates with a 3-year cumulative incidence of CNS relapse of 15.2% in patients who had  $\geq 3$  extranodal sites (El-Galaly, *et al* 2017)<sup>28</sup>.

Some centres adopt a pragmatic approach offering CNS prophylaxis to patients with a high (4-6 points) CNS-IPI score and to any patient with involvement of 3 or more extranodal sites, irrespective of the CNS-IPI.

CNS involvement in DLBCL tends to occur early, either during systemic chemotherapy or shortly after its completion, with many studies reporting median time from DLBCL diagnosis to CNS

relapse of approximately 6 months (Kansara et al, 2017<sup>29</sup>). Thus, it is logical to aim to deliver CNS directed prophylaxis as early as possible for those at risk.

It is also important to recognise that patients with high IPI DLBCL have a significant risk of systemic relapse, and some may receive regimens with more intensive protocols incorporating CNS-directed therapy, e.g. R-CODOX-M/R-IVAC. The additional value of intrathecal chemotherapy included in this protocol is uncertain when used for patients with DLBCL.

Intrathecal (IT) chemotherapy has been widely used in high-risk patients with DLBCL for many years despite a lack of robust evidence demonstrating its efficacy. This has come under more scrutiny in the rituximab era given the predominance of parenchymal relapse.

A recent systematic review of the efficacy of IT CNS prophylaxis included fourteen studies and a total of 7357 patients treated with rituximab or obinutuzumab-based immunochemotherapy. Standalone IT prophylaxis was not found to be a univariable or multivariable factor associated with a reduction of CNS relapse in any study (Eyre *et al*, Haematologica 2019<sup>30</sup>). Given that IT chemotherapy does not meaningfully penetrate the brain parenchyma (the commonest CNS compartment for relapse) the role of IT prophylaxis may be limited in the prevention of CNS relapse. Reflecting the uncertainty around the efficacy of IT prophylaxis, systemically administered CNS prophylaxis in the form of high dose intravenous methotrexate (HD-MTX) has been increasingly employed in recent years. However, there has been no randomised study demonstrating a benefit of HD-MTX CNS prophylaxis and there remains a lack of consensus regarding delivery (timing, dose and number of cycles).

A BCSH Good Practice Paper (GPP) regarding CNS prophylaxis is expected for publication in 2020.

For more information, readers should consult the British Society of Haematology Guidelines<sup>31</sup> and NICE NHL guidelines

(<https://www.nice.org.uk/guidance/NG52/chapter/Recommendations#management-of-diffuse-large-bcell-lymphoma>).

## 7.4 Response assessment

*Contrast-enhanced CT scan should be performed after 3-4 cycles of R-CHOP if there is no clinical way to assess response. PET/CT should be performed at the end of treatment, 6 weeks post-completion of chemotherapy or 12 weeks post-radiotherapy.*

In advanced disease, if there is no palpable disease at diagnosis to follow or other evidence of responding disease, it is usual to perform interim imaging after 3-4 cycles of chemotherapy to ensure patients are responding to chemotherapy. At present an interim PET scan cannot be recommended due to its low positive predictive value and scant evidence that changing treatment after a positive PET scan influences outcome (Dührsen *et al*, JCO 2018<sup>32</sup>). Therefore, contrast enhanced CT scan is recommended. However, at the end of treatment, a negative PET scan has a high negative predictive value for outcome and therefore is recommended. These recommendations are in line with the 2016 NICE guidance (NG52). PET positive lesions at the end of treatment require biopsy to confirm active disease. An alternative approach would be to repeat a PET scan at a 3-month interval if clinical suspicion of active disease is low. Post-radiotherapy, a PET should be performed 12 weeks post-treatment.

## 7.5 Relapsed disease

*For eligible patients, salvage platinum-based chemotherapy followed by high-dose chemotherapy and autologous stem cell transplant (autoSCT) for chemosensitive disease*

The occurrence of relapse after R-CHOP chemo-immunotherapy is poor, especially relapses observed 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 and ideally achievement of CMR, associated with superior outcome post- autologous stem cell transplant [autoSCT]) with salvage chemo-immunotherapy regimens, and in responding patients proceed to consolidation with high-dose chemotherapy and autoSCT (2016 NICE guidance NG52).

All patients should receive rituximab as part of the salvage regimen if rituximab naïve or the relapse occurs 6 months or more after previous rituximab administration. The evidence for addition of rituximab to salvage therapy for those relapsing within 6 months is limited but has limited toxicity and therefore can be in line with local practice. The choice of salvage therapy is often transplant centre variable, but regimens such as R-GDP, R-DHAP, R-ESHAP, R-ICE, R-IVE, R-GemP, R-Gem-Ox are appropriate. The Coral trial reported a superior PFS with the use R-DHAP (rather than R-ICE) in patients with GC phenotype (based on the Hans algorithm).<sup>33</sup>

In a randomised study, R-GDP has been shown to have equivalent efficacy but reduced toxicity, need for hospitalisation and preserved quality of life compared with R-DHAP (Crump, *et al.*, 2014<sup>34</sup>). R-GDP was associated with both lower costs and similar quality-adjusted outcomes compared with R-DHAP in patients with relapsed or refractory lymphoma and its use is recommended.

For patients not achieving a complete or very good partial response to any of the above salvage therapies, consideration should be given to treatment with licenced CD19 CAR-T products (axicabtagene ciloleucel and tisagenlecleucel), if patients fulfil NHSE CDF eligibility criteria, or clinical trials incorporating other novel agents including alternative CART. Alternatively, treatment can be changed to another salvage regimen, using non-cross-resistant agents (R-IVE or R-Mini-BEAM (note stem cell toxic), the polatuzumab containing regimen (with bendamustine and rituximab), 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 or early relapse (<6–12 months) carries a very grave prognosis and consideration to CAR-T treatment or entry to trials testing novel agents should be sought. If CAR-T treatment is considered, patients need to be urgently referred to one of the NHSE commissioned CAR-T centres according to local referral pathways. 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 important for all patients with haematological malignancies.



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. Patients with concomitant immunocompromise (HIV or post-solid organ transplant) will receive additional opportunistic infection prophylaxis and should be jointly managed with an HIV physician or transplant physician respectively.

## 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 Holistic Needs Assessment (HNA) 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 should be completed by the named clinical nurse specialist/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).

## 10 Follow-up Arrangements

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

Follow up thereafter may be conducted according to local practice as in some cases patients are transferred to the self-management pathway 1 year after completion of therapy. Routine review is then not conducted and instead precipitated at patient's request. The risk of relapse beyond 2 years is <10%.

**Year 2:** 4-monthly

**Year 3:** 6-monthly (although discharge to the primary care setting after 2 years with appropriate guidance to both patient and GP is recommended).

NICE guidance 2016 (NG52) suggests that patients in complete remission can be discharged after 3 years and BSH guidelines suggest this can be considered after 2 years as the relapse rate is so low after this timepoint.

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.

## 11 Further Specific Aggressive B-cell NHL Variants

### 11.1 Primary mediastinal (thymic) large B-cell lymphoma

*6 cycles of R-CHOP-14 and ISRT.*

*Or*

*R-DA-EPOCH +/- ISRT*

This is a large 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 (PMBL) accounts for 2–4% of NHLs 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 presenting 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 ISRT. R-CHOP given at a 14-day interval (with PJP prophylaxis) was associated with a favourable outcome in this lymphoma subtype in the UK NCRI R-CHOP 14 vs 21 trial.<sup>35</sup>

Data are emerging on the utilisation of DA-EPOCH-R<sup>36</sup> without the need to include irradiation. However, the numbers reported in this study were relatively few and these results will require confirmation in larger prospective studies. The delivery of DA-EPOCH-R is also more complex in terms of pharmacy support and a requirement for dynamic blood count monitoring and dose-adjustment and thus should only be given in centres experienced in the delivery of complex chemotherapy regimens.

The International Extranodal Lymphoma Study Group clinical trial (IELSG37) has completed recruitment and may reveal whether ISRT can be omitted in PET-ve patients.

### 11.2 Primary DLBCL of the testis

*6 cycles R-CHOP, CNS Prophylaxis and contralateral scrotal irradiation.*

*CNS Prophylaxis: Consider 2-3 cycles of high-dose methotrexate for suitable patients. (Or 4-6 doses of intrathecal methotrexate if concern re potential toxicity of HD-MTX)*

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 2-3 cycles of high-dose methotrexate ( $>3\text{gm}/\text{m}^2$  over 3hrs) delivered early during treatment (as delayed administration is associated with a higher risk of SCNSL). This can be administered during R-CHOP on D8-14 (with G-CSF commenced after MTX clearance to ensure the next cycle of R-CHOP can be delivered on a 21-day cycle).<sup>37</sup>

IT prophylaxis may be considered, and although its efficacy is unclear, it has been (IELSG10) and continues to be (IELSG30) incorporated into IELSG trials for patients with testicular lymphoma. In the present IELSG30 trial both IT and IV MTX ( $1.5\text{g}/\text{m}^2$ ) are administered, acknowledging older age of presentation. Ideally  $>3\text{gm}/\text{m}^2$  are administered for CNS prophylaxis to sufficiently fit patients in light of PK data and earlier studies. If unable to deliver HD-MTX (due to patient's PS, organ function, co-morbidities etc.) IT methotrexate may be considered for this rare group of patients, but as outlined above its efficacy is unclear.

### 11.3 Primary CNS lymphoma (PCNSL)

*For patients less than 70 years with WHO PS  $\leq 2$  (and  $\leq 65\text{yrs}$  if PS  $\leq 3$ ), 4 cycles of MATRix chemotherapy and consolidation with a thiotepa-based autoSCT. Mobilisation of PBSC should be scheduled after 2<sup>nd</sup> course of MATRix.*

The usual histology of PCNSL is DLBCL (90% of cases). The treatment of primary DLBCL of the CNS includes remission induction with regimens that contain high-dose methotrexate of at least a dose of  $3\text{g}/\text{m}^2$  every 2–3 weeks. The addition of cytarabine and thiotepa improve remission rate and outcome. Chemotherapy treatment should be given in conjunction with rituximab as the combination of R-chemo has been shown to further improve response rates and survival. 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 in patients less than 70 years with PS  $\leq 2$  (and  $\leq 65\text{yrs}$  if PS 3).<sup>38</sup>

Fit patients  $> 70$  years may tolerate the combination of R-MTX-Ara-C and be considered for consolidation PBSC. However although a recent review of the outcomes of patients treated with MATRix (n=156) outside the trial setting recapitulated the IELSG32 trial outcomes for patients who fit the trial criteria, conversely, older patients ( $>70$  years) with impaired performance status experienced inferior outcomes when treated with MATRix (although less patients received 4 courses of MATRix or underwent consolidation PBSC and this cohort received more dose reductions) and this patient cohort should therefore be considered for age adapted regimens (data submitted to Brit J Haematology 2019).

For more frail patients, a less intensive induction regimen should be considered. This should include rituximab and high-dose methotrexate, with the addition of alkylating agents such as procarbazine (PRIMAIN, Fritsch *et al*, Leukemia 2017<sup>39</sup>) or temozolamide<sup>40</sup>.

Remission should be followed by consideration of consolidation. Consolidation autoSCT with thiotepa conditioning has been shown to be efficacious<sup>41</sup>. Of note, if a patient is being considered for an autoSCT and being treated with the MATRix regimen, then stem cells should be harvested following the second (or less favoured: 3<sup>rd</sup>) cycle as repeated thiotepa-containing regimens are stem cell toxic. An alternative to autoSCT is whole brain radiotherapy with the knowledge that even in those <60 years there is a risk of neurotoxicity (Soussain *et al*, PRECIS, JCO 2019).<sup>42</sup>

For elderly, more frail patients, unsuitable for autologous stem cell transplant, alternative options are maintenance with oral procarbazine<sup>39</sup>, low-dose whole brain radiotherapy (23.4Gy)<sup>43</sup>, or observation. If available, patients should be entered into clinical trials.

For patients with relapsed disease, enrolment into a clinical trial or consideration of regimens such as R-IE (ifophamide and etoposide) should be considered.<sup>44</sup> Consolidation autoSCT with thiotepa conditioning should be considered. Whole brain radiotherapy is an option for patients who have not previously received radiotherapy after discussion regarding potential neurotoxic sequelae.

PCNSL in the immunosuppressed (i.e. HIV) setting is usually EBV positive and responds to less intensive strategies. HD-MTX with concurrent rituximab and aRT is recommended (Gupta *et al*, 2016, Moulignier *et al*, 2017).

## 11.4 Intravascular large B-cell lymphoma

Intravascular large B-cell lymphoma is a rare subtype of extranodal DLBCL characterised by the presence of lymphoma cells 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, is very aggressive and responds poorly to chemo-immunotherapy. The disease is best treated with chemo-immunotherapy with CNS prophylaxis (HD-MTX) and, where appropriate in responding patients, consideration may be given to consolidation with autoSCT (with funding approval) in view of the poor prognosis. In patients with suspected CNS disease, higher intensity regimens with CNS penetrating drugs (HD MTX/ARA-C) such as R-CODOX-M/IVAC should be considered if patients are fit enough to tolerate such regimens.<sup>45</sup>

## 11.5 HIV-related DLBCL

*Consider regimens used for non-HIV patients. Treat with concurrent anti-retroviral treatment under joint care with HIV physician. Specific antimicrobial prophylaxis may be required.*

*PCNSL (see above)*

DLBCL, along with Burkitt lymphoma, are the two most common subtypes of HIV-related NHL lymphoma and both are AIDS-defining illnesses. All patients require a similar work up as for HIV-negative cases. Prognostic factors associated with survival in the post-anti-retroviral therapy (aRT) era include the IPI and CD4 cell count at diagnosis (CD4 <100 cells/μl predictive of worse outcome). All patients should be managed closely with input of both haemato-oncologists and HIV

physicians to recognise and deal with the potential toxicities of aRT therapy and chemotherapeutic 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 aRT 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. For a more comprehensive review of systemic HIV-related lymphoma the reader is directed to consult the BHIVA guidelines in *HIV Medicine* (2014).<sup>46</sup>

## 11.6 PTLD – DLBCL

*All patients should be considered for immune suppression reduction. Single agent rituximab (weekly for 4 weeks) should be considered for monomorphic CD20 positive B-cell lymphoma. If complete response has not been achieved after 4 doses, escalate to standard anthracycline-based chemotherapy. If CR is achieved administer 4 further doses of weekly rituximab.*

*Participation in a clinical trial should be considered.*

The most common form of post-transplant lymphoproliferative disorder (PTLD) is the monomorphic histological subtype. Of these, the majority are classified as DLBCL and are often EBV positive by EBER in situ hybridisation. Sometimes there may be histological overlap between DLBCL PTLD and Burkitt type PTLD and FISH studies are required to separate the subtypes. In some forms, the bone marrow may be the only site of involvement and a bone marrow aspirate and trephine biopsy is recommended. There have been no direct comparative studies of imaging modalities in PTLD but FDG-PET at presentation is recommended. The data on the subsequent 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 transplant physicians, haemato-oncologists, haemato-pathologists 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), which should be carried out in close conjunction with the transplant physicians. Consideration of a clinical trial (TIDAL, ITREC) is recommended. Patients may respond to RIS and single agent rituximab, especially those 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 those with high-risk disease or those not responding to IS reduction and rituximab monotherapy, then rituximab plus anthracycline chemotherapy is recommended.<sup>47</sup> If CR is achieved after 4 doses of rituximab, a further 4 doses of weekly rituximab is recommended (Trappe *et al*, JCO 2017<sup>48</sup>).

For patients with CNS involvement RIS, local radiotherapy +/- steroids is an option, but for younger fitter patients HD-MTX should be considered if appropriate. The use of EBV-CTLs has been shown to be effective but is currently not commissioned.

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