Guidelines for the management of non-Hodgkin’s and Hodgkin’s lymphoma in adults

Approved by Pathway Board for Haematological Malignancies

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These guidelines should be read in conjunction with the latest National Cancer Drug Fund information, 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 this section 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 health care practitioners using them to adapt them for safe use within their institutions and for the individual needs of patients.
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**Guideline authors**

<table>
<thead>
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<th>Year</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td>Dr Kirit Ardeshna, Dr Kate Cwynarski, Dr Jeff Davies, Dr Claire Hemmaway, Dr John Lambert, Dr Chris McNamara, Dr Silvia Montoto, Dr Sugi Sivabalasingham</td>
</tr>
<tr>
<td>2013</td>
<td>Dr Kirit Ardeshna, Dr Kate Cwynarski, Dr Chris McNamara, Dr Silvia Montoto, Dr Rebecca Auer and Dr Claire Hemmaway, Anish Tailor</td>
</tr>
<tr>
<td>2010</td>
<td>Dr Kirit Ardeshna, Dr Kate Cwynarski, Dr Andres Virchis, Dr Chris McNamara, Prof David Linch and Aoife Shields</td>
</tr>
<tr>
<td>2007</td>
<td>Dr Kirit Ardeshna, Dr Kate Cwynarski, Dr Ming Lee, Dr Chris McNamara, Prof David Linch, Dr Alan Ramsay and Mr Simon Cheesman</td>
</tr>
<tr>
<td>2005</td>
<td>Dr Cathy Burton, Dr Kirit Ardeshna and Prof David Linch</td>
</tr>
<tr>
<td>2003</td>
<td>Dr Lynny Yung and Prof David Linch</td>
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INTRODUCTION

The NHLs are a heterogenous group of disorders, with 2 main subtypes comprising over two-thirds of cases: diffuse large B-cell lymphoma (DLBCL), an aggressive lymphoma, and follicular lymphoma (FL), which follows a more indolent course. There are many less common subtypes, each with distinct clinical and pathological features. Some of the NHLs are potentially curable and thus access to timely sophisticated diagnostic services and expert clinical opinion is necessary to ensure accurate diagnosis and tailored therapy. Current therapy can only be improved by changing practice based, where possible, on the findings of well-designed clinical trials. These guidelines aim to outline best practice based on the current evidence accepting that regular updating will be necessary as new evidence emerges. Wherever possible, it is recommended that patients are entered into clinical trials. Preference is given to trials approved by the NCRI Lymphoma Study Group, receiving CTAAC (or LRF/LA) approval. Some patients will not wish to enter trials and for these patients treatment option(s) are recommended. Patients receiving salvage chemotherapy for relapsed lymphoma (ESHAP, DHAP, ICE, IVE. IGEV, miniBEAM), those receiving RCODOX-M/RIVAC for Burkitt’s Lymphoma or DLBCL, and those managed with curative intention for Primary central nervous system lymphoma should be treated in a level 2b or 3 unit. In addition, patients with potentially curable relapsed lymphoma should be discussed and preferably seen in a transplant unit early.
**Required investigations at diagnosis for all patients with suspected lymphoma**

- FBC, blood film and cell markers as appropriate to exclude B-CLL or acute leukaemia
- Monospot test – if considered clinically.
- ENT examination if enlarged cervical node above the thyroid notch in patients at risk of epithelial tumours to exclude epithelial tumours of head and neck
- Surgical excision: For disease above the thyroid notch this should be an ENT or Head and Neck surgeon
- Excision biopsy. Core biopsy may be appropriate if surgical biopsy cannot be readily obtained. Fine needle aspirate should not be performed except in suspected cases of T-lymphoblastic lymphoma or Burkitt lymphoma (usually in children or young adults) when a diagnosis can be made on the morphology and immunophenotype and therapy can be urgent. Major surgery should be avoided if at all possible.
- Unfixed nodes should ideally be divided and transported in separate saline and formalin pots. If unfixed nodes are taken the specimen should be sent to the lab without delay and the lab informed of its impending arrival. Samples requiring transport to remote locations for analysis require appropriate transport media and temperature control.
- Request forms accompanying the specimen must include relevant clinical and laboratory information, including previous pathological diagnoses

**Histopathology procedures and standards**

- Each MDT meeting should have at least one designated Pathologist who will review material from all new lymphoma diagnoses.
- All new diagnoses of lymphoma should be subject to central review by a specialist haematopathologist, and should be discussed at the appropriate MDT meeting.
- Histopathology laboratories reporting lymphoma should have the facility to carry out immunohistochemistry using a basic panel of antibodies locally, and there should be access within the network to a wider range of antibodies and to molecular techniques.
- All laboratory methods including immunohistochemistry and molecular technique are subject to standard quality assurance systems.
- All lymphomas are to be reported according to the WHO classification system and should include relevant prognostic biomarkers where possible.
- For the majority of cases a preliminary report should be available within 5 working days of receiving the specimen. More complex cases, and those requiring extensive
immunohistochemistry and/or molecular analysis will take longer to report. Production of an interim report is recommended in such cases.

- Full details of specimen handling and reporting are to be found in the Pathology Guidelines for Haematology-Oncology.

**taging**

- Clinical history and examination, with particular attention to nodal areas, ENT examination if disease above the thyroid notch, Waldeyer ring, liver and spleen
- ECOG Performance status
- Geriatric scale assessment
- B symptoms
- FBC and blood film, ESR, liver and renal function, urate, LDH, bone profile, immunoglobulins, serum protein electrophoresis, beta-2 microglobulin
- Consider reticulocyte count, B12 and folate, iron studies, TFT, CRP, and autoantibody screen, coagulation screen, group and save
- DAT (if fludarabine therapy/other indication)
- HepBsAg, HepBsAb, HepBcAb, anti HCV Ab, VZV Ab, CMV Ab and HIV 1 and 2
- HTLV-1 in selected T cell lymphoma cases
- Consideration of EBV PCR (PTLD)
- Consider chest X-ray
- PET/CT is the gold standard imaging investigation for all FDG-avid lymphomas (HL and all NHL apart from SLL/CLL, LPL/WM, MF and MZL; unless there is suspicion of aggressive transformation)
- Neck/chest/abdomen/pelvis CT (not ‘whole body’ as neck is not included) for non FDG-avid histologies
- If a PET/CT is performed a BM biopsy is no longer indicated for HL. Bone marrow examination in NHL is routine in all subtypes but DLBCL. BM biopsy is only needed in DLBCL if the PET is positive or discordant histology (ie low grade lymphoma in the BM) would impact on the management (a negative PET in DLBCL most likely excludes high grade infiltration).
- Immunophenotyping of peripheral blood (MCL, raised lymphocyte count) or bone marrow or lymph node biopsy material when appropriate
- Cerebrospinal fluid examination if clinical signs of CNS disease. Cytological assessment by cytospin and immunophenotyping (by flow cytometry) if cells seen. Indications for
intrathecal prophylaxis are listed in appendix 2. Intrathecal prophylaxis should be administered at time of first CSF examination in these patients. In patients in whom CSF involvement is suspected but who do not fall into high risk categories listed in appendix 2, it is reasonable to administer IT MTX at time of diagnostic lumbar puncture

- MRI scan if neurological involvement suspected. MRI if stage I/II nasopharyngeal, paranasal sinus or long bone disease as this will help RT planning

**Staging system definition**

Ann Arbor staging classification for lymphoma:

The lymphatic structures are as follows: lymph nodes, Waldeyer ring, spleen, appendix, thymus, Peyer patches)

<table>
<thead>
<tr>
<th>Table 2. Revised Staging System for Primary Nodal Lymphomas</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage</strong></td>
</tr>
<tr>
<td>Limited</td>
</tr>
<tr>
<td>I</td>
</tr>
<tr>
<td>II</td>
</tr>
<tr>
<td>II bulky*</td>
</tr>
<tr>
<td>Advanced</td>
</tr>
<tr>
<td>III</td>
</tr>
<tr>
<td>IV</td>
</tr>
</tbody>
</table>

**NOTE.** Extent of disease is determined by positron emission tomography-computed tomography for avid lymphomas and computed tomography for nonavid histologies. Tonsils, Waldeyer’s ring, and spleen are considered nodal tissue.
*Whether stage II bulky disease is treated as limited or advanced disease may be determined by histology and a number of prognostic factors.

Modifying characteristics:

A: no symptoms

B: unexplained fever over 38°C, drenching night sweats, weight loss >10% in 6 months

The size of the largest diameter needs to be recorded

E: involvement of single, contiguous or proximal, extranodal nodal site (only relevant for stage I-II)
<table>
<thead>
<tr>
<th>Grade</th>
<th>ECOG</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
</table>
**Prognostic scores**

**Follicular lymphoma international prognostic index (FLIPI)**

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Number of adverse factors</th>
<th>% of patients</th>
<th>5-year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>0-1</td>
<td>36%</td>
<td>91%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2</td>
<td>37%</td>
<td>78%</td>
</tr>
<tr>
<td>High-risk</td>
<td>3-5</td>
<td>27%</td>
<td>52%</td>
</tr>
</tbody>
</table>

**Risk factors:** age >60; LDH >ULN (upper limit of normal); stage III-IV; Hb <120g/L; number nodal areas >5

**Follicular lymphoma international prognostic index 2 (FLIPI 2)**

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Number of adverse factors</th>
<th>% of patients</th>
<th>5-year PFS</th>
<th>5-year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>0</td>
<td>20%</td>
<td>79%</td>
<td>98%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1-2</td>
<td>53%</td>
<td>51%</td>
<td>88%</td>
</tr>
<tr>
<td>High-risk</td>
<td>3-5</td>
<td>27%</td>
<td>20%</td>
<td>77%</td>
</tr>
</tbody>
</table>

**Risk factors:** age >60; β2microglobulin>ULN; BM involvement; Hb <120g/L; longest diameter of largest node >6cm

Number of nodal areas as per FLIPI
CERVICAL
PRE-ACCESSORY
UPPER CERVICAL
MID-TO-LOWER CERVICAL
POSTERIOR CERVICAL
SUPERIOR CLAVICULAR

AXILLARY
AXILLARY

MESENTERIC
CELIAC
SPLENIC (HEPATIC) HILAR
PORTAL
MESENTERIC

INGUINAL
INGUINAL
FEMORAL

OTHERS: EPITROCHLEAR, POPLITEAL
Mantle cell lymphoma

**MIPI score**
describes a prognostic score for MCL based on 4 independent prognostic factors:

- Age
- Performance status
- LDH
- Leucocyte count

According to the simplified MIPI, patients can be classified into low risk (44% of patients, median OS not reached), intermediate risk (35%, 51 months), and high risk groups (21%, 29 months).

The MIPI score is calculated as follows:

\[
\text{MIPI score} = [0.03535 \times \text{age (years)}] \\
+ 0.6978 \ (\text{if ECOG} > 1) \\
+ [1.367 \times \log_{10}(\text{LDH/ULN})] \\
+ [0.9393 \times \log_{10}(\text{WBC count})]
\]

A score < 5.7 indicates low-risk disease, 5.7 - 6.2 indicates intermediate risk, and > 6.2 high risk.


Like the MIPI, the simplified MIPI (s-MIPI) predicts survival significantly better than the International Prognostic Index. Similarly the s-MIPI identifies 2 risk groups, low and intermediate versus high risk. The more easily applied s-MIPI is just as powerful as the MIPI.

**Simplified MIPI: Risk factors: age; ECOG; LDH; WBC**

<table>
<thead>
<tr>
<th>Points</th>
<th>Age, yrs</th>
<th>ECOG</th>
<th>LDH ULN</th>
<th>WBC 10^9/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;50</td>
<td>0-1</td>
<td>&lt;0.67</td>
<td>&lt;6.7</td>
</tr>
<tr>
<td>1</td>
<td>50-59</td>
<td>-</td>
<td>0.67-0.99</td>
<td>6.7-9.99</td>
</tr>
<tr>
<td>2</td>
<td>60-69</td>
<td>2-4</td>
<td>1.0-1.49</td>
<td>1.0-14.99</td>
</tr>
<tr>
<td>3</td>
<td>≥70</td>
<td>-</td>
<td>≥1.5</td>
<td>≥15.0</td>
</tr>
</tbody>
</table>

For each prognostic factor, 0-3 points are given to each patient and points summed to a maximum of 11. Patients with 0-3 points are classified as low risk, 4-5 points intermediate risk, 6-11 points high risk. LDH is weighted according to the ration of ULN.

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Sum of points</th>
<th>% of patients</th>
<th>5-year PFS</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>0-3</td>
<td>44%</td>
<td>-</td>
<td>not reached</td>
</tr>
<tr>
<td>Intermediate</td>
<td>4-5</td>
<td>35%</td>
<td>-</td>
<td>51 months</td>
</tr>
<tr>
<td>High</td>
<td>6-11</td>
<td>21%</td>
<td>-</td>
<td>29 months</td>
</tr>
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</table>
**International prognostic index for patients with aggressive lymphoma (IPI)**

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Number of adverse factors</th>
<th>% of patients</th>
<th>4-year PFS*</th>
<th>4-year OS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>0-1</td>
<td>28%</td>
<td>85%</td>
<td>82%</td>
</tr>
<tr>
<td>Intermediate-low</td>
<td>2</td>
<td>27%</td>
<td>80%</td>
<td>81%</td>
</tr>
<tr>
<td>Intermediate-high</td>
<td>3</td>
<td>21%</td>
<td>57%</td>
<td>49%</td>
</tr>
<tr>
<td>High-risk</td>
<td>4-5</td>
<td>24%</td>
<td>51%</td>
<td>59%</td>
</tr>
</tbody>
</table>

*Risk factors: age >60; LDH >ULN; stage III-IV; PS ECOG >2; extra-nodal sites >2

*Data on patients treated with R-CHOP*

**Enhanced IPI (Zhou et al, Blood 2014)**

<table>
<thead>
<tr>
<th>NCCN-IPI</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
</tr>
<tr>
<td>&gt;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>LDH, normalized</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 stage III-IV</td>
<td>1</td>
</tr>
<tr>
<td>Extranodal disease <a href="http://www.bloodjournal.org/content/123/6/837.long?sscheckd=true#fn-4">http://www.bloodjournal.org/content/123/6/837.long?sscheckd=true#fn-4</a> (BM, CNS, liver, GIT, lung)</td>
<td>1</td>
</tr>
<tr>
<td>Performance status ≥2</td>
<td>1</td>
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</tbody>
</table>

**Comparison of NCCN-IPI to IPI for risk**

<table>
<thead>
<tr>
<th></th>
<th>Score</th>
<th>5-γ OS</th>
<th>5-γ PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NCCN-IPI</td>
<td>IPI</td>
<td>NCCN-IPI</td>
</tr>
<tr>
<td>NCCN cohort (n = 1650)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>0-1 (1%)</td>
<td>0-1 (38%)</td>
<td>96%</td>
</tr>
<tr>
<td>L-I</td>
<td>2-3 (42%)</td>
<td>2 (26%)</td>
<td>82%</td>
</tr>
<tr>
<td>H-I</td>
<td>4-5 (31%)</td>
<td>3 (22%)</td>
<td>64%</td>
</tr>
<tr>
<td>High</td>
<td>≥6 (8%)</td>
<td>4-5 (14%)</td>
<td>33%</td>
</tr>
</tbody>
</table>
Prognostic index for PTCL-NOS (PIT)

Risk factors: age >60; LDH >ULN; PS ECOG >2; BM infiltration

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Number of adverse factors</th>
<th>% of patients</th>
<th>5-year PFS</th>
<th>5-year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>0</td>
<td>20%</td>
<td>-</td>
<td>62%</td>
</tr>
<tr>
<td>Group 2</td>
<td>1</td>
<td>33%</td>
<td>-</td>
<td>53%</td>
</tr>
<tr>
<td>Group 3</td>
<td>2</td>
<td>26%</td>
<td>-</td>
<td>33%</td>
</tr>
<tr>
<td>Group 4</td>
<td>3-4</td>
<td>21%</td>
<td>-</td>
<td>18%</td>
</tr>
</tbody>
</table>
**Prognostic Score for advanced HL (Hasenclever index)**

<table>
<thead>
<tr>
<th>Number of adverse factors</th>
<th>% of patients</th>
<th>5-year PFS</th>
<th>5-year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>7%</td>
<td>84%</td>
<td>89%</td>
</tr>
<tr>
<td>1</td>
<td>22%</td>
<td>77%</td>
<td>90%</td>
</tr>
<tr>
<td>2</td>
<td>29%</td>
<td>67%</td>
<td>81%</td>
</tr>
<tr>
<td>3</td>
<td>23%</td>
<td>60%</td>
<td>78%</td>
</tr>
<tr>
<td>4</td>
<td>12%</td>
<td>51%</td>
<td>61%</td>
</tr>
<tr>
<td>≥5</td>
<td>7%</td>
<td>42%</td>
<td>56%</td>
</tr>
</tbody>
</table>

**Risk factors:**
- Age >45
- Male gender
- Stage IV
- Hb <105g/L
- Lymphocyte count <0.6x10^9/L-8%
- Leucocyte count ≥15x10^9/L
- Albumin <40g/L
## Response criteria

### 2014 International Working group response criteria

<table>
<thead>
<tr>
<th>Response and Site</th>
<th>PET-CT-based Response</th>
<th>CT-based response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete</strong></td>
<td>Complete metabolic response</td>
<td>Complete radiologic response (all of the following): Target nodes/lesions must regress to &lt; 1.5 cm in L.D. No extranodal sites of disease</td>
</tr>
<tr>
<td>Lymph nodes and extranodal sites</td>
<td>Score 1, 2, or 3 with or without a metabolic lesion on PET-CT, or it is recognized that the lesion is not a part of the disease process. Uptake may be greater than normal mediastinum and/or liver, but not in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy of an interval scan.</td>
<td></td>
</tr>
<tr>
<td>Nonmeasured lesion</td>
<td>Not applicable</td>
<td>Absent</td>
</tr>
<tr>
<td>Organ involvement</td>
<td>Not applicable</td>
<td>Regress to normal</td>
</tr>
<tr>
<td>New lesions</td>
<td>None</td>
<td>Condition persists</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>No evidence of FDG avid disease in marrow</td>
<td>Normal by morphology; if indeterminate, IHC negative</td>
</tr>
<tr>
<td>Partial</td>
<td>Partial metabolic response</td>
<td>Partial remission (all of the following): At inception, these findings suggest responding disease: Target nodes/lesions must regress to &lt; 1.5 cm in L.D. No extranodal sites of disease</td>
</tr>
<tr>
<td>Lymph nodes and extranodal sites</td>
<td>Score 4 or 5 with reduced uptake compared with baseline and residual masses of any size. At end of treatment, these findings indicate residual disease: Target nodes/lesions must regress to &lt; 1.5 cm in L.D. No extranodal sites of disease</td>
<td></td>
</tr>
<tr>
<td>Nonmeasured lesion</td>
<td>Not applicable</td>
<td>Absent</td>
</tr>
<tr>
<td>Organ involvement</td>
<td>Not applicable</td>
<td>Regression to normal</td>
</tr>
<tr>
<td>New lesions</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>Residual uptake higher than uptake in normal marrow but reduced compared with baseline, uptake consistent with reactive changes from chemotherapy allowed. If there is persistent focal changes in the marrow, there is the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy of an interval scan.</td>
<td>None</td>
</tr>
<tr>
<td><strong>No response or stable disease</strong></td>
<td>No metabolic response</td>
<td>None</td>
</tr>
<tr>
<td>Target nodes/lesions, extranodal lesions</td>
<td>Score 4 or 5 with no significant change in FDG uptake from baseline at initial or end of treatment</td>
<td>Target nodes/lesions must regress to &lt; 1.5 cm in L.D. No extranodal sites of disease</td>
</tr>
<tr>
<td>Nonmeasured lesion</td>
<td>Not applicable</td>
<td>Absent</td>
</tr>
<tr>
<td>Organ involvement</td>
<td>Not applicable</td>
<td>Regression to normal</td>
</tr>
<tr>
<td>New lesions</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>No change from baseline</td>
<td>No change from baseline</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>Progressive metabolic disease</td>
<td>Progression disease requires at least 1 of the following:</td>
</tr>
<tr>
<td>Individual target nodes/lesions</td>
<td>Score 4 or 5 with an increase in intensity of uptake from baseline and/or new lesion or new lesion with progression</td>
<td>Progressive disease requires at least 1 of the following:</td>
</tr>
<tr>
<td>Extranodal lesions</td>
<td>New FDG assessment is consistent with lymphoma at initial or end of treatment assessment: An individual nodal lesion must be abnormal with: L.D. &gt; 1.5 cm and increase by &gt; 20% from PET</td>
<td>Progressive disease requires at least 1 of the following:</td>
</tr>
<tr>
<td>Nonmeasured lesion</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

(continued on following page)
<table>
<thead>
<tr>
<th>Table 2. Revised Criteria for Response Assessment (continued)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response and Site</strong></td>
</tr>
<tr>
<td>New lesions</td>
</tr>
<tr>
<td>New lesions</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>New lesions</td>
</tr>
<tr>
<td>Bone marrow</td>
</tr>
</tbody>
</table>

Abbreviations: SRS, 5-point scale; CT, computed tomography; PCG, percutaneous core biopsy; H&E, hematoxylin and eosin; LD, largest diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; FFD, cross product of the LD and perpendicular diameter; SOD, shortest axis perpendicular to the LD; SOD, sum of the product of the perpendicular diameters for multiple lesions.

* A score of 3 in many patients indicates a good progress with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response to avoid undertreatment. Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferentially be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-node lesions include those in solid organs (i.e., liver, spleen, kidneys, lungs, GI tract, cutaneous lesions), or those resistant to palpation. Nonmeasurable lesions: Any disease not selected as measured, dominant disease, and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, hepatic or splenic disease, abdominal masses, and other lesions that cannot be continued and followed by imaging. In Pauwels’ ring or in extranodal sites (i.e., GI tract, bone marrow). PCG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (i.e., with marrow activation as a result of chemotherapy or myeloid growth factors).
Considerations prior to commencement of therapy and supportive care issues

1.1.1 Conservation of reproductive function

Males: Semen cryopreservation should be offered to all post-pubertal males in whom a future family is a consideration. Often, potentially fertile men are unable to provide a specimen or the specimen is of inferior quality, although very low sperm numbers are required for ICSI (Intracytoplasmic sperm injection). A testicular biopsy may achieve better sperm quality and is now offered in many fertility centres.

Referrals for sperm banking should be made to the relevant centre (Barts/UCLH). HIV+ patients can have sperm cryopreserved at Barts or Chelsea and Westminster.

Results of Hep B, C and HIV must be made available.

Females: Options for female patients are more limited. Frozen embryo banking is a possibility if there is an available partner and time constraints are not to the fore i.e. this is an option for indolent disease, but not for aggressive lymphomas. Referral for ovum and ovarian tissue storage, if time permits, should be considered (pending funding approval). Ovarian stimulation followed by egg storage takes a minimum of 2 weeks and may take up to 5 weeks depending upon the stage of the patients’ menstrual cycle at referral. Prompt referral to Melanie Davies at UCLH (Fax/e-mail letters to: Ms Shamin Shariff. Fax: 0207 3809600. E-mail: shamin.shariff@uclh.nhs.uk. Or phone 0207 3809697) or at Barts, is recommended.

Potential fertility preservation measure in pre-menopausal women if insufficient time for embryo or oocyte cryopreservation (‘aggressive’ lymphomas):

GNRH analogues/antagonists:

Gonadotrophin releasing hormone (GNRH) analogues such as Goserelin (3.6mg s/c) can be administered monthly, commencing ASAP and prior to chemotherapy. Patients should be warned of ‘post menopausal’ side-effects whilst the agent is administered. If chemotherapy can not be delayed for 10 days after first administration of GNRH analogue a GNRH antagonist (such as cetorelix/cetrotide 3mg s/c) is used to avoid the ‘initial flare’ associated with GNRH analogues (although evidence demonstrating its efficacy is scant). Data to support the efficacy of any agent are scant but treatment is generally well tolerated.

1.1.2 Cardiopulmonary dysfunction

Patients <70 years of age who are asymptomatic and have no history of cardiopulmonary disease do not require formal assessment of cardiac function.
Patients >70 years of age or those with a previous history of diabetes, cardiac or respiratory disease must have a formal assessment of cardiac function e.g. echocardiogram or MUGA scan, if treatment with potentially cardiotoxic drugs is planned. Referral to a cardiologist may be necessary.

1.1.3 Tumour Lysis Syndrome (TLS)
This is a result of profound biochemical disturbances brought about by chemotherapy. Of note, in patients with rapidly proliferating lymphomas such as Burkitt’s lymphoma) can present with spontaneous TLS before starting chemotherapy. For such patients request U&E + urate levels at least twice a day. Correction of biochemical abnormalities prior to commencement of chemotherapy reduces, but does not eliminate the risk. Use of allopurinol to prevent this is routine practice but rasburicase may be used for patients with rapidly proliferating lymphomas (BL) or significant tumour bulk. G6PD status should be checked prior to administration of rasburicase in the relevant ethnic groups. (BCSH guidelines 2015)

1.1.4 Use of haemopoietic growth factors
Use should comply with guidelines
The use of EPO is not recommended

1.1.5. Management of patients with HIV infection
Discuss all cases of lymphoma in HIV+ patients with Lymphoma Consultant with specialist interest (Dr Kate Cwynarski at RFH, Dr Silvia Montoto at Barts, Prof Lee at UCLH). Contact HIV/I&I Team for consideration of HAART and prophylactic antibiotics and refer them for follow-up to the HIV-lymphoma joint clinic (ICDC at RFH, Grahame Hayton Unit at RLH and Mortimer Market at UCLH) for joint management

Follow up in patients with lymphoma

Follow-up in patients with aggressive NHL is directed at early diagnosis of relapsed disease and identifying complications of therapy.
Follow up in Hodgkin lymphoma must now concentrate on the long-term sequelae of treatment as the survival rates are now approaching 90% with some of the newer protocols, better supportive care and improved salvage regimes.
The major issues are second malignancy, pulmonary and cardiac toxicity, sub-fertility and relapse. The incidence of second malignancy in survivors of Hodgkin lymphoma is
significantly greater than the expected incidence of primary tumours in the general population.

For patients with both aggressive NHL and advanced Hodgkin Lymphoma:-
Clinic visit pattern may vary and some patients are discharged to primary care setting after 2 years.
3-monthly in year 1
4-6 monthly in years 2
If follow up after 2 years patients will be seen less frequently

Routine investigations:
Thorough history and physical examination
Enquiry about presence of B symptoms
Performance status
Full blood count, renal and liver function, ESR at each visit for the first year, thereafter as indicated, and LDH if high index of suspicion
Thyroid function tests annually following radiotherapy to neck/mediastinum.

Imaging
For patients where remission is uncertain a CT or CT/PET scan should be performed 3 months after completion of last therapy and since last scan.
No CT scans or PET/CT should be performed on a routine basis thereafter unless previous scans were equivocal, there is clinical cause for suspicion or they are required as part of trial protocol.

INDOLENT NHL

- Follicular lymphoma grades 1, 2, 3a
- Marginal zone/gastric MALT lymphoma

Follicular lymphoma grade 1, 2, 3a

This form of lymphoma is second only in incidence to DLBCL, which equates to around 2,500 cases in the UK each year, with a median age of onset of 60 years. It is characterised by a chronic course of relapses and remissions, with around half the patients presenting with
stage IV disease. The disease carries a heterogeneous prognosis with the usual cause of death being disease resistance or high grade transformation.

It should be noted that follicular large cell lymphoma (follicular lymphoma grade 3b) follows a more aggressive course and should be treated according to the guidelines for the aggressive large cell lymphomas.

**Early stage disease (stage I)**

Stage I makes up 10% of patients with follicular lymphoma. Radiotherapy to localised disease should be given in all cases (‘watch and wait’ is acceptable but is not the standard).

**Advanced stage disease (stages II-IV)**

In asymptomatic patients with stage II-IV disease a ‘watch-and-wait’ policy may be adopted, as there has been no significant survival advantage shown between expectant management and immediate treatment in this group of patients. However, this may not be acceptable to some patients.

### 1.1.5 Asymptomatic patients with no indication for treatment

Watch and Wait if acceptable to patient. There are two main sets of criteria of indication for treatment: the BNLI and the GELA:

<table>
<thead>
<tr>
<th>BNLI criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapidly progressive disease</td>
</tr>
<tr>
<td>Life threatening organ involvement</td>
</tr>
<tr>
<td>Bone/kidney/liver infiltration</td>
</tr>
<tr>
<td>B symptoms/ pruritus</td>
</tr>
<tr>
<td>Cytopenias due to BM involvement (Hb&lt;100g/L, WCC&lt; 3 x10^9/L, platelets&lt;100 x10^9/L)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GELF criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulky disease: nodal/extra nodal ≥7 cm</td>
</tr>
<tr>
<td>3 involved nodal areas, each with a LN ≥ 3 cm</td>
</tr>
<tr>
<td>Spleen ≥ 20 cm</td>
</tr>
<tr>
<td>Pleural effusion/ ascites</td>
</tr>
<tr>
<td>ECOG ≥ 2</td>
</tr>
<tr>
<td>B-symptoms</td>
</tr>
<tr>
<td>Elevated LDH/ B2 microglobulin</td>
</tr>
</tbody>
</table>
1.1.6 Symptomatic patients

Consider inclusion in clinical trials:

For patients not entered into trials, options are:

1) Bendamustine with Rituximab is recommended (Rummel et al, Lancet 2013).

Alternatives include:

2) R-CVP x 8 (see Appendix1).

3) R-CHOP x 6 (see Appendix 1).

4) Chlorambucil(CB)-rituximab (see Appendix 1)

Different CB regimens with or without rituximab can be used depending on local practice.

- CB 10 mg od x 14d every 28 d (with or without monthly rituximab, up to 8 doses)
- CB 10 mg od x 28d, followed by 10mg od x 14d every 28d (with or without monthly rituximab, up to 8 doses)
- CB 10 mg od x 42d with or without 4 weekly rituximab, followed by x 3 cycles of 10 mg od 14d every 28 d

5) Single agent rituximab

Toxicity is greater with R-CHOP than with other immuno-chemotherapy schedules. R-CHOP is recommended in patients with a clinically aggressive lymphoma or those who need a rapid response (i.e compression symptoms)

Single agent chlorambucil remains useful treatment for frail patients or patients wishing to avoid intravenous infusions at hospital. Single agent rituximab should be considered in patients who wish to avoid chemotherapy.

Rituximab maintenance therapy (375mg/m2 every 8 weeks for 2 years) is recommended as an option for the treatment of people with FL that has responded to first-line induction therapy with rituximab in combination with chemotherapy. Treatment should start 2 months after the last dose of first-line induction therapy and continue until the disease progresses, or for a maximum period of 2 years.

Relapsed disease
A repeated biopsy should be performed in every possible case to rule out histological transformation, as this will dictate the management.

A second remission should be obtained and consolidation with an autologous (or allogeneic) stem cell transplant considered in patients deemed fit enough. The length of first remission should be taken into account.

To achieve 2\textsuperscript{nd} and subsequent remission

Second and subsequent treatments will obviously depend on prior therapy, the philosophy being to avoid regimens previously administered. The options, as in first line, include R-B, R-CVP and R-CHOP. In addition, fludarabine containing regimens (FMD, FC) and regimens used as second-line therapy for aggressive lymphomas (R-ICE, R-ESHAP, R-DHAP) should be considered. Patients resistant to rituximab and alkylating agents should be considered for idelalisib. Patients who relapse having already received rituximab within the last 6 months, should not be retreated with rituximab.

Patients achieving 2\textsuperscript{nd} and subsequent remission:

Haematopoietic Stem Cell Transplantation

Consideration should be given to consolidation with either an autologous or allogeneic transplant in young patients in second (or subsequent) remission, as this appears to increase time until progression and OS and may be curative in a small minority of patients

Patients up to the age of 60-65 may also be considered for a low-intensity sibling/matched unrelated allograft.

Such patients should be discussed early with a transplant centre.

Rituximab maintenance

Rituximab maintenance therapy is recommended as an option for the treatment of people with relapsed FL in remission induced with chemotherapy with or without rituximab. It is administered at 3 month intervals for up to 2 years.

A recent randomised study has demonstrated a PFS advantage for patients receiving rituximab maintenance following an autograft (Pettengell, JCO, 2013).
**Ibritumomab Tiuxetan (Zevalin)**

Ibritumomab tiuxetan is licensed radioimmunotherapy (RIT) for the treatment of adult patients with rituximab relapsed or refractory CD20+ follicular lymphoma. In the case of second and subsequent relapse of FL, RIT is an established treatment option, especially in the following clinical settings:

- Low risk/non-bulky disease where the main aim of therapy is to control symptoms and maintain quality of life
- Elderly patients
- Those with contra-indications to chemotherapy

In an analysis of 4 studies in follicular lymphoma longer term responses with Zevalin were seen in patients with non bulky (<5cm) disease at relapse and those with a localised relapse.

**Transformed FL (not synchronous)**

Patients with transformed disease should receive R-CHOP x 6-8 or, if they have received this previously, second-line therapy for aggressive lymphoma (R-ESHAP, R-ICE, R-DHAP). Consolidation of the response with ASCT is the standard in young and fit patients, with the exception of patients who are chemotherapy-naïve at the time histological transformation (i.e previous W&W or local RT) as they can be managed expectantly post chemotherapy. Allografting is also an option and patients should be discussed with a transplant centre. Patients who relapse having already received rituximab within the last 6 months, should not be retreated with rituximab.

**Summary of treatment for follicular lymphoma**

**Localised disease**

- Radiotherapy
- Expectant management

**Advanced disease**

**Initial therapy**

- Expectant management
- Clinical Trial - [see NCRI trial link](#)
- Rituximab in combination with chemotherapy

**Relapsed disease**

- Clinical Trial - [see NCRI trial link](#)
• B+-R
• FC+-R
• FMD+-R
• CHOP+-R
• ESHAP+-R
• ICE+-R
• DHAP+-R
• CB +/-
• Palliative RT
• Idelalisib
• Zevalin

Consolidation of patients in second or subsequent remission
• Transplantation (second or subsequent remission) – autoPBSCT or RI-alloSCT
• Maintenance rituximab
Mantle Cell Lymphoma

Any patient with gastrointestinal symptoms at presentation or relapse should be investigated by OGD or colonoscopy given the propensity of MCL to involve the GI tract.

1.1.7 Patients with indolent disease
Most patients present with symptomatic advanced stage disease requiring therapy. However, in a small number of asymptomatic patients a watch and wait policy may be adopted. Observational studies have shown that up to one third of patients with MCL may be observed for a period of months to years before developing indications for therapy with no negative impact on their overall survival. Such patients generally present with isolated splenomegaly and a lymphocytosis and are thought to represent an indolent form of the disease,

1.1.8 First line therapy
Patients should be considered for clinical trials

Transplant-eligible patients

Patients should be treated with regimens which include Rituximab and high dose cytarabine, followed by consolidation with BEAM + ASCT for those who achieve remission. Induction protocols include:
1) Nordic MCL 2 protocol – R-maxiCHOP alternating with R-HD AraC
2) R-CHOP$_{21}$ x3 followed by R-DHAP x3

Patients should be restaged after 3-4 cycles and after this autologous stem cells should be harvested off the back of cytarabine components of induction chemotherapy e.g cycle 6 of Nordic protocol in responding patients whenever possible.

Consideration should be given to allogeneic stem cell transplantation in CR1 for very high risk patients (e.g. high MIPI) instead of autologous transplantation. Wherever possible, allogeneic transplantation for MCL should be done in the context of a clinical trial

Transplant-ineligible Patients
Patients should be treated with R-Benda or R-CHOP x 6 followed by rituximab maintenance for those achieving remission.
Frail patients who are not fit enough for CHOP or bendamustine chemotherapy should be treated with an alternative Rituximab-containing regimen (e.g., R-Chlorambucil) followed by maintenance rituximab in responders.

**Summary of first-line treatment for MCL**

![Treatment Flowchart]

**CNS prophylaxis**
This is not recommended as part of first line treatment as incidence is low (4% cumulative incidence European Network study). For younger patients, CNS directed therapy in the form of HD AraC is already part of the treatment recommendation. However, while not routinely justified for all patients, CNS prophylaxis may particularly benefit patients with blastic histology at diagnosis.

**Cyclin D1 negative MCL**
This rare subgroup of MCL has a similar clinical course to Cyclin D1 positive MCL and should be managed in the same way
1.1.9 Non-responsive, progressive or relapsed disease

Patients should be considered for clinical trials

**Younger patients <65y**

Suitable salvage protocols include, B-R, R-ESHAP, R-HDAC, R-BAC or bortezomib (in combination with high dose cytarabine ± Rituximab, R-HAD+B) and ibutinib. No salvage regimen has been demonstrated to be superior over others. Younger fitter patients relapsing after prior BEAM/ASCT should be considered for allogeneic transplantation.

**Older patients >65y**

Suitable salvage protocols include ibrutinib, R-Bendamustine, Bortezomib (S/C), FC±R, R-CHOP, Temsirolimus and R-Chlorambucil. Patients who relapse having already received Rituximab within the last 6 months, should not be retreated with Rituximab.
Extranodal Marginal Zone Lymphomas of Mucosa Associated Lymphoid Tissue (MALT Lymphoma)

Summary

- Biopsy material must be reviewed by an experienced haematopathologist before considering any therapy.
- All patients should be considered for enrolment in clinical trials where available.

Gastric MALT lymphoma

- *Helicobacter pylori* eradication therapy should be offered to all patients with localised *Helicobacter pylori*- positive gastric MALT, without any other concurrent therapy.
- Offer alternate *Helicobacter pylori* eradication regimens to patients with localised *Helicobacter pylori*- positive gastric MALT lymphoma in whom first-line antibiotic therapy fails i.e. there is persistent *Helicobacter pylori* antigen in the stool 8 weeks following therapy.
- Consider observation without therapy in patients with localised *Helicobacter pylori*-positive gastric MALT who respond clinically and endoscopically but who have residual disease on surveillance biopsies of the stomach.
- Offer chemotherapy (e.g. chlorambucil, CVP - cyclophosphamide, vincristine, prednisolone, bendamustine,) in combination with rituximab in patients with localised *Helicobacter pylori*-negative gastric MALT or those who fail *Helicobacter pylori* eradication therapy. Avoid the use of anthracyclines, in the absence of disease transformation.
- Consider radiotherapy**, as an alternative to chemotherapy/chemo-immunotherapy or in chemotherapy/chemo-immunotherapy failures in patients with localised *Helicobacter pylori*-negative gastric MALT or those who fail *Helicobacter pylori* eradication therapy.
- In the absence of life-threatening complications surgery must not be recommended. This is because of the risk of short and long term complications of gastrectomy coupled with the availability of the effective therapies mentioned above.
- Consider rituximab monotherapy for those patients in whom neither radiotherapy or chemotherapy are appropriate.
- Offer chemotherapy (e.g. chlorambucil, CVP - cyclophosphamide, vincristine, prednisolone, bendamustine) with rituximab in patients with disseminated disease.
• Consider *Helicobacter pylori* eradication therapy for all patients with disseminated *Helicobacter pylori*-positive gastric MALT

• Consider endoscopic follow-up with multiple biopsies, for up to two years following a remission being achieved, to monitor for disease regression and subsequent relapse.

• Long term follow-up is recommended as relapses are common after initial remission and most frequently occur at distant sites.

*A* proton-pump inhibitor combined with a two antibiotics (either clarithromycin, amoxycillin or metronidazole) forms the basis of the “triple therapy” approach. This is administered for at least 10–14 days.

**(24-30 Gy radiation to the stomach and and peri-gastric nodes)**

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**Non-gastric MALT**

• For patients with non-gastric MALT consider the following factors before recommending any therapy: site of involvement, potential for organ dysfunction, whether the disease is localised or disseminated, the morbidity of any therapy and the overall fitness of the patient.

• Observation alone should be considered for all patients with asymptomatic, non-progressive, localised disease that does not threaten a vital organ or structure.

• Consider radiotherapy for patients with localised, non-gastric MALT

• Consider chemotherapy (e.g. chlorambucil, CVP- cyclophosphamide, vincristine, prednisolone, bendamustine) in patients with disseminated non-gastric MALT who require treatment or in those patients who are not suitable for radiation therapy. In the absence of disease transformation anthracyclines should be avoided in this patient group because of the excellent long-term survival and the availability of alternatives with demonstrable efficacy.

• Consider the addition of rituximab to chemotherapy.

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MALT lymphoma accounts for approximately 7% to 8% of all B-cell lymphomas; the median age at presentation is 61 years and the stomach is the most frequently involved organ. Other
sites that may be involved include the salivary glands, eyes, lung, intestinal tract, skin, and thyroid gland. Non-gastric MALT lymphomas have been associated with autoimmune diseases and chronic infections including *Chlamydia psittaci* infection in some cases of ocular adnexal MALT lymphomas, *Campylobacter jejuni* infection in cases of immunoproliferative small intestinal disease, *Borrelia burgdorferi* infection in cutaneous MALT lymphomas and Hepatitis C virus infection. The clinical behaviour is similar to other low-grade lymphomas; high-grade histologic transformation can occur but is rare.

**Staging considerations for MALT lymphoma**

Up to 25% of gastric and 46% non-gastric MALT have disseminated disease at presentation so appropriate staging is indicated including CT scanning, bone marrow examination and gastroduodenal endoscopy with multiple biopsies. For patients presenting with gastric MALT consideration should be given to endoscopic ultrasound scan for evaluation of the depth of infiltration if this is not evaluable by CT. There is a strong association between gastric MALT lymphoma and chronic *Helicobacter pylori* infection and testing for this pathogen is indicated in all cases of gastric MALT lymphoma with a sensitive assay e.g. stool antigen test. Hepatitis C antibody (anti-HCV) serostatus is associated with non-gastric MALT lymphomas. Reverse transcriptase polymerase chain reaction (RT-PCR) for viral RNA is indicated if antibody-positive.

An alternative staging system first proposed by Blackledge et al., and later modified by the International Workshop in Lugano, Switzerland, is listed below:

Stage I: confined to GI tract (single primary, or multiple, discontiguous lesions)
- Stage I1: infiltration limited to mucosa with or without submucosal involvement
- Stage I2: infiltration into muscularis propria, subserosa or serosa, or both.

Stage II: extending into abdomen from primary GI site
- Stage II1: local nodal involvement (paragastric in gastric lymphoma)
- Stage II2: distant nodal involvement.

Stage III: penetration of serosa to involve adjacent organ or tissues.

Stage IV: disseminated extra-nodal involvement or concomitant supra-diaphragmatic nodal involvement.

Endoscopic otolaryngology is performed only when there are symptoms or signs of Waldeyer ring involvement.
**Gastric MALT lymphomas (stage IE)**

*Therapy for localised disease*

The recommended initial therapy for early-stage *H. pylori*-positive gastric MALT lymphoma is a combination of antibiotics plus a proton-pump inhibitor (PPI). The commonly used regimens are:

- Omeprazole, amoxicillin, and clarithromycin
- Omeprazole, metronidazole, and clarithromycin (for penicillin-allergic patients)
- Omeprazole, tetracycline, metronidazole, and bismuth.

Salvage therapies should be discussed with the local microbiologist; regimens used in cases of resistance to clarithromycin- or metronidazole-based therapies include:

- Omeprazole, tetracycline, metronidazole, and bismuth (mentioned above)
- Levofloxacin, amoxicillin, and omeprazole
- Rifabutin, amoxicillin, and omeprazole.

The duration of treatment is usually 10 to 14 days for triple therapy, or 7 days for quadruple therapy. *H. pylori* eradication rates of all 3 commonly used regimens exceed 85%.

Note that there is no evidence to support the use of additional chemotherapy in patients who respond to antibiotic eradication therapy.

There is no definitive treatment recommendation for patients who fail *H. Pylori*-eradication therapy or who are *H. pylori*-negative at diagnosis. Different therapeutic interventions have been recommended, but there are no randomized studies available to make evidence-based decisions. It is opinion that patients who are *H. pylori*-negative should trial antibiotic therapy due to the acceptable toxicity profile of the latter and the potential for false-negative test results.

Patients are generally considered to have failed antibiotic therapy when there is no regression at repeat endoscopy 2 months after eradication therapy, or when there is lack of complete regression at approximately 18 months after treatment.

The IELSG19 trial is the largest randomised study conducted in MALT lymphoma and included patients with gastric MALT who had not responded to antibiotic therapy. Chlorambucil versus
chlorambucil plus rituximab vs rituximab alone were compared. Preliminary results demonstrate that the R-chlorambucil improves the response rate and event free survival compared to chlorambucil or rituximab alone but at most recent follow-up this had not translated into improved overall survival. Therefore, rituximab with chemotherapy (chlorambucil/CVP/Bendamustine etc) remains the recommended option for patients with localised disease who fail antibiotic therapy.

Localised *H. pylori*-negative gastric MALT lymphoma or *H. pylori*-positive gastric MALT lymphoma showing poor response to antibiotic therapy has also been treated with radiation therapy to the stomach and perigastric lymph nodes. Radiotherapy (total dose of 24-30 Gy) results in excellent long term disease control but with the potential for long term morbidity in a condition with excellent long-term survival.

*Follow-up for gastric MALT lymphoma*

Endoscopic evaluation should occur 2 months after the end of therapy and then at 6 monthly intervals for 2 years. Histologic assessment of suspicious areas detected at the time of the procedure should be encouraged. *H. pylori*-positive patients should have repeat assessment to confirm eradication. If *H. pylori* has not been eradicated by 2 months, alternative second line antibiotic therapy should be given. If there is tumour progression at any stage chemotherapy should be considered with radiotherapy reserved for patients refractory to or intolerant of chemotherapy. The authors acknowledge that some clinicians will opt for radiotherapy in the first instance, especially in elderly patients.

Patients who are systemically well and have stable disease or partial response to antibiotic therapy should generally not be declared to have failed until at least 1 year as responses can be slow.

Note that some retrospective studies have identified a small increase in the risk of gastric cancer in patients with a history of gastric MALT lymphoma; gastro-intestinal symptoms should be investigated promptly in any patient with a history of this disease.

*Patients with advanced gastric MALT lymphoma*

Disease not confined to the stomach should be treated with systemic chemotherapy but if the patient is *H pylori*-positive, eradication therapy should still be attempted and can result in nodal responses. The chemotherapy regimen choice depends on the patient's medical status,
previous treatments, and the overall goal of therapy. Options reported in the literature include:

- Rituximab in combination with chlorambucil or cyclophosphamide, vincristine, and prednisone (R-CVP) or bendamustine are reported.

**Non-gastric extranodal MALT lymphoma**

About 25% of patients with nongastric MALT lymphoma present with disseminated disease.

**Localised disease**

**Salivary gland**

- Salivary gland MALT lymphomas behave in an indolent manner even in the absence of treatment. Many of these cases are monitored without therapy. When treated, there is no significant difference in outcome among patients treated with surgery, radiation therapy, or chemotherapy. Hence, all three modalities of treatment can be used when observation is not appropriate and the risks of each option have been considered.

**Ocular adnexa, lacrimal glands, and orbit**

- Radiation therapy is considered the treatment of choice. *Chlamydia psittaci* eradication with doxycycline has been proven to produce regression of these lymphomas in some but not all studies and should be considered if *Chlamydia psittaci* is detected in the biopsy specimen.

**Lung**

- For localised disease, surgery (limited resection) plus radiation therapy or chemotherapy is usually advocated. There are case reports of extended schedules of rituximab offering local disease control for this very rare tumour. If the disease is multifocal, then chemotherapy, immunotherapy or both may be considered.

**Skin**

- Recommended treatment is surgical excision with or without radiation therapy, or observation (especially in case of multiple lesions). Radiation therapy is generally advised if the excision margins are incomplete. Isolated case reports of *Borrelia*
*burgdorferi* treatment leading to complete regression of these tumors have been published, but there are insufficient data to recommend this as standard practice.

**Thyroid**

- Local disease is usually treated with surgery with or without radiation therapy. In advanced cases supplemental chemotherapy is offered.

**Breast or dura**

- Excision surgery with or without radiation therapy is the preferred modality of treatment.

**Disseminated disease**

Rituximab with chemotherapy (chlorambucil, bendamustine, CVP).

**Nodal Marginal Zone Lymphoma**

NMZL is an infrequent primary nodal B-cell neoplasm that morphologically resembles lymph nodes involved by marginal zone lymphoma of extra-nodal types but without evidence of extra-nodal or splenic disease. It accounts for <2 % of all lymphoid malignancies. The presence of extra-nodal disease should be excluded by adopting the staging strategy outlined above.

It is important to recall that 50-80% of patients with this illness will survive for more than 5 years. This is an indolent disease and observation is an appropriate strategy in the asymptomatic patient. For limited stage disease, surgery and radiotherapy has been recommended based on small numbers from retrospective studies; in advanced stage patients immuno-chemotherapy (rituximab + polychemotherapy) is recommended, again based on small numbers. The utility of anthracycline is not completely defined.

**Splenic Marginal Zone Lymphoma**

Consider observation alone of patients who are asymptomatic with blood counts within normal limits.

If symptomatic or cytopenic consider therapy with chemotherapy (e.g. chlorambucil, CVP, bendamustine) in combination with rituximab or with rituximab induction alone. Rituximab maintenance may be considered.
If Hep C + consider anti viral therapy (IFN +/- ribavirin).
**AGGRESSIVE NHL**

Diffuse large B cell lymphoma (DLBCL) is the most common non-Hodgkin’s lymphoma (NHL) accounting for 30-40% of all cases. Although most patients with advanced disease are cured with R-CHOP chemotherapy, about 10-15% have primary refractory disease and a further 20-30% relapse. The outlook for non-responders to R-CHOP is poor, although a significant minority can be cured by high dose therapy (HDT) and stem cell transplantation (SCT).

Treatment approaches differ according to the following factors:

- **Stage**
- **Disease bulk** (<10cm vs. ≥10cm)
- **IPI risk group**
- **Presence of primary extranodal disease**
- **Co-morbidities**

**Early stage DLBCL (stage IA or IIA disease)**

**Recommendations**

- **Non-bulky** (<7.5 cm) stage IA DLBCL presenting at sites associated with low morbidity for radiotherapy (e.g. groin, neck or axilla): 3 x RCHOP-21 chemotherapy followed by radiotherapy (30Gy)

- **Localised disease** either non-bulky stage I and IIA DLBCL disease involving a site where the acute and late toxicity associated with radiation is preferably avoided should be treated with 6 cycles of RCHOP-21

- **Bulky stage IA/IIA DLBCL** should be treated with 6 cycles of RCHOP-21 with consideration of 30Gy RT to initial sites of bulk

- **Extranodal stage IA DLBCL** should be treated with 6 cycles of RCHOP-21 with consideration of RT

**Consider concomitant H pylori eradication therapy for DLBCL stomach**

Patients with early stage DLBCL (stage IA or IIA disease) are treated variably with either full course chemotherapy or abbreviated chemotherapy with or without radiotherapy. In the pre-Rituximab era, the SWOG 8736 showed that in localised aggressive NHL, combined modality treatment with 3 cycles of CHOP followed by involved field radiotherapy (IFRT) produced
superior 5-year PFS (77% vs 64%) and OS (82% vs 72%) compared to 8 cycles of CHOP (Miller, et al 1998). However, this difference was lost with longer follow-up suggesting that 3 cycles of chemotherapy may be inadequate for some patients with early stage disease. A BCCA study showed 5-year OS of 95% with 3 cycles of CHOP and IFRT in young patients with limited stage DLBCL and no adverse factors (Shenkier, et al 2002). The ECOG 1484 randomised complete responders after 8 cycles of CHOP to receive IFRT (30 Gy) or to observation alone and demonstrated an improvement in 6-year PFS with IFRT (73% vs 56%) (Horning, et al 2004). The Groupe d’Etude des Lymphomes d’Adulète performed a randomised study of elderly patients with limited stage disease and low risk IPI (GELA LNH 93-4). There was no benefit from adding radiotherapy to 4 courses of CHOP chemotherapy (Bonnet, et al 2007). In young patients (<60 years) with limited stage disease, the GELA LNH 93-1 study demonstrated a 5-year OS advantage for the intensive ACVBP/MIA chemotherapy regimen over 3 cycles of CHOP and 40 Gy IFRT(Reyes, et al 2005). However, this study included patients with bulk disease (>10 cm) for whom 3 cycles of CHOP may be inadequate treatment. In a sub-analysis, no survival difference was found between the 2 groups when comparing patients presenting with non-bulky disease only. Furthermore, in both the above studies, there was a high loco-regional failure rate after radiotherapy (21%) raising questions about the RT quality assurance measures employed.

The benefit of combined modality treatment has been substantiated in the Rituximab era. The SWOG 0014 study reported a 4-year PFS of 88% and OS of 92% when Rituximab was added to 3 cycles of CHOP and IFRT (Persky, et al 2008). This represented an improvement over historical data from the pre-Rituximab era (4-year PFS and OS of 78% and 88% respectively). The Mab Thera International trial (MInT) trial, reported benefit in both OS and EFS when Rituximab was added to CHOP-like chemotherapy in young (<60 years) patients with low risk IPI disease (Pfreundschuh, et al 2006). Most patients in this study had limited stage disease and IFRT was given to bulk (>7.5 cm) and extranodal disease. The optimal number of RCHOP cycles for early stage disease is not clear. The German FLYER trial is currently comparing 4 vs 6 cycles of RCHOP for low IPI DLBCL patients.

Whilst there are no published randomised trials of RT in the Rituximab era to guide treatment decisions, a single centre retrospective analysis demonstrated an improvement in OS and PFS for patients receiving RT in CR after 6-8 cycles of RCHOP chemotherapy. For patients with Stage I and II disease, the 5-year OS and PFS with RT were 92% and 82% whereas without RT they were 73% and 68% respectively (Phan, et al 2010).

In conclusion, RT decreases local recurrence rates and for elderly patients and some younger patients with limited stage disease, 3-4 cycles of RCHOP followed by RT may be preferable, especially for sites where RT is well tolerated e.g. groin, axilla and neck. In contrast, a full
course of 6-8 cycles of RCHOP may be preferable where RT might result in debilitating late toxicity such as xerostomia following parotid treatment or increased secondary cancer risk, for example breast cancer following mediastinal radiotherapy in younger women, albeit the increased number of cycles of R-CHOP increases the risk of heart failure (Mulrooney et al BMJ 2009).

1.1.10

1.1.11 Advanced disease – non-bulky stage I with risk factors, bulky stage I, II-IV

Consider inclusion in clinical trials

All patients with advanced disease treated outside of clinical trials should receive 6 courses of R-CHOP21 in accordance with NICE guidance. R-CHOP14 appeared equally efficacious in the RCHOP 14 vs RCHOP 21 trial but the study was not powered to detect non inferiority. R-CHOP14 may be used (with pre-emptive G-CSF and septrin prophylaxis) if patient’s preference (Cunningham et al, Lancet 2013). In the NCRI study patients received 8 doses of rituximab.

Impressive outcomes have been described after ACVBP (Recher et al, Lancet 2011) but this approach is not widely used in the UK – and the regimen incorporates vindesine, IV HD-MTX and IT MTX, and the patient cohort were <60 years.

Advanced disease and reduced ejection fraction:

Consider

- Reduced dose anthracycline (ie asymptomatic patients with ejection fractions between 40 and 50%)
- R-GCVP (anthracycline in CHOP-R substituted by gemcitabine; Fields JCO 2014)
- R-CEOP (anthracycline in CHOP-R substituted by etoposide - 50 mg/m² IV on day 1 and 100 mg/m² PO on D2, D3; ASH 2009)

These protocols have not been formally compared with RCHOP prospectively.

Patients with high-risk IPI DLBCL continue to have suboptimal outcomes in the Rituximab era with predicted 5-year survival of 50-55% with RCHOP. A number of studies have attempted to improve outcomes for high-risk patients using either dose intensifying regimens or ASCT in first remission with conflicting data. Early results from a prospective phase II NCRI UK study using the dose intense R-CODOX-M/ R-IVAC regimen have also shown encouraging results which appear superior to historical data (McMillan, et al 2015).
Patients with DHLs (double hit) have poor outcomes with RCHOP chemotherapy. Intensified chemotherapy regimens such as R-CODOX-M/R-IVAC or DA-EPOCH-R are sometimes used for treating Burkitt’s or grey zone lymphomas intermediate between DLBCL and Burkitt lymphoma. Transplant consolidation in first remission is also considered. At present there is insufficient evidence to recommend any of these strategies although retrospective studies suggest efficacy (Petrich, et al 2014).

Consolidation radiotherapy has traditionally been used in trial protocols for bulk and extranodal disease. In an amendment to the German RICOVER-60 trial, the value of adding 36 Gy IFRT to initial sites of bulk (>7.5 cm) or extranodal disease was evaluated. Patients receiving IFRT had superior EFS, PFS and OS (Held, et al 2014). Whether radiotherapy can be spared in patients achieving a complete metabolic response to chemotherapy on PET scan remains unknown and forms the basis of ongoing investigation.

**Advanced disease and frail/elderly (>80 years) patients**

*Consider inclusion in clinical trials*

**Patients with impaired performance status (WHO >2) at presentation, should be considered for a steroid pre-phase prior to assessing fitness for standard or modified RCHOP**

*Consider*

- Reduced dose (50-75% dose) anthracycline
- R-GCVP
- Mini R-CHOP (Peyrade et al, 2011)
- R-CVP
- PMitCEBO

Primary GCSF prophylaxis is recommended for patients aged >65, frail patients and those with significant comorbidities.

**Primary mediastinal DLBCL (PMBCL)**

*Consider inclusion in clinical trials*

**Patients with PBLBCL should receive standard chemotherapy (RCHOP21/14)+/- RT.**

Whether RT can be omitted from PET negative patients is unclear with data predominantly from small Phase II studies. The IELSG37 study (randomized, multicentre, two-arm phase III study assessing the role of mediastinal radiotherapy after Rituximab containing chemotherapy regimens to patients with newly diagnosed PMLBCL) is open in the UK. The
aim of the trial is to evaluate the role of radiotherapy in PMBCL patients, who have become “PET-negative” after a combined R-chemotherapy regimen.

Presently radiotherapy consolidation is considered a ‘standard of care’ in this disease, although some will omit RT in those who are PET negative after chemotherapy or in young women where there is concern of a high risk of breast cancer - after discussion with patient).
1.1.12 Restaging and management of partial response

Patients are routinely restaged by CT scan after 4 courses of R-CHOP chemotherapy in many centres. Results from the PET-substudy of R-CHOP$_{21}$ are awaited regarding the role of interim scans and are not recommended in routine practice. However if there is clinical concern earlier interim scanning (CT or PET-CT) may be performed.

PET-CT scan is performed 6-8 weeks after completion of (R-CHOP x 6) therapy (Cheson 2007, Barrington 2014).

Patients in PR on CT scan after 4# with no improvement after R-CHOPx6 should be restaged with FDG-PET scan. Those with a positive PET scan should be considered for salvage therapy, and those with a negative scan should be closely observed. In general, re-biopsy of suspicious lesions should be considered.

The decision to offer consolidation radiotherapy should be made at presentation (ie. to bulk disease or bony lesions) and not to residual FDG-avid lesions in those treated with curative intent, as PET-positive lesions may represent more widespread disease. RT may be offered to those with PET-positive lesions(s) and who are ineligible for salvage chemotherapy.

1.1.13 Management of primary refractory disease and first relapse

_Consider inclusion in clinical trials_

_Patients fit for PBSCT:_

These patients should first receive salvage treatment with a non-cross-resistant regimen: ESHAP, ICE, DHAP, IVE and mini-BEAM$_{12-16}$. All patients should receive rituximab with their salvage treatment if rituximab naïve or if it is longer than 6 months since previous rituximab treatment.

Patients should receive 2 courses of R-ESHAP/R-ICE$_{17-19}$ chemotherapy as salvage and restaged. If the patient is in CR or near CR (PR), stem cell collection following further salvage chemotherapy or cyclophosphamide + G-CSF is performed, prior to BEAM-conditioned PBSCT.

*Patients not responding to 2 courses of R-ESHAP/R-ICE should be changed to another salvage regimen (R-IVE,R-mini-BEAM, gemcitabine containing regimen or agents such as Pixantrone, lenalidamide, brentuximab). Stem cell harvest and BEAM autograft should then be carried out in those with chemo-responsive disease.
Cases should be considered on an individual basis. Selected patients may be considered for allogeneic bone marrow transplantation or reduced-intensity allograft.

*Patients who progress through first-line salvage therapy are very unlikely to have a sustained response to second or third line salvage therapy and consideration should be given to palliation 20.

- **Patients unfit for PBSCT should be considered for clinical trials.**
- Rituximab-Gemcitabine-Oxaliplatin – IV regimen (El Gnaoui et al, 2007)
- Ptxantrone
- Lenalidamide
- Brentuximab
- Bendamustine
- R-CCEP (CCNU, cyclophosphamide, etoposide and prednisolone –PO)
- PMtCEBO+/-R
- Gemcitabine (1000mg/m² - 1250mg/m² weekly
- Experimental therapies (kinase inhibitors etc)

### 1.1.14 Palliative approaches (s/c ara-C/po etoposide)

### 1.1.15 Summary of Treatment

**Localised disease**

<table>
<thead>
<tr>
<th>Stage I, I.e. non-bulky</th>
<th>R-CHOP x 3+/- RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>No risk factors</td>
<td>(or R-CHOP x 4-6)</td>
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**Advanced disease (Stage II-IV) in patients aged >18 years**

Therapy as per trials

R-CHOP₂₁ (or RCHOP₁₄) x 6
Primary refractory/relapsed disease (fit for PBSCT)

ESHAP/ICE-+/R x2

response

no response

ESHAP/ICE-+/R + PBSCH

R-IVE or alternative salvage

response

no response

BEAM autograft R-IVE + PBSCH

mini-BEAM

or palliation or experimental therapy

BEAM autograft
**Peripheral T-cell Lymphomas**

*Consider inclusion in clinical trials*

Generally the T-cell lymphomas have a poorer response to therapy and shorter survival than the B-cell lymphomas. Prognostic factors should be taken into account to decide initial therapy. Autograft (or allogeneic SCT) in first remission should be considered (except for patients with ALK+ ALCL) (BCSH Guidelines 2011).

Presently CHOP$_{21}$ (or CHOP$_{14}$) is considered standard 1st line therapy (although other centres use GEM-P) and studies are ongoing to address optimal therapy. The addition of etoposide to CHOP has only been shown to improve outcome in young, good risk patients (Schmitz et al, 2010).

If CR or PR to initial therapy is not achieved, patients should go on to a salvage regimen as for DLBC lymphomas.

If patients relapse consideration should be given to *inclusion in clinical trials, brentuximab, salvage therapies* and consolidation with an allograft in second remission.

**Intestinal T-cell Lymphoma**

*Consider inclusion in clinical trials*

CHOP is standard therapy but consideration of high dose chemotherapy and autologous bone marrow transplantation for suitable patients should be made.

Preliminary data using CHOP followed by 3 courses of IVE and intermediate dose methotrexate and autograft are encouraging (Sieniawski et al, 2011).

**Extranodal NK/T Cell Lymphoma, nasal type**

*Consider inclusion in clinical trials*

The distinction at diagnosis between localised disease and disseminated disease is important as this tumour is radiosensitive and localised disease is thus potentially curable with radiotherapy (5-year OS of 40-75%). In addition the relative insensitivity to chemotherapy means that disseminated disease has a dismal prognosis and consideration of experimental therapy may be considered as first line.

Patients with localised disease should receive radiation with 50-55Gy early in the treatment course. The value of additional chemotherapy (etoposide-based, gemcitabine-based
(gemcitabine, oxaliplatin, L-asparaginase and dexamethasone (GELOX (gemcitabine, oxaliplatin, and L-asparaginase [Wang et al, Cancer 2012] or GOLD regimen) or asparaginase-based) remains unclear but is considered conventional.

Asparaginase-containing regimens (ie. SMILE regimen that incorporates dexamethasone, methotrexate, ifosphamide, asparaginase and etoposide) should be considered in disseminated disease and relapsed or refractory disease. Consolidation with auto/allo-SCT may be considered.

Haemophagocytic lymphohistiocytosis, (HLH) is a recognised complication and mode of presentation of T-cell and NK-cell tumours.

**Burkitt Lymphoma**

*Consider inclusion in clinical trials*

Patients under 60yrs should still be treated according to the LY10 protocol with the addition of rituximab. Choice of RCODOX-Mx3 (low risk) or RCODOX-M/RIVACx2 (high risk) depends on risk grouping as below. Patients >60 years should be considered for the age-adjusted protocol of RCODOX-M/RIVAC. Cases should be considered on an individual basis. R-CHOP plus intrathecal chemotherapy may be considered for those not suitable for intensive therapy.

HIV+ patients with Burkitt lymphoma should also receive R-CODOX-M/IVAC as the outcome has shown to be equivalent to HIV- patients (references: Alwan et al, 2015, Barnes et al 2011 and Rodrigo et al 2012). In addition the survival of HIV-ve patients with BL treated with chemotherapy regimens employed in HIV-DLBCL (CHOP, CDE) remains poor (Lim et al, JCO 2005, n=363, Spina et al, JCO, 2005).

**Low Risk**

All patients treated with this protocol must fall into the IPI low risk group i.e. they must have at least 3 of the factors identified below:-

a) Normal LDH level

b) WHO performance status 0-1

c) Ann Arbor stage I-II

d) Number of extra-nodal sites (e.g. bone marrow, GI tract, CNS) ≤1

**High Risk**

All remaining patients are high risk. They should have 2 or more of the following features:
a) Raised LDH level
b) WHO performance status 2-4
c) Ann Arbor stage III-IV
d) Number of extra nodal sites >1

Refractory Burkitt Lymphoma

Patients with biopsy-proven refractory disease respond very poorly to salvage therapies and should be considered for experimental therapies or palliation.

Lymphoblastic Lymphoma/Leukaemia

See ALL Guidelines.

HTLV-1 Associated ATLL

Consider inclusion in clinical trials

These guidelines were produced by the London ATLL group

1) Patients with ATLL should be treated with combination chemotherapy such as CHOP with zidovudine 250mg bd + IFN-α 3MIU 3/wk (Hodson et al, 2011). The ZDV/IFN-α should be started during the first week of chemotherapy. It is unclear whether pegylated IFN should be recommended but it has been used. A worldwide meta-analysis suggested that leukaemic phases of ATL may be treated effectively with ZDV/IFN-α (and the omission of chemotherapy) (Bazarbachi et al, 2010).

2) G-CSF should be co-administered as required.

3) Intrathecal therapy recommended routinely.

4) Prophylaxis against opportunistic infections including PCP, Cryptococcus and HSV/HZV. Screen/empirically treat for Strongyloidiasis (ivermectin if positive serology). Monitor CMV PCR.

5) Assessment for allogeneic SCT at outset (and tissue type patient and siblings).

6) Restage after 4 cycles to continue to a maximum of 6 cycles of CHOP

7) Maintenance arms (if not for transplant) would contain zidovudine 250mg + IFN-α. Dose of interferon may be increased from 3MIU 3/wk to maximum 9 MIU od.

8) Indefinite duration of maintenance (if do not proceed to allogeneic SCT).

9) Patients with disease not responding to CHOP chemotherapy should be changed to second-line, non-cross resistant therapy (ESHAP). The outlook in these patients is poor (>90% mortality at 6 months). The use of anti-CD25 antibody or other agents should be considered.
Blood counts, liver function tests should be regularly monitored when on antiviral therapy.

**Primary CNS Lymphoma (PCNSL)**

*Consider inclusion in clinical trials*

Pathologically there may be one or more discrete intraparenchymal tumours (approx 15% cases) with or without CSF involvement, or there may be isolated meningeal disease as leptomeningeal lymphoma.

If patients are treated outside the setting of a clinical trial:

1) All patients should be offered chemotherapy as first line treatment if they are sufficiently fit. Chemotherapy should consist of a regimen that includes HD-MTX doses of $\geq 3000\text{mg/m}^2$ delivered over a maximum of 2-3 hours at intervals of not more than 2-3 weeks, with HD-Ara-C. The randomised IELSG32 study showed that 4 cycles of MATRIX (R-MTX/Ara-C/Thiotepa) was associated with CR, PFS and OS advantage. This is the recommended treatment for patients considered fit for intensive therapies.

2) Consolidation WBRT may be considered in patients who achieve CR with MTX-based chemotherapy. In patients under 60 years of age, WBRT should be offered to patients unless there is a significant neurocognitive deficit following chemotherapy. A number of studies are trying to address whether consolidation with BCNU/thiotepa-conditioned-PBSCT, can replace WBRT (IELSG32 results expected 2016). In patients aged 60 years or over, neurocognitive side-effects are more likely to outweigh potential benefits and WBRT should be reserved for/if relapse.

3) Dexamethasone is the treatment of choice for short-term palliation but should be avoided before biopsy.

4) Whole brain radiotherapy can provide effective palliation but should not be used as first-line therapy in patients who are sufficiently fit to receive chemotherapy because there is a high rate of relapse with a median survival of 12-18 months.

Chemotherapy recommendations (further details in Appendix 1).

1) 4 cycles of MATRIX (Rituximab (D-5, D0), MTX 3500mg/m$^2$ on d1 followed by cytarabine 2000mg BD on days 2 and 3, thiotepa D4) G-CSF d 8-14 recommended.

2) Patients not thought to be able to tolerate such therapy should receive up to 6 cycles of MTX 3500mg/m$^2$ every 2 weeks.
Patients in CR can be considered for BCNU/thiotepa-conditioned-PBSCT or WBRT bearing in mind neurocognitive side effects. Patients should be involved in this decision.

Generally if pts in CR
- <60yrs PBSCT probably recommended (although some centres offer WBRT upfront instead)
- >60 it is usually appropriate to defer radiotherapy until relapse.

Patients with residual disease post chemo should be offered RT bearing in mind possible side effects. The role of autografting these patients is being assessed presently in a number of UK centres.

Neurocognitive assessment at diagnosis, after treatment and at least annually afterwards should be performed. This ideally should be assessed by a clinical neuropsychologist but if not available, a MMSE should be recorded.

**Relapsed PCNSL**
*Consider inclusion in clinical trials*(TIER)*
Consideration for R-IIE regimen +/- PBSCT (using thiotepa/carmustine conditioning). This salvage regimen is well tolerated and effective in patients with relapsed disease.
Use of rituximab/dexamethasone/temozolamide may be considered

Consideration for WBRT in the RT-naïve patient. This is with palliative intent and may be associated with neurotoxicity in those previously treated with MTX-containing chemotherapy.

**Secondary CNS Lymphoma (SCNSL)**
*Consider inclusion in clinical trials*(IELSG42)*
Treatment options depend on whether secondary CNS lymphoma at diagnosis or at relapse and whether patients are eligible for an autograft.

At diagnosis (ie. CNS disease + evidence of untreated systemic disease)
R-MTX/Ara-C +/- thiotepa (MATRIX) or R-CODOX-M/R-IVAC, (or R-CHOP/HD-MTX), R-IIE. R-ICE or R-IDARAM x 2 courses and reassess with a view to further courses.

At relapse
R-HD-MTX/Ara-C x2 courses and reassess.
If a durable remission is obtained consideration should be given to a thiotepa/BCNU conditioned PBSCT.

Patients not fit enough for such intensive therapy should be considered for repeated courses of HDMTX (+ depocyte if meningeal disease).

Consideration for WBRT for palliation of symptomatic

*IDARAM is a regimen comprising idarubicin, dexamethasone, cytosine arabinoside and methotrexate*27. Each drug has properties that lend themselves to their use in CNS lymphoma. Idarubicin does not cross the blood-brain barrier like all anthracyclines, but its metabolite idarubinicol does. Systemic methotrexate and cytosine arabinoside are both capable of entering the CSF in cytotoxic quantities. This regimen is generally well tolerated, with significant CNS toxicity seen in about 15% patients.

**Post-Transplant Lymphoproliferative Disease (PTLD)**

*Consider inclusion in clinical trials*

This is a collection of clinically and pathologically diverse tumours associated with iatrogenic immunosuppression following transplantation. In the majority of cases tumourigenesis results from a defect in EBV-specific cytotoxic T-cell activity leading to uncontrolled EBV-driven outgrowth of latently infected B-lymphocytes.

Below are guidelines for patients with PTLD post solid organ transplantation. PTLD occurring after BMT should be discussed with the BMT team.

Reference to BCSH guidelines is recommended.
(http://www.bcshtaguidelines.com/documents/PTLD_mngmt_bjh_2_0710.pdf)

**Initial Management**

a) Reduce immunosuppression - produces tumour regression in 20-50% of cases though this may not be possible before other therapy is instituted if the patient is unwell.

b) Single agent Rituximab (the efficacy of this can be ‘predicted’ according to the ‘PTLD score’ (Choquet et al, 2007).

c) If localised disease, radiotherapy may be suitable.

If no response/aggressive disease consider:

a) CHOP-R (Trappe et al, 2012)
b) PMiTCEBO-R - a weekly chemotherapy regimen with continuous steroids for the first few weeks may be considered.\textsuperscript{28}

c) Adoptive immunotherapy with EBV-specific CTLs to selectively reconstitute EBV-driven immunity\textsuperscript{29} (via ctlbank (Aberdeen) at NSS.ctlbank@nhs.net).

Use of antivirals as treatment or prophylaxis is not recommended.
HODGKIN LYMPHOMA

Classification

Under the WHO Classification the nomenclature of Hodgkin’s Disease has been modified and is now known as Hodgkin Lymphoma.

There are 2 distinct entities:

- Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLPHL)
- Classical Hodgkin Lymphoma

Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLPHL)

1.1.16 Management of NLPHL

The management of NLPHL differs from that of classical Hodgkin Lymphoma.

**Localised, stage I_A disease** should be treated by radiotherapy. Where complete excision has occurred it may be reasonable to withhold radiotherapy but this is not our recommended practice at the current time.

**More advanced LPHL** i.e. stages II-IV should be treated as follows:

According to the guidelines for advanced classical Hodgkin Lymphoma with the addition of rituximab.

Adults unable to tolerate more intensive regimens CVP-R.

1.1.17 Relapsed disease

Relapse may occur after 10-15 years. It should be noted that NLPHL can relapse as a large cell lymphoma (12% transformation at 10 years), and it is therefore important to establish the histology of the relapse and accurately stage these patients. Rituximab has been reported to be effective in relapsed disease.²⁷
Classical Hodgkin Lymphoma

1.1.18  Management of Classical Hodgkin Lymphoma

GHSG risk factors

1. Clinical Risk Factors

- Large mediastinal mass, size at least one third of the maximum thorax diameter
- Extra-nodal disease*
- Involvement of three or more nodal areas (see 2 below)
- Elevated erythrocyte sedimentation rate (> 50 mm/h for stages IA, IIA and > 30 mm/h for stages IB, IIB)

2. Lymph Node Areas‡

- Area A: right cervical + right infra-/supra-clavicular/nuchal lymph nodes
- Area B: left cervical + left infra-/supra-clavicular/nuchal lymph nodes
- Area C: right/left hilar + mediastinal lymph nodes
- Area D: right axillary lymph nodes
- Area E: left axillary lymph nodes
- Area F: lymph nodes of the upper abdomen (spleen hilum, liver hilum, coeliac)
- Area G: lymph nodes of the lower abdomen
- Area H: right iliac lymph nodes
- Area I: left iliac lymph nodes
- Area K: right inguinal + femoral lymph nodes
- Area L: left inguinal + femoral lymph nodes

3. Early, Intermediate and Advanced Stages of Hodgkin Lymphoma

On the basis of the Ann Arbor staging criteria, the GHSG subdivides Hodgkin lymphoma patients into the following risk groups:

Early stages (early favourable)

- Stage IA (involvement of a single lymph node region or a single extra-nodal focus, no B-symptoms §) without risk factors
- Stage IB (involvement of a single lymph node region or a single extra-nodal focus, one or more B-symptoms) without risk factors
- Stage IIA (involvement of two or more lymph node regions or extra-nodal structures on the same side of the diaphragm, no B-symptoms) without risk factors
• Stage IIB (involvement of two or more lymph node regions or extra-nodal structures on the same side of the diaphragm, one or more B-symptoms) without risk factors

**Intermediate stages (early unfavourable)**

• Stage IA or IB and stage IIA with one or more risk factors
• Stage IIB, only if the risk factors ‘high ESR’ and/or ‘involvement of ≥ 3 lymph node areas’ are present but not if there is extra-nodal involvement and/or large mediastinal mass

**Advanced stages**

• Stage IIB with risk factors, extra-nodal involvement and/or large mediastinal mass
• Stage IIIA (involvement of lymph node regions on both sides of the diaphragm or extra-nodal involvement with or without nodal involvement, no B-symptoms)
• Stage IIIB (involvement of lymph node regions on both sides of the diaphragm or extra-nodal involvement with or without nodal involvement, with one or more B-symptoms)
• Stage IV A (disseminated involvement of one or more extra-lymphatic organs with or without nodal involvement, no B-symptoms)
• Stage IVB (disseminated involvement of one or more extra-lymphatic organs with or without nodal involvement, with one or more B-symptoms)

* Extra-nodal involvement is defined as localised involvement of an extra-lymphatic tissue (by continuous growth from an involved lymph node or in close anatomic relation) that is treatable by irradiation.

‡ Please note: The definition of lymph node areas for the definition of risk factors does not correspond to the Ann Arbor definition of lymph node regions.

§ B-symptoms include: unexplained fever >38°C, drenching night sweats, unexplained weight loss > 10% of body weight within the last 6 months.

*Treatment of localised disease i.e. stage I_A-II_A (and some cases of IIB without mediastinal bulk and extranodal disease)*

Off study the recommendation for favourable localised disease without adverse risk factors a) large mediastinal mass, b) extranodal disease c) elevated ESR (>50mm/hr without B symptoms or >30mm/hr with B symptoms) d >2 involved regions) is now considered to be 2 courses of ABVD chemotherapy with 20Gy involved site radiotherapy (ISRT)* as consolidation.

Off study the recommendation for unfavourable localised disease is ABVDx4 +30Gy ISRT*.
*For females under 35 years of age with mediastinal or axillary involvement consideration can be given to using 4-6 courses ABVD with no radiotherapy. The exact number of courses needs to be defined.

The decision to omit radiotherapy from the management of IA/IIA non-bulky patients should involve discussion with a radiation oncologist. Patients choosing to omit radiotherapy need to be aware of the balance of risks between radiation and additional cycles of chemotherapy and the increased risk of early relapse (3-7%) if radiotherapy is omitted.

In the RAPID study radiotherapy was omitted on the basis of a negative PET scan (Deauville 1 and 2) after 3 courses in patients without mediastinal bulk. Although this approach was not shown to be non inferior to consolidation radiotherapy the 3yr PFS was excellent 91% vs 95% with RT

Radiotherapy should not normally be omitted in patients presenting with bulk disease.

Treatment of Advanced Disease i.e. Stages IIb-IV
The treatment of anatomically advanced Hodgkin lymphoma is chemotherapy.
The preferred approach is to start with ABVD in patients with all Hasenclever scores rather than using Escalated BEACOPP in those with high Hasenclever score (4+). Patients with a negative PET scan (Deauville 1, 2, 3) after 2 cycles of ABVD should receive 4 further courses of AVD. Those with a positive PET scan (Deauville 4 or 5) after 2 cycles can be escalated to receive Esc BEACOPP x4.

The decision whether to give consolidation radiotherapy should be made at the outset. Consolidation radiotherapy is not indicated for patients in CR by CT following ABVD or those with residual masses >2.5cm if on metabolic CR after Esc BEACOPP. It is uncertain whether RT can be omitted if metabolic CR is achieved after ABVD but it is our general practice.

Young fit patients with advanced stage disease with residual PET avid lesions following ABVD are usually recommended to undergo salvage chemotherapy and stem cell transplantation rather than radiotherapy.
Negative end-of-treatment 18F-FDG PET has a 96% negative predictive value for progression or early relapse in advanced-stage disease.

The positive predictive value is less reliable, with false-positives occurring because of infection, inflammation, increased uptake of 18F-FDG in brown fat, and reactive changes after treatment. Thus, to ascertain whether relapse has occurred, histological evidence is preferable to 18F-FDG PET alone. If biopsy is difficult and interval scan should be performed for progression.

Older patients and patients not fit for anthracycline
If older and fit enough use ABVD but caution with G-CSF because of the increased risk of lung toxicity. Omission of bleomycin and concomitant use of G-CSF is another option.

Consideration to VEPEMB chemotherapy or ChlVPP chemotherapy +/- radiotherapy.

Escalated BEACOPP is not clearly better than ABVD in pts over 60 (all Hasenclever scores) and should not be used.

Frail patients can be managed with the SHAMASH regimen or single agent chemotherapy with steroid/chlorambucil/procarbazine.
Advanced disease stage IIB-IV

2 x ABVD

PET negative
(Deauville 1-3)

PET positive
(Deauville 4, 5)

4 x AVD

PET positive

PET negative

Consider salvage or RT
(if significant residual
PET avid mass and not
suitable for salvage)

Esc BEACOPP x 3

Esc BEACOPP x 1
1.1.19 Primary Resistant and Relapsed Hodgkin lymphoma

Patients with advanced Hodgkin lymphoma not in CR after standard chemotherapy or who achieve CR but relapse within 5 years of initial treatment should:

1) have a baseline PET/CT scan
2) have tissue typing undertaken (as well as tissue typing of any sibs who could potentially be donors) and
3) receive 2 courses of ESHAP (IVE if over 60 or renal impairment) or IGEV chemotherapy.

Patients who are PET negative (Deauville 1-3) following the first 2 cycles of salvage should have stem cells harvested providing the bone marrow is clear, and go on to receive high dose therapy with a BEAM autograft with radiotherapy to residual masses.

If patients have achieved a CR following the first 2 cycles of salvage ESHAP mobilisation can be done following cyclophosphamide + G-CSF.

Patients who are PET positive (Deauville 4 and 5) and non-progressive following the first 2 cycles of ESHAP should proceed to 2nd line salvage. If mCR obtained they can proceed to autologous transplant however if they fail to achieve mCR fit patients should be lined up for a reduced intensity allograft provided the response is sufficient and non progressive and a donor can be found.

Those with disease unresponsive to first line salvage with ESHAP (if >60 IVE) or IGEV should receive brentuximab vedotin x 3. If response sufficient to proceed to transplant autologous stem cells can be collected or a 4th dose given whilst the donor is prepared. MiniLEAM can be used if failure following brentuximab. Other alternatives include single agent gemcitabine or bendamustine or checkpoint inhibitors if available. Consideration should be given to the addition of rituximab if RS cells CD20+.

Patients relapsing after 5 years should be discussed as transplantation may not always be necessary.
Chemotherapy failures: NR/PR or relapse < 5 years

ESHAP (IVE if >60)/IGEV x2

PET- (mCR) PET+ (PR/SD/PD)

LEAM or BEAM

mCR Brentuximab x3

PBSCT

Radiotherapy to residual

PR Progressive

Reduced intensity allograft

miniLEAM

(Gemcitabine bendamustine immune checkpoint blockade)
APPENDICES

Appendix 1: Chemotherapy Regimens

It should be noted that the protocols provided here are for guidance only. In all cases, local policy regarding prescription and administration of cytotoxic agents must be followed. (See local chemotherapy protocols for details of drug administration).

1.1.20 R-CHOP-21 (R-CHOP-14)

Cycle to be repeated at 21 (or 14) day intervals

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose/Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>375mg/m$^2$ IV</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>750 mg/m$^2$ iv day 1</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>50 mg/m$^2$ iv day 1</td>
</tr>
<tr>
<td>Vincristine</td>
<td>1.4 mg/m$^2$ (max 2 mg) iv day 1</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>100 mg po days 1-5</td>
</tr>
</tbody>
</table>

R-CHOP14

Add septrin prophylaxis and pre-emptive G-CSF

Mini-CHOP-R (patients aged over 80 years)$^{42}$

Cycle to be repeated at 21 day intervals

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose/Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>375mg/m$^2$ IV</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>400mg/m$^2$ IV bolus on day 1</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>25mg/m$^2$ IV bolus on day 1</td>
</tr>
<tr>
<td>Vincristine</td>
<td>1mg flat dose IV infusion on day 1</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>40mg/m$^2$ PO days 1 to 5 inclusive</td>
</tr>
</tbody>
</table>

1.1.21 R-CVP

Cycle to be repeated at 21 day intervals

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose/Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>375mg/m$^2$ iv day 1</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>750 mg/m$^2$ iv day 1</td>
</tr>
<tr>
<td>Vincristine</td>
<td>1.4 mg/m$^2$ (max 2 mg) iv day 1</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>100 mg po days 1-5</td>
</tr>
</tbody>
</table>
1.1.22  R-GCVP
Cycle to be repeated at 21 days intervals
Gemcitabine 750mg/m² IV D1 and D8 of each cycle

Gemcitabine escalated to 875mg/m² for cycle 2 and 1g/m² for subsequent cycles provided no haematological toxicity observed
G-CSF to be prescribed from day 9 for 7 days

1.1.23  PMitCEBO
Cycle to be repeated at 14-day intervals

- Mitoxantrone 7mg/m² iv day 1
- Cyclophosphamide 300mg/m² iv day 1
- Etoposide (VP16) 150mg/m² iv day 1
- Vincristine 1.4mg/m² (max 2mg) iv day 8
- Bleomycin 10,000IU/m² iv (bolus) day 8
- Prednisolone 50 mg/day week 1-4
  then 50 mg alt days weeks 5-treatment end

Cotrimoxazole 960 mg bd Mon, Wed, Fri from week 1 until 2 weeks after treatment end (or follow local practice guidelines)

1.1.24  Rituximab/ Fludarabine/Cyclophosphamide
Cycle to be repeated at 28-day intervals

- Rituximab 375mg/m² iv infusion day 1
- Fludarabine 40mg/m² po days 2,3,4
- Cyclophosphamide 250mg/m² po days 2,3,4

Given as 28 day cycle.

Should oral administration not be possible, intravenous doses are fludarabine 25mg/m2 iv and cyclophosphamide 250mg/m² iv.

Supportive care with co-trimoxazole/pentamidine and aciclovir prophylaxis for at least 6 months post therapy is required. All blood products should be irradiated.
## 1.1.25 NORDIC MCL2 Protocol

### NORDIC MCL-2
Cycle length = 21 days for 6 cycles
Alternating cycles of MAXI-CHOP and HD cytarabine with Rituximab from cycle 1

### MAXI-CHOP total of 3 cycles to be given

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage &amp; Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide IVI</td>
<td>1200mg/m² on Day 1</td>
</tr>
<tr>
<td>Doxorubicin IVB</td>
<td>75mg/m² on Day 1</td>
</tr>
<tr>
<td>Vincristine IVI</td>
<td>1.4 mg/m²; max 2 mg on Day 1</td>
</tr>
<tr>
<td>Prednisolone PO</td>
<td>100mg OM Days 1 to 5</td>
</tr>
<tr>
<td>Rituximab IVI</td>
<td>375mg/m² on Day 1 from Cycle 1 onwards</td>
</tr>
</tbody>
</table>

### High Dose Cytarabine total of 3 cycles to be given

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage &amp; Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytarabine IVI</td>
<td>3g/m² BD (every 12hours) on Day 1 &gt;60y 2g/m²</td>
</tr>
<tr>
<td>Cytarabine IVI</td>
<td>3g/m² BD (every 12hours) on Day 2 &gt;60y 2g/m²</td>
</tr>
<tr>
<td>Rituximab IVI</td>
<td>375mg/m² on Day 1 from Cycle 2 onwards</td>
</tr>
<tr>
<td>Rituximab IVI</td>
<td>375mg/m² on Day 9 from Cycle 6 ONLY</td>
</tr>
</tbody>
</table>

### Supportive care drugs Suggested Dosage & Frequency or as per local policy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage &amp; Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allopurinol PO</td>
<td>300mg OM</td>
</tr>
<tr>
<td>NB: Rasburicase can be considered for patients with high tumour burden</td>
<td></td>
</tr>
<tr>
<td>Aciclovir PO</td>
<td>200mg PO QDS</td>
</tr>
<tr>
<td>Fluconazole PO</td>
<td>400mg OM</td>
</tr>
<tr>
<td>Co-trimoxazole PO</td>
<td>960mg OD on M/W/F</td>
</tr>
<tr>
<td>Lansoprazole PO</td>
<td>30mg OM</td>
</tr>
<tr>
<td>Metoclopramide PO</td>
<td>20mg TDS 5 days prn</td>
</tr>
<tr>
<td>Ondansetron</td>
<td></td>
</tr>
</tbody>
</table>

### High Dose Cytarabine only

<table>
<thead>
<tr>
<th>Prednisolone 0.5% eye drops</th>
<th>Apply every 2 hours during waking hours</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Eye drops are started 6-12 hours before initiation of cytarabine infusion and continued for 3 days following the last dose of cytarabine.</td>
</tr>
</tbody>
</table>

| Dexamethasone PO | 4mg BD for 3 days |

G-CSF to be given with each cycle
Then cycle 6 to be used as stem cell mobilisation
1.1.26  **R-HAD+B**

Treatment is repeated every 21 days for 4 cycles

- **Dexamethasone**: 40 mg daily days 1-4
- **Bortezomib**: 1.5mg/m² IVB day 1 and 4
- **Cytarabine**: 2000mg/m² (<60y); 1000mg/m² (≥60y) IVI day 2 and 3
- **Rituximab**: 375 mg/m² administered on day 0 of every treatment cycle for those patients who are not refractory to prior rituximab containing regimens

1.1.27  **Bortezomib**

Repeat every 21 days for up to 8 cycles

- **Bortezomib**: 1.3mg/m² SC on days 1, 4, 8 and 11

1.1.28  **CODOX-M**

- **Cyclophosphamide**: 800mg/m² iv day 1
- **Vincristine**: 1.5mg/m² (max 2mg) days 1 and 8
- **Doxorubicin**: 40mg/m² iv day 1
- **Cytarabine**: 70mg *intrathecal* days 1 and 3
- **Cyclophosphamide**: 200mg/m² iv daily days 2-5
- **Methotrexate**: 300mg/m² over 15minutes/1hr day 10
  - (>60yrs 100mg/m²)
  - 2700mg/m² over 3 hours/23hrs
  - (>60yrs 900mg/m²)

(For folinic acid rescue; methotrexate levels; hydration and urinary alkalinisation schedules follow local protocol)

- **Methotrexate**: 12mg *intrathecal* day 15
- **G-CSF**: 5mcg/kg sc daily from day 13 until neutrophil recovery

If rituximab is to be given: 375mg/m² on days 1 and 10 of each course and see below.
1.1.29  IVAC

**Etoposide**  
60mg/m² iv daily  
days 1-5

**Ifosfamide**  
1500mg/m² iv daily over 1 hour days 1-5  
(>60yrs 1000mg/m²)

**Mesna**  
360mg/m² mixed with each ifosfamide dose}  
and 2520mg/m² iv by continuous 23hr infusion} days 1-5  
(Nb Mesna doses may differ from trust to trust)

**Cytarabine**  
2000mg/m² iv twice daily  
days 1 and 2  
(>60yrs 1000mg/m²)

**Methotrexate**  
12mg *intrathecal*  
day 5

**G-CSF**  
5mcg/kg sc daily  
from day 7  
until neutrophil recovery

If rituximab is to be given: 375mg/m² on day 1 of each course and see below.

For patients receiving 2 courses of R-CODOX-M/IVAC two further doses of rituximab should be administered on Day 21 and 42 after day one of the final course of IVAC to bring the total of rituximab infusions to 8.

**NB** The CODOX-M and IVAC regimens in this policy are for fit adults younger than 60.  
Dose adjustments in brackets for patients >60yrs.

1.1.30  Anti Helicobacter pylori therapy (suggested):

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Frequency</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>1 gm</td>
<td>bd</td>
<td>7 days</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>500mg bd</td>
<td></td>
<td>7 days</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>30mg</td>
<td>bd</td>
<td>7 days</td>
</tr>
</tbody>
</table>

If penicillin sensitivity substitute metronidazole 400mg bd for 7 days for amoxicillin
If macrolide intolerant substitute metronidazole 400 mg bd for 7 days for clarithromycin

* or as according to local policy

Second line anti-Helicobacter therapy should be discussed with a gastroenterologist after culture and sensitivities assessed at a reference centre
1.1.31  MATRIX chemotherapy

Repeat every 21 days for 4 cycles

**Rituximab 375mg/m² IV infusion day -5 and day 0**

- Methotrexate 500mg/m² IV infusion over 15 mins followed by
- Methotrexate 3000mg/m² IV infusion over 3 hours on day 1
- Cytarabine 2000mg/m² IV infusion over 1 hour BD on days 2 and 3 (4 doses in total)
- Thiotepa 30mg/m² iv day 4

*(For folinic acid rescue; methotrexate levels; hydration and urinary alkalinisation schedules follow local protocol)*

G-CSF is recommended from day 8 to day 14

1.1.32  R-IE

- Rituximab 375mg/m² IV day 1
- Etoposide 250mg/m² IV day 1
- Mesna 400mg/m² pre each Ifosfamide dose
- Ifosfamide + mesna 2000mg/m² IV days 1-3
- Mesna post Ifosfamide 1200mg/m² days 1-3

1.1.33  IDARAM

- Methotrexate 12.5mg intrathecal day 1 (Routine in course 1 only. see below)
- Idarubicin daily 10mg/m² IV days 1 and 2
- Dexamethasone 100mg daily IV infusions of 12h duration days 1-3
- Cytarabine daily 1000mg/m² IV over 1 hour days 1 and 2
- Methotrexate 2000mg/m² IV over 2 hours day 3

*(For folinic acid rescue; methotrexate levels; hydration and urinary alkalinisation schedules follow local protocol)*

Intrathecal Therapy:

All patients will receive intrathecal chemotherapy on day 1. CSF will be analysed for lymphomatous involvement by flow cytometry. Further intrathecal injections are not recommended unless the disease is largely leptomeningeal as the IDARAM chemotherapy will cross into the CSF. In the case of LM disease intrathecal methotrexate can be repeated with each course. **Patients who have a clear CSF from the outset will therefore receive only one intrathecal injection on day 1.**
Concomitant Medication: Patients should receive pegfilgrastim 6mg s.c. on day 5 of each cycle or G-CSF from D7.

Hodgkin protocols

1.1.34 ABVD

(Treatment interval 28 days)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td>25mg/m²</td>
<td>iv</td>
<td>days 1,15</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>10,000IU/m²</td>
<td>iv</td>
<td>days 1,15</td>
</tr>
<tr>
<td>Vinblastine*</td>
<td>6mg/m²</td>
<td>iv</td>
<td>days 1,15</td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>375mg/m²</td>
<td>iv</td>
<td>days 1,15</td>
</tr>
</tbody>
</table>

* Dose should be capped at 10mg

1.1.35 CHLVPP

Chlorambucil 6mg/m² (max 10mg) orally once each day on days 1 to 14 inclusive
Vinblastine 6 mg/m² (max 10 mg) IV infusion once each day on day 1 and 8
Procarbazine 100mg/m² (max 150mg) orally once each day on days 1 to 14 inclusive
Prednisolone 40mg/m² (max 60mg) orally once each day on days 1 to 14 inclusive

Repeat course every 28 days, maximum 8 cycles
1.1.36 VEPEMB
(from the SHIELD Study www.shieldstudy.co.uk)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vinblastine</td>
<td>6mg/m² (max 10mg)</td>
<td>iv</td>
<td>day 1</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>500mg/m²</td>
<td>iv</td>
<td>day 1</td>
</tr>
<tr>
<td>Procarbazine</td>
<td>100mg/m²</td>
<td>po</td>
<td>days 1-5</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>30mg/m²</td>
<td>po</td>
<td>days 1-5</td>
</tr>
<tr>
<td>Etoposide</td>
<td>60mg/m²</td>
<td>po</td>
<td>days 15-19</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>6mg/m²</td>
<td>iv</td>
<td>day 15</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>10,000IU/m²</td>
<td>iv</td>
<td>day 15</td>
</tr>
</tbody>
</table>

Cycle is repeated every 28 days for up to 6 cycles.

**Dose variation:** Because of available tablet dose (Procarbazine and Etoposide) it frequently occurs that the exact dose per square metre is not possible. It is recommended to use the higher dose where possible.

Chemotherapy Schedule Modifications
Dose decisions to be made on Day 1 and 15 of each course. The aim is to give full doses rather than dose reductions.

1) Granulocyte count > 2.0 x 10⁹/l and/or platelet count > 100 x10⁹/l give full dose.
2) Granulocyte count 1.0 – 2.0 x 10⁹/l and/or platelet count 50-100 x 10⁹/l, delay 1 week and give G-CSF support.
3) Granulocyte count <1.0 x 10⁹/l and/or platelet count < 50 x 10⁹/l, delay until granulocytes > 2.0 x 10⁹/l. Give G-CSF support to minimise delay.

In patients where granulocyte count remains chronically reduced (<2.0 x 10⁹/l) in spite of growth factor support, proceed with 50% reduction of all drugs except prednisolone and bleomycin.

Pilot data indicates that G-CSF support is necessary to maintain dose intensity, but this is variable in the number of days per course in individual patients. It increases as the patient proceeds through the protocol. If G-CSF is to be used, utilise between days 7 to 15 and days 21 to 28 of the monthly schedule.
1.1.37 Escalated dose BEACOPP

Esc BEACOPP

Cycles of BEACOPP are 22 days each

B Bleomycin 10,000IU/m² iv/im day 8
E Etoposide 200mg/m² iv days 1-3
A Adriamycin 35mg/m² iv day 1
C Cyclophosphamide 1250mg/m² iv day 1
O Vincristine 1.4mg/m² (max 2mg) iv day 8
P Procarbazine 100mg/m² po days 1-7
P Prednisone 40mg/m² po days 1-14

First day of next cycle = day 22

4 cycles of escalated dose BEACOPP are to be considered in patients with a Deaville score 4/5 on PET CT after 2 cycles of ABVD

1.1.38 Baseline BEACOPP

Doxorubicin is 25mg/m²
Cyclophosphamide is 650mg/m²
Etoposide is 100mg/m²
Rest of the doses are the same

Mandatory concomitant treatment with escalated dose BEACOPP:

1) MESNA 250mg/m² prior to the cyclophosphamide infusion, then mesna 500mg/m² orally at 2 hours and 6 hours after the cyclophosphamide infusion. Patients should drink ≥ 2.5 l on this treatment day.

2) G-CSF prophylaxis from day 8 until leucocyte recovery. G-CSF prophylaxis for baseline BEACOPP is optional.

Rituximab in salvage regimens

Rituximab is given on D1 (prior to chemotherapy) and one dose just after completion of chemotherapy i.e. d4 5 6 or 7 for 1st and subsequent cycles, i.e. 2 doses of rituximab with each course of salvage chemotherapy (if not received rituximab in last 6 months).
1.1.39 ESHAP +/-R

Etoposide (VP16) 40mg/m² iv days 1-4
Methylprednisolone 500mg iv days 1-5
Cytarabine 2000mg/m² iv day 1
Cisplatin 25 mg/m² iv (continuous infusion) days 1-4

Growth factor support is optional with first cycle. For mobilisation, refer to local mobilisation policy.

Methylprednisolone may be changed to oral (equivalent dosing) for patient choice.

Patients with renal impairment or who are thought not able to tolerate Cisplatin, the option to switch to Carboplatin is available (ESHAC). Carboplatin dosed at AUC5 over 1 hour on day 1.

1.1.40 IGEV

Vinorelbine 20mg/m² IV infusion day 1
Gemcitabine 800mg/m² IV infusion days 1 and 4
Ifosfamide 2000mg/m² IV infusion days 1 to 4
Mesna 2600mg/m² IV infusion over 24 hours concurrently with ifosfamide days 1 to 4
Mesna 2600mg/m² IV infusion over 12 hours day 5
Prednisolone 100mg OD PO days 1 to 4

G-CSF from days 7 to 12 of each course.

For mobilisation, refer to local mobilisation policy.

1.1.41 IVE +/-R

Ifosfamide 3000mg/m² iv days 1-3
VP16 (etoposide) 200mg/m² iv days 1-3
Epirubicin 50 mg/m² iv day 1

Mesna 1600mg/m² iv 15 mins prior to ifosfamide infusion, then 2400mg/m² mesna in 1litre normal saline over 24 hours, repeated for 3 days in total. (Dosing of mesna may differ from trust to trust).

Phenytoin prophylaxis 300mg po nocte may be given at discretion of treating physician.

Growth factor support is optimal with first 2 cycles of chemotherapy.

For mobilisation after 3rd cycle, refer to local mobilisation policy.
1.1.42 Mini-BEAM +/-R

30 minutes prior to Carmustine give anti-emetics and chlorphenamine 10mg iv.

Day 1  Carmustine  60mg/m\(^2\)  od iv over 1 hour  
Days 2, 3, 4, 5  Cytarabine  100mg/m\(^2\)  bd iv over 30 minutes  
Days 2, 3, 4, 5  Etoposide  75mg/m\(^2\)  od iv over 1 hour  
Day 6  Melphalan  30mg/m\(^2\)  od iv over 30 minutes  

N.B

In the event of carmustine supplies becoming limiting, oral lomustine (CCNU) at 2/3 of the dose of carmustine can be substituted (e.g. 40mg/m\(^2\) Lomustine equivalent to 60mg/2Carmustine in Mini-BEAM). This dose has been used as part of the LACE protocol, which is similar to BEAM (Ref: Perz et al, BMT 2007)

1.1.43 R-ICE +/-R

3 cycles every 3 weeks

Day 1  Rituximab  375mg/m\(^2\)  od iv  
Rituximab given Day -2 and Day 1 of 1st cycle  
Day 1, 2, 3  Etoposide  100mg/m\(^2\)  od iv (in 500ml normal saline over 30-60 mins)  
Day 2  Carboplatin  max. 800mg  od iv (in 500ml 5% dextrose over 60 mins)  

Dose calculated as area under the curve (AUC 5), i.e 5 x [25 + creatinine clearance]

Day 2  Ifosfamide  5000mg/m\(^2\)  od iv in 3L 5% dextrose  
Mixed with an equal amount of mesna and administered as a continuous infusion over 24 hrs (total dose should be divided equally into 3 doses with each litre run over 8 hrs). Further mesna (iv or oral) should be continued for 6-12 hours.

G-CSF day 6-13 of each cycle (recommended cycles 1, 2, mandatory cycle 3)
1.1.44 R-DHAP +/-R

3 cycles every 3 weeks

Day 1  Rituximab  375mg/m²  od iv

Rituximab given Day -2 and Day 1 of 1st cycle

Day 1  Cisplatin  100mg/m²  od iv in 3L normal saline

Administered as a continuous infusion over 12 hrs (total dose should be divided equally into 3 doses in with each litre run over 4 hrs)

Day 3  Cytarabine  2000mg/m²  bd iv in 1L normal saline over 3 hrs

Doses separated by 1L of 4% glucose, 0.18% sodium chloride over 9 hrs

Day 1, 2, 3, 4  Dexamethasone  40mg  od iv/po

G-CSF day 6-13 of each cycle (recommended cycles 1, 2, mandatory cycle 3)

Hydration regimen for cisplatin

Pre hydration:  1L 0.9% saline + 20mmol KCl + 1gram MgSO₄ over 2hrs
               Mannitol 10% 500ml over 1hr

Cisplatin given as described above.

Post hydration:  1L 0.9% saline + 20mmol KCl + 1gram MgSO₄ over 4 hrs
               1L glucose 4%, saline 0.18% + 20mmol KCl + 1gram MgSO₄ over 6 hrs

Maintain urine output of at least 100mls/hr. If urine output < 100ml/hr, give frusemide 20-40mg iv

1.1.45 Bendamustine

Cycle to be repeated at 28-day intervals

Bendamustine 120mg/m² over 60minutes in 500mls N/S on days 1and 2.

Prophylaxis with aciclovir and co-trimoxazole should be used (and continued for at least 6 months post completion of therapy). Irradiated blood products are indicated.
1.1.46 GEM-P
Gemcitabine 1000mg/m² IV infusion on days 1, 8 and 15
Methylprednisolone 1000mg IV infusion on days 1-5
Cisplatin 100mg/m² IV infusion on day 15

28 day course, maximum 6 courses
Methylprednisolone may be switched to oral, to prevent patients having to attend as an outpatient (equivalent dosing)

1.1.47 Brentuximab
Cycle to be repeated at 21-day intervals, maximum of 16 cycles
  Brentuximab 1.8mg/kg IV (max 180mg) day 1

1.1.48 R-CCEP
Cycle to be repeated at 28- day intervals
  Rituximab 375mg/m² IV day 1
  Lomustine 80mg/m² po day 1
  Cyclophosphamide 100mg po od days 1-10
  Etoposide 100mg/m² po od days 1-5
  Prednisolone 60mg/m² po od days 1-14

1.1.49 R-GemOX
Cycle to be repeated at 14-day intervals. Up to 8 cycles
  Rituximab 375mg/m² IV day 1
  Gemcitabine 1000mg/m² IV day 2
  Oxaliplatin 100mg/m² IV day 2
1.1.51 GELOX regimen (every 21 days)

Gemcitabine 1000 mg/m$^2$ D 1 and 8
Oxaliplatin 130 mg/m$^2$ D 1
L-asparaginase 6000 IU/m$^2$ D 1-7

If patients develop grade 4 hematologic toxicity, then the doses of all chemotherapy drugs were reduced by 20% in all subsequent cycles.

After at least 2 cycles of GELOX, patients were referred for RT. Then, they received GELOX for 2 to 4 cycles within 1 week after the completion of RT, resulting in a maximum total of 6 cycles of GELOX.

Dose modifications outlined (Wang et al, Cancer 2012)

1.1.52 SMILE

Methotrexate 2000mg/m$^2$ IV over 3 hours day 1
Dexamethasone 40mg IV days 2-4
Etoposide 100mg/m$^2$ IV over 1 hour on days 2-4
Ifosfamide 1500mg/m$^2$ IV over 1 hour on days 2-4
Asparaginase E.Coli (Medac) 6000 U/m$^2$ IV on days 8, 10, 12, 14, 16, 18, 20.
An IV test dose before IV administration is recommended (1000 U IV as a short infusion 1 hour before the beginning of treatment).

G-CSF should be prescribed from day 6 until count recovery or successful harvest

May be repeated after 28 days or on full haematological recovery.

1.1.53 R-BAC

Rituximab (375 mg/m$^2$) intravenously [IV] on day 1
Bendamustine (70 mg/m$^2$) IV on days 2 and 3

Cytarabine (800mg/m$^2$) IV on days 2 to 4

Repeated every 28 days for four to six cycles
Appendix 2: Suggested regimen for CNS prophylaxis

Methotrexate 12.5 mg IT with each cycle of R-CHOP x 6
Systemic treatments including high dose Methotrexate/ Cytarabine

All patients with Burkitt Lymphoma should receive CNS prophylaxis with both intrathecal and high-dose systemic chemotherapy, as the observed incidence of CNS relapse without prophylaxis is about 20%. Recommended treatment is RCODOX-M/RIVAC which contains methotrexate and cytarabine intrathecal therapy and high-dose systemic chemotherapy with methotrexate and cytarabine.

There is no evidence to support routine use of CNS prophylaxis in any patients with low-grade lymphoma.

For aggressive lymphomas, the incidence of CNS relapse is around 5%. Although this is a relatively low incidence, the outcome of patients suffering a CNS relapse is very poor; 2-4 months median survival. Amongst the aggressive lymphomas, there is an increased risk with the blastoid variant of mantle cell lymphoma and ATLL and possibly NK cell lymphoma and primary mediastinal B-cell lymphoma.

Anatomical sites where involvement by lymphoma is associated with a higher risk of CNS relapse include:
Testis
Breast
Epidural space
Kidney/adrenal

Multivariate analyses support a raised LDH and involvement of more than 1 extranodal site as strongest predictors of subsequent CNS relapse. A high or intermediate-high IPI score also increases the risk.
Methods of delivery of CNS therapy include:

a) Direct introduction via lumbar puncture or centrally placed Ommaya reservoir (suggested doses for administration via Ommaya reservoir: methotrexate 12mg; cytarabine 50mg; liposomal cytarabine (Depocyte) 50mg.)

b) High-dose systemic chemotherapeutic agents that penetrate into CSF, e.g. methotrexate, cytarabine

c) Standard dose chemotherapy that can penetrate CSF, e.g. ifosfamide, idarubicin. Limited data but effective in treatment of CNS lymphoma

d) Cranial or cranio-spinal radiotherapy. Not usually used as prophylaxis except in rare cases to reduce risk of direct extension/invasion into CSF

Current recommendations are that CNS prophylaxis should be given to patients with:

a) Evidence of lymphoma at any of the above sites

b) Raised LDH and involvement of more than 1 extranodal site (15% of all DLBCL).

Flow cytometry of CSF may become a standard staging procedure. There is a 10x increase in incidence of patients with CNS disease by flow cytometry than conventional morphology.
**Appendix 3: Maximum Anthracycline doses**

The following recommendations are for adult patients and are based on information from various sources, including the drug manufacturers and the references below.

They are typically based at or below the cumulative dose at which the incidence of chronic cardiotoxicity has been shown to reach 5%.

Also included is one possible method of calculating the anthracycline exposure of a patient who has received two or more different anthracyclines.

Table 1 - Recommended cumulative maximum anthracycline doses

<table>
<thead>
<tr>
<th>Drug</th>
<th>Maximum recommended cumulative dose (mg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daunorubicin¹</td>
<td>600</td>
</tr>
<tr>
<td>Doxorubicin²³</td>
<td>450</td>
</tr>
<tr>
<td>Epirubicin⁴</td>
<td>900</td>
</tr>
<tr>
<td>Idarubicin – IV⁵</td>
<td>150</td>
</tr>
<tr>
<td>Idarubicin – PO⁶</td>
<td>400</td>
</tr>
<tr>
<td>Mitoxantrone⁷</td>
<td>160</td>
</tr>
</tbody>
</table>

NB Aside from the cumulative anthracycline dose, other risk factors for cardiotoxicity should be taken into account. These include any underlying cardiovascular disease, prior mediastinal irradiation and older age.

**Example calculation:**
A patient with NHL has previously received 6 x CHOP-R and 2 x IVE.
How much of their anthracycline “allowance” have they used?

6 x CHOP-R = 6 x 50mg/m² doxorubicin

= 300mg/m² doxorubicin

= ~ 2/3 cumulative anthracycline allowance

2 x IVE = 2 x 50mg/m² epirubicin

= 100mg/m² epirubicin

= ~ 1/9 cumulative anthracycline allowance

Total = 2/3 + 1/9

= ~ 7/9 of anthracycline allowance

Patient has around ~ 2/9 of their cumulative anthracycline allowance left.
Table 2 - Commonly used haematology chemotherapy regimens and their anthracycline content:

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Anthracycline</th>
<th>Dose per course (mg/m²)</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABVD</td>
<td>Doxorubicin</td>
<td>50</td>
<td>Per 28 day cycle</td>
</tr>
<tr>
<td>AML 17 AIDA Induction</td>
<td>Idarubicin (IV)</td>
<td>48</td>
<td>AML 17</td>
</tr>
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<td>AML 17 AIDA 1st Consolidation</td>
<td>Idarubicin (IV)</td>
<td>20</td>
<td>AML 17</td>
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<td>AML 17 AIDA 2nd Consolidation</td>
<td>Mitoxantrone</td>
<td>50</td>
<td>AML 17</td>
</tr>
<tr>
<td>AML 17 AIDA 3rd Consolidation</td>
<td>Idarubicin (IV)</td>
<td>12</td>
<td>AML 17</td>
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<tr>
<td>Baseline BEACOPP</td>
<td>Doxorubicin</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>CHOP</td>
<td>Doxorubicin</td>
<td>50</td>
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<tr>
<td>CODOX-M</td>
<td>Doxorubicin</td>
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<td></td>
</tr>
<tr>
<td>D(90)A 3+10</td>
<td>Daunorubicin</td>
<td>270</td>
<td>AML 17</td>
</tr>
<tr>
<td>D(60)A 3+10</td>
<td>Daunorubicin</td>
<td>180</td>
<td>AML 17</td>
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<td>DA 3+8</td>
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<td>DA 2+5</td>
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<td>Hyper-CVAD</td>
<td>Doxorubicin</td>
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<td>IVE</td>
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<td>Doxorubicin</td>
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<tr>
<td>MiDAC</td>
<td>Mitoxantrone</td>
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<td>AML 17</td>
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<tr>
<td>PAD</td>
<td>Doxorubicin</td>
<td>36</td>
<td>PADIMAC</td>
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<tr>
<td>PMitCEBO</td>
<td>Mitoxantrone</td>
<td>7</td>
<td>Each 2-week cycle</td>
</tr>
<tr>
<td>Stanford V</td>
<td>Doxorubicin</td>
<td>25</td>
<td>Each 2-week cycle</td>
</tr>
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<td>Daunorubicin</td>
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<td>UKALL 14</td>
</tr>
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<td>UKALL 2011 Regimen A Delayed Intensification</td>
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<tr>
<td>Z-DEX</td>
<td>Idarubicin (PO)</td>
<td>40</td>
<td></td>
</tr>
</tbody>
</table>

References

1) Daunorubicin. Summary of Product Characteristics. Winthrop pharmaceuticals, June 2010
6) Zavedos capsules. Summary of Product Characteristics. Pharmacia, November 2010
Appendix 4: Late toxicity evaluation

The 30-year cumulative incidence of heart disease among adult survivors receiving 40-45 Gy of extended-field or mantle RT is approximately 30%; the incidence of second cancers is similar. Contemporary involved-field RT reduces irradiated volumes and produces significant reductions in normal tissue dose compared with historic treatments, thus significantly reducing the associated risks.

Cardiovascular dysfunction

Radiation produces dose-dependent cardiac damage. Coronary artery disease is the most common form of cardiac morbidity, accounting for approximately 40%-50% of adverse cardiac events. Valvular disease is less common, typically has a late onset (> 10 years after RT), and is related to higher doses (> 30 Gy) or young age at treatment. Anthracyclines (e.g. doxorubicin) are particularly noted to cause a cardiomyopathy with heart failure. It is recommended that the maximum cumulative dose is not exceeded, although some patients develop cardiomyopathy at lower doses. For example: Doxorubicin 450mg/m$^2$, Mitoxantrone 160mg/m$^2$, Epirubicin 900mg/m$^2$ idarubicin IV 150mg/m$^2$ (see appendix 3).

Cardiac status should be assessed in symptomatic patients who have received mediastinal radiation or anthracycline therapy. Patients should be assessed for cardiovascular risk factors and if elevated (e.g. blood pressure, lipids) treated accordingly. The incidence of coronary heart disease and valvular disease are also increased in recipients of chemotherapy/radiotherapy.

Cerebrovascular dysfunction

In patients who have received radiotherapy to the neck/mediastinum, Carotid Doppler studies should be performed in symptomatic patients and asymptomatic patients with evidence of a carotid bruit. Risk factors (e.g. blood pressure and serum lipids) should be monitored and, if elevated, treated appropriately.

Pulmonary dysfunction

Drugs, especially bleomycin (especially at cumulative dose greater than 300,000IU), busulphan, cyclophosphamide and carmustine, and radiotherapy can cause pulmonary fibrosis. Pulmonary function tests including spirometry and diffusion capacity should be performed in symptomatic patients treated with any of these agents. Referral to a respiratory physician should be considered, and in severe cases heart, lung or heart/lung transplantation may be appropriate.
Second malignancy

Chemotherapy for lymphoma is associated with an increased risk of myelodysplasia and acute myeloid leukaemia arising some 2-7 years later, often with cytogenetic abnormalities of chromosomes 5, 7 or 12. Secondary leukaemia related to etoposide tends to occur early, after 2-3 years, whereas leukaemia related to alkylating agents tends to occur 5-7 years later.

Chemotherapy is also associated with an increased risk of second solid tumours, although previous radiotherapy is the greater risk factor. Young women (<25 years) whose breasts have been incidentally irradiated have been shown to have a greatly increased risk of developing breast cancer. Patients fall into three risk groups, the highest risk patients are those who received radiotherapy in their teens (when the breast was developing), the second group are those in their 20s who did not have children prior to development of the disease and the third, lowest risk, group are those who have had children prior to diagnosis. Early referral to a breast screening programme is strongly advised for any woman < 35 years who has received radiotherapy to the mediastinal or surrounding area. These patients should be counselled and the DoH recommends entry into a breast screening programme, from 8 years after radiotherapy or by age 30, whichever comes later. This involves annual MRI imaging between the ages of 30-39, annual MRI +/- mammography between ages 40-49, and annual mammography +/- MRI after the age of 50. The need for an annual MRI is reviewed yearly based on the background density of the breasts.

The absolute risk of colorectal cancer among HL survivors is increased, although the onset of this risk is delayed compared with breast cancer. Some expert groups recommend that patients who received abdominal RT doses ≥ 25 Gy (eg, for para-aortic RT) should consider colorectal cancer screening 10 years after treatment or by age 35, whichever comes later.

Endocrine and metabolic disorders

Various combinations of chemotherapy, cranial irradiation (CI) and/or bone marrow transplantation after total body irradiation (BMT/TBI) will result in several late endocrine and metabolic complications, particularly in adult survivors of childhood NHL. Investigations should include IGF1, TFTs, testosterone (in males if symptomatic or if radiotherapy to the brain or testes). Vitamin D levels should be checked and replacement therapy initiated if low to reduce the risks of osteoporosis. Dexascan should be performed at baseline in female patients who have undergone premature menopause, male patients with hypogonadism and patients who have been treated with TBI and long terms steroids. Follow up scans will depend
upon the baseline result and should not be repeated more than every 2 years. Further guidance is available in the National Osteoporosis Guidelines.

**Follow-up for patients with concerns about sexual function/fertility**

Males: Consider semen analysis in men wishing to father children. Recovery of fertility in patients rendered azoospermic following chemotherapy can occur more than 1 year following completion of therapy (over 5 years in patients treated with alkylating agents). In individuals with specific concerns, referral to an endocrinologist or urologist may be indicated.

Females: Spontaneous regular menstruation implies ovulatory cycles and sex hormone analysis is not indicated. However this should not be taken as an indication of normal fertility as regular menstruation and ovulation can be maintained in the presence of a severely depleted ovarian reserve.

If menstruation is abnormal, the cycle pattern should be recorded. Serum FSH, LH and oestradiol should be measured during menses (or at any time if menstruation has ceased) and the patient’s management and consideration for HRT/local hormonal agents (vaginal oestrogen tablet, Vagifem (25 µg of Estradiol) which for the first week is given once a day at night as a tablet vaginally and the maintenance is twice a week) This is also best discussed with a gynaec-endocrine team.

A woman’s reproductive life is likely to be shortened as a consequence of treatment and so pregnancy, if desired, should not be unduly delayed. It is unusual to recommend conception however, within 1-2 years of obtaining remission.

Patients with stored gametes or ovarian tissue wishing to become pregnant should be discussed with the appropriate fertility centre.

Additional investigations should be carried out as determined by clinical suspicion or as directed by trial protocol.

Patients should be advised strongly against smoking, and should avoid sunburn.

New symptoms should be reported without undue delay.

**For patients who have undergone splenectomy as part of their lymphoma treatment, BCSH guidelines should be followed**
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Sehn et al The revised IPI is a better predictor of outcome than the standard IPI for patients with DLBCL treated with RCHOP. Blood 2007 109 1857-61.


Yok-Lam Kwong al. SMILE for natural killer/T-cell lymphoma: analysis of safety and efficacy from the Asia Lymphoma Study Group. Blood October 11, 2012 vol. 120 no. 15 2973-2980

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