London Cancer

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

Reviewed and agreed by the Pathway Board

3rd August 2013
INTRODUCTION

Required investigations at diagnosis for all patients with suspected lymphoma
Histopathology procedures and standards
Staging
Staging system definition
Prognostic scores
Follicular lymphoma international prognostic index (FLIPI)
International prognostic index for patients with aggressive lymphoma (IPI)
Prognostic score of advanced HL (Hasenclever index)
Response criteria
Considerations prior to commencement of therapy and supportive care issues
Conservation of reproductive function
Cardiopulmonary dysfunction
Tumour Lysis Syndrome (TLS)
Use of haemopoietic growth factors
Management of patients with HIV infection
Follow up in patients with lymphoma
Late toxicity evaluation

INDOLENT NHL

Follicular Lymphoma grade 1, 2, 3a
Early stage disease (stage I)
Advanced stage disease (stages II-IV)
Asymptomatic patients with no indication for treatment
Symptomatic patients
Relapsed disease
Transformed follicular NHL (not synchronous)
Summary of treatment for follicular lymphoma
Chronic Lymphocytic Lymphoma/Small Lymphocytic Lymphoma
Lymphoplasmacytoid Lymphoma
Mantle Cell Lymphoma
First line therapy
Non-responsive, progressive or relapsed disease
Extranodal Marginal Zone Lymphomas of Mucosa Associated Lymphoid Tissue (MALT Lymphoma)
Gastric MALT lymphomas (stage IE)
Non-gastric extranodal MALT lymphoma
Nodal Marginal Zone Lymphoma

AGGRESSIVE NHL

Large B Cell Lymphomas
Localised disease - non-bulky Stage I, with no additional risk factors
Advanced disease –non-bulky stage I with risk factors, bulky stage I, II-IV
Restaging and management of partial response
Management of primary refractory disease and first relapse
Summary of Treatment
Peripheral T-cell Lymphomas
HISTIOCYTIC TUMOURS

APPENDICES

Appendix 1: Tumour Lysis Syndrome................................................................. 60
Appendix 2: Guidelines for the Use of Rasburicase 32-35................................. 60
Appendix 3: Guidelines for the use of Haematopoietic Colony-stimulating Factors in Adult Oncology and Haematology Patients......................................................... 61
Appendix 4: Chemotherapy Regimens.................................................................. 62
  R-CHOP-21 (R-CHOP-14).................................................................................. 62
  R-CHOP14 .......................................................................................................... 62
  R-CVP .................................................................................................................. 62
  R-GCVP .............................................................................................................. 63
  PMitCEBO ......................................................................................................... 63
  Rituximab/ Fludarabine/Cyclophosphamide ...................................................... 63
  NORDIC MCL2 Protocol ................................................................................... 64
  R-HAD+B .......................................................................................................... 65
  Bortezomib ....................................................................................................... 65
  CODOX-M ......................................................................................................... 65
  IVAC .................................................................................................................... 66
  Anti Helicobacter pylori therapy (suggested): .................................................... 66
  HD-MTX+HD Ara C .......................................................................................... 67
  R-I-E ................................................................................................................... 67
  IDARAM ............................................................................................................. 67
  ABVD ............................................................................................................... 68
  Stanford V ......................................................................................................... 68
  CHLVPP ............................................................................................................. 68
  VEPEMB .......................................................................................................... 69
  Escalated dose BEACOPP ............................................................................... 69
  Baseline BEACOPP ......................................................................................... 70
  ESHAP +/-R ...................................................................................................... 71
  IGEV ............................................................................................................... 71
  IVE +/-R .......................................................................................................... 71

60
Guideline authors

Version 5 2013  Dr Kirit Ardeshna, Dr Kate Cwynarski, Dr Chris McNamara,
Dr Silvia Montoto, Dr Rebecca Auer and Dr Claire Hemmaway

Version 4 2010  Dr Kirit Ardeshna, Dr Kate Cwynarski, Dr Andres Virchis,
Dr Chris McNamara, Prof David Linch and Aoife Shields

Version 3 2007  Dr Kirit Ardeshna, Dr Kate Cwynarski, Dr Ming Lee,
Dr Chris McNamara, Prof David Linch, Dr Alan Ramsay and
Mr Simon Cheesman

Version 2 2005  Dr Cathy Burton, Dr Kirit Ardeshna and Prof David Linch

Version 1 2003  Dr Lynny Yung and Prof David Linch
INTRODUCTION

Non-Hodgkin lymphoma was on the increase in the Western world with an incidence of over 5000 per annum in the UK, rising by 3-5% p.a. The rate of increase of this condition exceeds that of most other cancers, the reason for this is unclear.¹ ² This rise is now slowing. 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 national 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. This does not necessarily imply that this option is better than others, and the proposed restriction to one or at most two regimens is to allow standardisation, which facilitates staff familiarity, audit and research.
**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 node to lab (divided node to be 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 Haemato-Oncology.

Staging
• Clinical history and examination, with particular attention to nodal areas, ENT examination if disease above the thyroid notch, Waldeyer’s ring, liver and spleen.
• ECOG performance status.
• 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.
• Consider chest x-ray.
• Neck/chest/abdomen/pelvis CT (not ‘whole body’ as neck is not included).
• Bone marrow examination in NHL is routine. Only to be performed in Hodgkin lymphoma in certain instances, i.e. HIV+ and advanced stage.
• 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 6. 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 6 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, para-nasal sinus or long bone disease as this will help RT planning.
- PET scanning at diagnosis improves the staging procedure and may occasionally alter initial therapy. A baseline PET is often useful when interpreting response to therapy, the Imaging Subcommittee of the International Harmonisation Project in Lymphoma produced guidelines strongly recommending a baseline pre-treatment PET scan.3 It is now possible to request a CT/PET with diagnostic CT scan (contrast injected after initial PET done). This can be useful at diagnosis and prevent the need for a diagnostic CT scan in addition to the PET/CT scan. These may not be acceptable in trials where treatment is altered on the basis of an interim PET scan.

Minimum recommendations for PET usage are:

1) Staging PET/CT at diagnosis for routinely FDG avid tumours which are potentially curable e.g. DLBCL, HL. Increasingly PET/CT scanning is performed in other lymphomas at presentation.
2) Evaluation of residual masses post treatment at appropriate time interval
3) Patients who have follicular lymphoma will usually be PET+. PET scan at diagnosis can be useful when interpreting later scans. If initial work up suggests stage I disease and IFRT is planned a PET/CT is recommended to ensure disease is stage I and that IFRT is appropriate.

It is important to remember false positives and false negative results occur. Across most studies there is ~15% false negative rate in HL/DLBCL. The false positive rate for HL is more marked at ~35% compared with ~15% in NHL.

**Staging system definition**

Staging laparotomy is no longer performed.
Ann Arbor staging classification for lymphoma:
The lymphatic structures are as follows: Lymph nodes, Waldeyer ring, Spleen, Appendix
Thymus, Peyer patches)
Stage I Involvement of a single lymph node region (I), or localised involvement of a single extralymphatic organ or site (IE)
Stage II Involvement of two or more lymph node regions on the same side of the diaphragm (II), or localised involvement of a single extralymphatic organ or site and its regional lymph node(s) with or without involvement of other lymph node regions on the same side of the diaphragm (IIIE)
Stage III Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by localised involvement of an associated extralymphatic organ or site (IIIIE), or by involvement of the spleen (IIIS), or both (IIIIE+S)
Stage IV Disseminated (multifocal) involvement of one or more extralymphatic organs, with or without associated lymph node involvement; or isolated extralymphatic organ involvement with distant (non-regional) nodal involvement

Modifying characteristics:
A: no symptoms
B: unexplained fever over 38°C, drenching night sweats, weight loss >10% in 6 months
X: bulky disease: - >one-third widening of mediastinum at widest point
>10cm maximum diameter of nodal mass
E: involvement of single, contiguous or proximal, extranodal nodal site

Extralymphatic disease, if localised and related to adjacent lymph node disease, does not adversely affect the survival of patients.

Lung involvement limited to one lobe, or perihilar extension associated with ipsilateral lymphadenopathy, or unilateral pleural effusion with or without lung involvement but with hilar lymphadenopathy is considered as localised extralymphatic disease.

Liver involvement is always considered as diffuse extralymphatic disease.
### ECOG Performance Status*

<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
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

<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>

**Risk factors:** age; ECOG; LDH; WBC
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 risk</td>
<td>6-11</td>
<td>21%</td>
<td>-</td>
<td>29 months</td>
</tr>
</tbody>
</table>

International prognostic index for patients with aggressive lymphoma (IPI)

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Sum of points</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

Revised 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>Very good</td>
<td>0</td>
<td>10%</td>
<td>94%</td>
<td>94%</td>
</tr>
<tr>
<td>Good</td>
<td>1-2</td>
<td>45%</td>
<td>80%</td>
<td>79%</td>
</tr>
<tr>
<td>Poor</td>
<td>3-5</td>
<td>45%</td>
<td>53%</td>
<td>55%</td>
</tr>
</tbody>
</table>

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

#the ‘Revised-IPI’ includes the same prognostic factors as the IPI but differs in the distribution of risk-group according to the number of adverse prognostic factors

Prognostic index for PTCL-NOS (PIT)

<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>

Risk factors: age >60; LDH >ULN; PS ECOG >2; BM infiltration
Prognostic score of 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>&gt;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

1999 International Working group response criteria

<table>
<thead>
<tr>
<th>Response category</th>
<th>Physical examination</th>
<th>Lymph nodes</th>
<th>Lymph node masses</th>
<th>Bone marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>CRu</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal &gt;75% decrease</td>
<td>Indeterminate Normal or indeterminate</td>
</tr>
<tr>
<td>PR</td>
<td>Normal Decrease in liver/spleen</td>
<td>Normal ≥50% decrease ≥50% decrease</td>
<td>Normal ≥50% decrease ≥50% decrease</td>
<td>Positive Irrelevant Irrelevant</td>
</tr>
<tr>
<td>Relapse/progression</td>
<td>Enlarging liver/spleen; new sites</td>
<td>New or increased (&gt;50%)</td>
<td>New or increased (&gt;50%)</td>
<td>Reappearance</td>
</tr>
</tbody>
</table>

In the revised response criteria PET has been incorporated and CRu has been eliminated (see next page).
Updated Response Definitions for Lymphoma incorporating PET scan

<table>
<thead>
<tr>
<th>Response</th>
<th>Definition</th>
<th>Nodal Masses</th>
<th>Spleen, Liver</th>
<th>Bone marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>Disappearance of all evidence of disease</td>
<td>(a) FDG-avid lymphomas or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT</td>
<td>Not palpable, nodules disappeared</td>
<td>Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative</td>
</tr>
<tr>
<td>PR</td>
<td>Regression of measurable disease and no new sites</td>
<td>≥50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT</td>
<td>≥50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen</td>
<td>Irrelevant if positive prior to therapy; cell type should be specified</td>
</tr>
<tr>
<td>SD</td>
<td>Failure to attain CR/PR or PD</td>
<td>(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapsed</td>
<td>Any new lesion or increase by ≥50% of previously involved sites from nadir</td>
<td>Appearance of a new lesion(s) &gt; 1.5 cm in any axis, ≥50% increase in SPD of more than one node, or ≥50% increase in longest diameter of a previously identified node &gt; 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy</td>
<td>&gt; 50% increase from nadir in the SPD of any previous lesions</td>
<td>New or recurrent involvement</td>
</tr>
</tbody>
</table>

Routinely FDG avid lymphomas=DLBCL, HL, FL, MCL

Variably avid lymphomas=other aggressive and indolent lymphoma

SPD= sum of the product of the diameters
Considerations prior to commencement of therapy and supportive care issues

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 should 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. At the current time, ovum and ovarian tissue storage is still a research practice and is not widely available (and may not be funded by NHS). 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 xx 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 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.

**Cardiopulmonary dysfunction**
Patients <70 years of age who are asymptomatic and have no history of cardiorespiratory 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.

**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 and urate levels at least twice a day. Correction of biochemical abnormalities prior to commencement of chemotherapy reduces, but does not eliminate the risk (see Appendix 1). 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.

**Use of haemopoietic growth factors**
Use should comply with guidelines (see Appendix 3).

The use of EPO is not recommended.

**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 visits
3-monthly in year 1
4-6 monthly in years 2, 3
6-monthly in years 4, 5
Annually thereafter

Routine investigations:
Thorough history and physical examination
Enquiry about presence of B symptoms
Performance status
Full blood count, renal and liver function,

The PPV of LDH is poor and this is not recommended as a routine test in follow up

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 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.

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/m², Mitoxantrone 160mg/m², Epirubicin 900mg/m² Idarubicin IV 150mg/m² (see appendix 6).

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 (eg, 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 25-30, whichever comes later. This involves annual mammograms until 50 years when they enter the national screening system. (MRI of the breasts is indicated if the breast tissue is too dense to adequately assess by mammography and should be considered for younger patients aged 30-40).

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 fortnight 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.

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 heterogenous 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 our policy). There is no indication for extended field radiotherapy. A PET/CT scan to confirm stage I disease is recommended prior to radiotherapy.

**Advanced stage disease (stages II-IV)**
In some 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.

**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:
**BNLI criteria**

- Rapidly progressive disease
- Life threatening organ involvement
- Bone/kidney/liver infiltration
- B symptoms/pruritus
- Cytopenias due to BM involvement (Hb<100g/L, WCC< 3 x10^9/L, platelets<100 x 10^9/L)

**GELF criteria**

- Bulky disease: nodal/extra nodal ≥7 cm
- 3 involved nodal areas, each with a LN ≥ 3 cm
- Spleen ≥ 20 cm
- Pleural effusion/ ascites
- ECOG ≥ 2
- B-symptoms
- Elevated LDH/ B2 microglobulin

**Symptomatic patients**

Consider inclusion in clinical trials:

For patients not entered into trials, options are:

Bendamustine with rituximab is recommended (Rummel et al, Lancet 2013). Maintenance rituximab is recommended if responding

Alternatives include:

- R-CVP x 8. Maintenance rituximab is recommended if responding
- R-CHOP x 6 + 2R. Maintenance rituximab is recommended if responding
- Chlorambucil with rituximab

Suggested regimens are:

a) 10mg daily Chlorambucil for 14 days, every 28 days;

b) 10mg Chlorambucil daily for the first 28 days, followed by 10mg daily for 14 days every 28 days;

c) 10mg Chlorambucil for 6 weeks followed by 3 blocks of chlorambucil (10mg daily x 2-weeks every 4 weeks).
With monthly rituximab (up to 8 doses) or weekly rituximab (x 4 doses).

Maintenance rituximab is recommended if responding.

Randomised comparative data between R-CHOP and R-CVP (Federico 2013), demonstrates prolongation of 3 yr PFS following RCHOP (68% vs 52%) though it is not known whether this will translate into overall survival benefit. Toxicity is greater with R-CHOP.

R-CHOP is recommended if there is clinical suspicion of high grade transformation or need for a rapid response.

Single agent chlorambucil remains useful treatment for frail patients or patients wishing to avoid intravenous infusions at hospital/clinic.

Rituximab maintenance therapy is recommended as an option for the treatment of people with follicular lymphoma that has responded to first-line induction therapy with rituximab in combination with chemotherapy. (375mg/m² every 2 months for 2 years). 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.

Three studies comparing TBI based autograft versus further conventional dose chemotherapy in patients responding to first line induction chemotherapy show that autografting patients in first remission does not result in an OS benefit. The PFS benefit seen in 2 of these studies is balanced by an increased risk of second cancers in the autograft arm. Autografting in first CR is not therefore recommended.

**Relapsed disease**

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

*To achieve 2nd and subsequent remission*
A wide range of therapies are available for patients relapsing with this disease and for patients not in trials, it is difficult to stipulate second and third line regimens as the initial therapy will have varied.

Where R-CVP was used as first line, bendamustine, fludarabine, a CHOP-like regimen or salvage therapy (ESHAP, ICE etc) (with or without rituximab) should be considered as further lines of treatment. Where R-CHOP was used as first line, bendamustine fludarabine (alone or as combination chemotherapy, such as FMD or FC, with or without rituximab) or ESHAP, ICE (with or without rituximab) should be considered. Repeated courses of chlorambucil can be very effective in securing further remissions especially if the response duration to the latest course of chlorambucil is more than 2 years. Concerns regarding the ability to mobilise stem cells after fludarabine should be taken into account. 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 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 the transplant centre.

Rituximab maintenance

Rituximab monotherapy as maintenance therapy, is recommended as an option for the treatment of people with relapsed stage III or IV follicular non-Hodgkin’s lymphoma in remission induced with chemotherapy with or without rituximab. It is administered at 3 month intervals for up to 2 years.

There has been no direct comparison of rituximab maintenance vs. autograft but it is recommended that patients who are deemed fit enough for autograft should follow this
route. A recent randomised study presented only in abstract form 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 follicular NHL (not synchronous)*

Patients with transformed disease should receive R-CHOP x 6-8 or if they have received this previously they can receive salvage chemotherapy (ESHAP+/-R or ICE+/-R x 2-3). In view of the data showing poor outcome following transformation in the pre rituximab era (1-2yr) autografting was generally advocated for patients who achieved a CR/PR. One group of patients who enjoyed a longer survival following transformation were those who received no prior therapy for their low grade disease and who achieved a CR following treatment of the transformed disease. This group is now not recommended to have an autograft. Allografting is also an option and patients should be discussed with the transplant centre.
Summary of treatment for follicular lymphoma

Localised disease
Radiotherapy
Expectant management

Advanced disease
Initial therapy
Clinical Trial - see NCRI trial link
Rituximab in combination with chemotherapy

Relapsed disease
Clinical Trial - see NCRI trial link
FC+/-R
FMD+/-R
CHOP+/-R
ESHAP+/-R
ICE+/-R
Palliative RT
Zevalin

Consolidation of patients in second or subsequent remission
Transplantation (second remission) – autoPBSCT or RI-alloSCT.
Maintenance rituximab.

Chronic Lymphocytic Lymphoma/Small Lymphocytic Lymphoma

See separate guidelines.

Lymphoplasmacytoid Lymphoma

See separate guidelines.
Mantle Cell Lymphoma

The majority of patients will 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 apparent 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, although additional clinical/pathological tools are needed to specifically identify this patient group.

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.

First line therapy
Patients should be considered for clinical trials
Patients who are fit enough for high dose therapy, 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 alternating with R-DHAP x3 (Delarue Blood 2013).

Consideration can be given to allogeneic stem cell transplantation (for example patients with high MIPI and/or blastoid variant) instead of autologous transplantation. Please discuss with transplant centre. Patients receiving an allograft from an HLA identical sibling or unrelated donor in first remission are eligible for the NCRN BSBMT mini allograft study which uses BEAM Campath conditioning.

Patients for whom autologous SCT is not considered appropriate should be treated with R-CHOP x6 followed by rituximab maintenance for those achieving remission.
A recent European MCL Network study (Kluin-Nelemans NEJM 2012) has shown a survival advantage for older patients treated with R-CHOP followed by rituximab maintenance when compared against R-CHOP and interferon maintenance. The same trial also showed a survival advantage for R-CHOP compared with R-FC for induction therapy.

Patients who are not fit enough for CHOP like chemotherapy should be treated with a Rituximab containing regimen (R-Bendamustine, R-Chlorambucil/ R-FC dose adjusted)

**Non-responsive, progressive or relapsed disease**

**Younger patients <65y**
- Patients should be considered for clinical trials
- Young patients should be considered for allograft after salvage therapy.
- Salvage therapy can be with FC±R, ESHAP±R, miniBEAM, R-HD AraC, R-Bendamustine, single agent bortezomib or bortezomib in combination with high dose cytarabine ± Rituximab (R-HAD+B).
- Application to the CDF may be required.

**Older patients >65y**
- Patients should be considered for clinical trials
- Outside of a clinical trial suitable treatment regimens include R-Bendamustine, Bortezomib (S/C), FC±R, R-CHOP, Temsirolimus (IFR required), R-Chlorambucil.
- Patients who relapse having already received Rituximab within the last 6 months, should not be retreated with Rituximab.

**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.
Extranodal Marginal Zone Lymphomas of Mucosa Associated Lymphoid Tissue (MALT Lymphoma)

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 and high-grade histologic transformation can occur.

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. 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. The presence of Chlamydia psittaci, Campylobacter jejuni, and Borrelia burgdorferi should be evaluated in non-gastric MALT lymphoma tissue biopsies.

Although the stomach and small intestine are more commonly involved than the large intestine, the latter can be affected; staging endoscopy of the entire GI tract should therefore be considered depending on the nature of the clinical presentation. The Ann Arbor staging system has limited value in this lymphoma.
An alternative staging system first proposed by Blackledge et al., and later modified by the International Workshop in Lugano, Switzerland, is more appropriate:

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 usually performed when there are symptoms or signs of Waldeyer ring involvement.

**Gastric MALT lymphomas (stage IE)**

MALT lymphoma of the stomach is the most common type of primary extranodal lymphoma and represents up to 50% of primary gastric lymphomas. The association with Helicobacter pylori infection has already been mentioned. In many centres this is assessed by the detection of *H. pylori* antigen in a stool sample.

**All patients should be considered for enrolment in clinical trials where available.**

*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. Involved-field irradiation (total dose of 30 Gy administered over 4 weeks) results in excellent long term disease control but with the potential for long term morbidity due to radiotherapy in a condition with excellent long-term survival.

Surgery is an inappropriate option for localised gastric MALT in the vast majority of patients given the availability of other modalities of therapy outlined above and the potential for metachronous lesions.

*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. Some centres perform annual OGD because of the reported increased risk of gastric carcinomas in *H. pylori*-positive patients (Zucca et al) but there is no evidence that this improves survival. 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. A lower threshold for declaring the patient to have failed primary treatment with antibiotics may be adopted in the following poorer risk prognostic groups:

1) *H. pylori*-negative cases
2) tumour invasion beyond the submucosa
3) t (11;18)(q21;q21)*
The two common cytogenetic abnormalities demonstrated in MALT lymphomas are t(11;18)(q21;q21), seen in 30% to 40% of gastric and lung MALT lymphomas, and t(14;18)(q32;q21)/IGH-MALT1, seen in 5% to 25% of nongastric MALT lymphomas. Five percent of all cases are accounted for by t(1;14)(p22;q32). More recently, t(3;14)(p14;q32)/IGH-FOXP1 has also been described in nongastric (thyroid, ocular, cutaneous) MALT lymphomas. Cytogenetic changes may be clinically important, as t(11;18)-positive cases are less likely to respond to H. pylori-eradication therapy and t(11;18)-positive cases are more likely to present with advanced-stage disease associated with aberrant expression of nuclear BCL10. Furthermore, t(11;18)-positive cases are less likely to transform to aggressive lymphomas as they are unlikely to develop secondary chromosomal abnormalities.

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 or fludarabine are reported.

Non-gastric extranodal MALT lymphoma
About 25% of patients with nongastric MALT lymphoma present with disseminated disease. Enrolment in clinical trials is recommended wherever possible.

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 etc).

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.

Enrolment in clinical trials wherever possible is recommended. 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 immunochemotherapy (rituximab + polychemotherapy) is recommended, again based on small numbers. The utility of anthracycline is not completely defined.

Splenic Marginal Zone Lymphoma

If asymptomatic and reasonable blood counts can W&W.
If symptomatic or cytopenic consider therapy. 
If Hep C + consider anti viral therapy (IFN +/- ribavirin).
Otherwise if isolated splenomegaly (+/- minimal BM involvement) consider splenectomy, splenic irradiation or single agent rituximab.
If splenomegaly plus significant BM involvement the use of single agent rituximab (induction followed by maintenance) is effective.
**AGGRESSIVE NHL**

For the purpose of clinical management ‘aggressive’ NHL has been divided into 7 categories as shown below:

- Diffuse large B cell lymphoma (DLBCL)
  - Primary mediastinal DLBCL
  - Anaplastic large cell lymphoma
  - Follicular lymphoma, grade 3b
- T cell lymphoma
- Burkitt
- Lymphoblastic lymphoma/leukaemia (precursor T or B cell) – in separate guidelines (ALL subgroup)
- HTLV-1 associated ATLL
- Primary CNS lymphoma
- Post-transplant lymphoproliferative disease

**Large B Cell Lymphomas**

The following should be treated according to this guideline:

- Diffuse large B cell lymphoma (DLCBL)
- Primary mediastinal DLBCL
- Anaplastic large cell lymphoma
- Follicular lymphoma, grade 3b

Treatment approaches differ according to the following factors:

- Stage
- Disease bulk (<10cm vs. ≥10cm)
- IPI risk group
- Presence of primary extranodal disease
- Co-morbidities
**Localised disease - non-bulky Stage I, with no additional risk factors**

Those with non-bulky stage I disease with no additional risk factors (age >60 years, elevated serum LDH, performance status >2) should receive 3 courses of R-CHOP chemotherapy and IFRT. Patients with no adverse risk factors have a 5 year overall survival of 94%. A further 1-3 courses of rituximab can be administered at 3 week intervals after the chemotherapy to give 4-6 doses of rituximab in total. This can be given concurrently with the radiotherapy.

If there are any adverse factors or the sequelae of radiotherapy are undesirable (e.g. dry mouth) 6 courses of R-CHOP (without radiotherapy) can be considered.

Patients who have bulky disease (>10cm) should also receive RT even if treated with 6xR-CHOP as a higher incidence of relapse (at site of bulk and elsewhere) is observed (Tomita et al, BJ Haem 2013).

One randomised study has shown CHOPx4 was equivalent to CHOPx4+IFRT in limited stage pts older than 60 with no risk factor (normal LDH, PS<2). Consideration can be given to this approach if radiotherapy is not thought feasible. (Bonnet JCO 25 2007 p787).

All other patients should be treated according to the advanced disease guidelines.

**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 R-CHOP21 in accordance with NICE guidance11. R-CHOP14 appeared equally efficacious in the RCHOP 14 vs RCHOP 21 trial but the study was not powered to detect non inferiority. Thus R-CHOP21 remains the standard of care although in some circumstances R-CHOP14 may be used (with pre-emptive G-CSF and septrin prophylaxis) if patient’s preference (Cunningham et al, Lancet 2013).

Impressive outcome has 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; ASH 2011)
- 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 and have only reported in abstract form.

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

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

Primary mediastinal DLBCL (PMBCL)

**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 involved mediastinal radiotherapy after Rituximab containing chemotherapy regimens to patients with newly diagnosed PMLBCL) will open soon 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).
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\textsubscript{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).

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.

Management of primary refractory disease and first relapse
Patients fit for PBSCT:
These patients should first receive salvage treatment with a non-cross-resistant regimen: ESHAP, ICE, DHAP, IVE and mini-BEAM\textsuperscript{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\textsuperscript{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, or R-mini-BEAM regimens). 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 not responding to ESHAP-R or IVE-R or R-mini-BEAM should be considered for gemcitabine.

**Patients unfit for PBSCT:**

- Clinical trial
- Rituximab-Gemcitabine-Oxaliplatin – IV regimen (El Gnaoui et al, 2007)
- R-CCEP (CCNU, cyclophosphamide, etoposide and prednisolone –PO)
- PMitCEBO+/-R
- Gemcitabine (1000mg/m\(^2\) - 1250mg/m\(^2\) weekly
- Experimental therapies (kinase inhibitors etc)
- Palliative approaches (s/c ara-C/po etoposide)
Summary of Treatment

Localised disease
Stage I, i.e. non-bulky → R-CHOP x 3 + IFRT
No risk factors
(or R-CHOP x 6)

Advanced disease (Stage II-IV) in patients aged >18 years
Therapy as per trials
R-CHOP\textsubscript{21} (or RCHOP\textsubscript{14}) x 6

Primary refractory/relapsed disease (fit for PBSCT)

- ESHAP/ICE+-/-R x 2
  - response
    - ESHAP/ICE+-/-R + PBSCH
    - BEAM autograft
    - mini-BEAM or palliation or experimental therapy
  - no response
    - R-IVE or alternative salvage
      - response
        - R-IVE + PBSCH
      - no response
        - BEAM autograft
Peripheral T-cell Lymphomas

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 (BCSH Guidelines 2011).

Presently CHOP\textsubscript{21} (or CHOP\textsubscript{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 an allograft in second remission.

Intestinal T-cell Lymphoma

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, 2010).

Extranodal NK/T Cell Lymphoma, nasal type

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 upfront. The value of additional chemotherapy (CHOP, etoposide-based or asparaginase-based) remains unclear but is considered conventional.

Asparaginase-containing regimens (ie. SMILE regimen that incorporates dexamethasone, methotrexate, ifosfamide, 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**

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: Wang et al 2003, Montoto et al, 2010, 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) \( \leq 1 \)

**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**

These guidelines were produced by the London ATLL group in June 2007  

1) Patients with ATLL should be treated with combination chemotherapy such as CHOP with zidovudine 250mg bd + IFN-a 3MIU 3/wk (Hodson et al, 2011). The ZDV/IFN subcutaneous should be started during the first week of chemotherapy. A worldwide meta-analysis suggested that leukaemic phases of ATL may be treated effectively with ZDV/IFN subcutaneous (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-a. Dose of interferon may be increased from 3MIU 3/wk to max 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 and viral load* should be regularly monitored when on antiviral therapy.

**Primary CNS Lymphoma (PCNSL)24-26**

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 ≥ 3000mg/m² delivered over a maximum of 2-3 hours at intervals of not more than 2-3 weeks, with HD-Ara-C. The randomised IELSG20 study showed that 4 cycles of MTX 3500mg/m² on d1 followed by cytarabine 2000mg BD on days 2 and 3 was superior to 4 cycles of MTX 3500mg/m² alone (RR to chemotherapy 69% vs. 40%; CR 46% vs. 18%) in pts up to the age of 75yrs. WBRT was administered in the majority of patients (3-year FFS was 38% vs. 21% (p=0.01). 3 yr OS 46% vs. 32% p=0.07) (Ferrari et al, Lancet 2009; 374: 1512–20).

2) Consolidation WBRT should 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-PBSC, can replace WBRT. 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 5).

1) 4 cycles of MTX 3500mg/m² on d1 followed by cytarabine 2000mg BD on days 2 and 3. 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/m² every 2 weeks.

Patients in CR can be considered for WBRT bearing in mind neurocognitive side effects. Patients should be involved in this decision.

Generally if pts in CR

<60yrs WBRT probably recommended (although some centres offer PBSCT 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*
Consideration for R-IE regimen +/- PBSCT. This salvage regimen is well tolerated and effective in patients with relapsed disease. Results using temozolamide have been disappointing.

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)**

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-CODOX-M/R-IVAC, (or R-CHOP/HD-MTX), R-IE. 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/carmustine conditioned autograft.
Patients not fit enough for such intensive therapy should be considered for repeated courses of HDMTX (+depocyte if meningeal disease).

*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)

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.bcshguidelines.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

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

Use of antivirals as treatment or prophylaxis is not recommended.

Transformed Lymphoma
**Transformed Follicular NHL (not synchronous)**

Patients with relapsed ‘indolent’ lymphoma should have a biopsy to rule out histological transformation. In most of the cases patients transform to DLBCL but cases of BL or LL have also been reported and they would warrant a different approach. Patients with histological transformation with DLBCL should be treated as DLBCL, that is with R-CHOP x6 (if they have not previously received this regimen) or with any DLBCL-second line chemotherapy regimen.

In view of the data showing poor outcome following transformation in the pre rituximab era (1-2 yr) autografting was generally advocated for patients who achieved a CR/PR. One group of patients who enjoyed a longer survival following transformation were those who received no prior therapy (ie W&W or RT) for their low grade disease and who achieved a CR following treatment of the transformed disease. This group is now not recommended to have an autograft.

Patients with a composite or discordant lymphoma at diagnosis i.e pt with evidence of ‘low-grade’ lymphoma in addition to high-grade’ should be treated as ‘high-grade’.

Allografting is also an option and patients should be discussed with the transplant centre.
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)

Management of NLPHL

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

**Localised, stage Ia disease** should be treated by involved field 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.

**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.\(^\text{27}\).
Classical Hodgkin Lymphoma

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 (spleen hilum, liver hilum, coeliac)
   - 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 IFRT* as consolidation.

Off study the recommendation for unfavourable localised disease is ABVDx4 +30GyIFRT*.

*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. Interesting data has been presented in abstract form at ASH 2012 regarding the RAPID study where radiotherapy was omitted on the basis of a negative PET scan after 3 courses and the full data are awaited with interest.

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

IFRT 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 use 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 ABVD. Those with a positive PET scan (Deauville 4 or 5) after 2 cycles should 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 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 CHLVP 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)

↓

4 x ABVD

PET positive (Deauville 4, 5)

↓

Esc BEACOPP x 3

PET positive

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

PET negative

↓

Esc BEACOPP x 1

RT = involved field radiotherapy
**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 or IGEV chemotherapy.

**Patients who are PET-** 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. Those responders with significant residual disease after ESHAPx2 can be mobilised of ESHAP and G-CSF.

**Patients who are PET+** and non-progressive following the first 2 cycles of ESHAP should proceed to reduced intensity allograft provided a donor can be found.

Those with disease unresponsive to ESHAP/IGEV should receive mini-BEAM though brentuximab vedotin could be considered as an alternative. Other alternatives include single agent gemcitabine or bendamustine. Consideration should be given to the use 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/IGEV x2
  - PET- (CR)
    - BEAM
    - PBSCT
    - Radiotherapy to residual
  - PET+ (PR/SD)
    - Reduced intensity SCT miniBEAM 1-2 courses
      - Response or stable disease
      - Progressive masses
        - Brentuximab vedotin
          - (Gemcitabine)
  - Progressive
APPENDICES

Appendix 1: Tumour Lysis Syndrome

Management includes:
Allopurinol 300mg po od (reduced dose in renal failure) to be commenced prior to chemotherapy.
Aggressive intravenous hydration with careful management of fluid balance.
Prompt correction of hypocalcaemia and hyperkalaemia.
Timely discussion of patients with a nephrologist may be necessary.
Rasburicase indicated as prophylaxis in patients allergic to allopurinol or in renal impairment prior to starting chemotherapy or in those considered high risk for tumour lysis (Burkitt or Burkitt-like lymphomas).

Appendix 2: Guidelines for the Use of Rasburicase 32-35

The acute nephropathy associated with tumour lysis syndrome is primarily due to an elevated uric acid level. Urate oxidase catalyses the oxidation of uric acid to allantoin, which is much more readily excreted than uric acid. Rasburicase is a recombinant form of urate oxidase.

Guidelines and indications for use:

Prophylaxis on initiation of chemotherapy
Metabolic disturbances
Phosphate equal to or above 2mmol/l
Creatinine out of the normal range. The rate of change is the most important factor. A doubling of the creatinine in a short period of time, i.e. 48hrs, in a well-hydrated patient and/or a clearance of less than 60ml/min is an indication for rasburicase
Potassium equal to or above 5.5mmol/l

Specific diseases
Burkitt or Burkitt-like lymphoma
Other high grade lymphomas only if metabolic disturbances as above
Other indications
Allopurinol allergy
**Administration**

Rasburicase to be used immediately prior to and during chemotherapy.

The recommended dose is 0.2mg/kg/day, given as a once daily 30-minute infusion in 50ml of 0.9% sodium chloride solution.

Duration of treatment varies between 3-5 days.

No dose adjustment is necessary in renal or hepatic impairment.

Rasburicase solution should be infused through a different line to that used for chemotherapy. If a separate line is not possible, the line should be flushed thoroughly with saline solution.

Contra-indications:

a) Hypersensitivity to uricases

b) G6PD deficiency

**Appendix 3: Guidelines for the use of Haematopoietic Colony-stimulating Factors in Adult Oncology and Haematology Patients**

ASCO Guidelines 2006.
Appendix 4: 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).

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

- Rituximab: 375mg/m²
- Cyclophosphamide: 750 mg/m² iv day 1
- Doxorubicin: 50 mg/m² iv day 1
- Vincristine: 1.4 mg/m² (max 2 mg) iv day 1
- Prednisolone: 100 mg po days 1-5

R-CHOP14
Add septrin prophylaxis and pre-emptive G-CSF

Mini-CHOP-R (patients aged over 80 years)

- Rituximab: 375mg/m² IV
- Cyclophosphamide: 400mg/m² IV bolus on day 1
- Doxorubicin: 25mg/m² IV bolus on day 1
- Vincristine: 1mg flat dose IV infusion on day 1
- Prednisolone: 40mg/m² PO days 1 to 5 inclusive

21 day cycle; maximum 8 cycles

R-CVP
Cycle to be repeated at 21 day intervals

- Rituximab: 375mg/m² iv day 1
- Cyclophosphamide: 750 mg/m² iv day 1
- Vincristine: 1.4 mg/m² (max 2 mg) iv day 1
- Prednisolone: 100 mg po days 1-5
**R-GCVP**

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

**PMitCEBO**

Cycle to be repeated at 14-day intervals

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/m²)</th>
<th>Route</th>
<th>Day(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitoxantrone</td>
<td>7</td>
<td>iv</td>
<td>1</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>300</td>
<td>iv</td>
<td>1</td>
</tr>
<tr>
<td>Etoposide (VP16)</td>
<td>150</td>
<td>iv</td>
<td>1</td>
</tr>
<tr>
<td>Vincristine</td>
<td>1.4(2)</td>
<td>iv</td>
<td>8</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>10,000</td>
<td>iv (bolus)</td>
<td>8</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>50</td>
<td>po</td>
<td>1-4</td>
</tr>
</tbody>
</table>

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)

**Rituximab/ Fludarabine/Cyclophosphamide**

Cycle to be repeated at 28-day intervals

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/m²)</th>
<th>Route</th>
<th>Day(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>375</td>
<td>iv infusion</td>
<td>1</td>
</tr>
<tr>
<td>Fludarabine</td>
<td>40</td>
<td>po</td>
<td>2,3,4</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>250</td>
<td>po</td>
<td>2,3,4</td>
</tr>
</tbody>
</table>

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.
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

| Cytarabine IVI | 3g/m² BD (every 12hours) on Day 1 >60y 2g/m² |
| Cytarabine IVI | 3g/m² BD (every 12hours) on Day 2 >60y 2g/m² |
| Rituximab IVI  | 375mg/m² on Day 1 from Cycle 2 onwards |
| Rituximab IVI  | 375mg/m² on Day 9 from Cycle 6 ONLY |

### Supportive care drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Suggested Dosage &amp; Frequency or as per local policy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allopurinol PO</td>
<td>300mg OM NB: Rasburicase can be considered for patients with high tumour burden</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 |

Neulasta 24 hrs after each cycle from cycle 1-5 or other G-CSF preparations
Then cycle 6 to be used as stem cell mobilisation
**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

**Bortezomib**
Repeat every 21 days for up to 8 cycles
Bortezomib 1.3mg/m² SC on days 1, 4, 8 and 11

**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 alkalisation 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.
**IVAC**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose and Route</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etoposide</td>
<td>60mg/m² iv daily</td>
<td>1-5</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>1500mg/m² iv daily</td>
<td>1-5</td>
</tr>
<tr>
<td></td>
<td>(&gt;60yrs 1000mg/m²)</td>
<td></td>
</tr>
<tr>
<td>Mesna</td>
<td>360mg/m² mixed with each ifosfamide dose and 2520mg/m² iv by continuous 23hr infusion</td>
<td>1-5</td>
</tr>
<tr>
<td></td>
<td>(Nb Mesna doses may differ from trust to trust)</td>
<td></td>
</tr>
<tr>
<td>Cytarabine</td>
<td>2000mg/m² iv twice daily</td>
<td>1-2</td>
</tr>
<tr>
<td></td>
<td>(&gt;60yrs 1000mg/m²)</td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>12mg <em>intrathecal</em></td>
<td>5</td>
</tr>
<tr>
<td>G-CSF</td>
<td>5mcg/kg sc daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>from day 7 until neutrophil recovery</td>
<td></td>
</tr>
</tbody>
</table>

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.

**Anti Helicobacter pylori therapy (suggested):**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>1 gm</td>
<td>bd</td>
<td>7</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>500mg</td>
<td>bd</td>
<td>7</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>30mg</td>
<td>bd</td>
<td>7</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
HD-MTX+HD Ara C
Methotrexate 500mg/m² IV infusion over 15 mins followed by
Methotrexate 3000mg/m² IV infusion over 3 hours
Cytarabine 2000mg/m² IV infusion over 1 hour BD on days 2 and 3 (4 doses in total)

(For folinic acid rescue; methotrexate levels; hydration and urinary alkalinisation schedules follow
local protocol)
G-CSF is recommended from day 8 to day 14

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

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
**ABVD**
(Treatment interval 28 days)

- **Doxorubicin** 25mg/m² iv days 1,15
- **Bleomycin** 10,000IU/m² iv days 1,15
- **Vinblastine** 6mg/m² iv days 1,15
- **Dacarbazine** 375mg/m² iv days 1,15
* *dose should be capped at 10mg

**Stanford V**

- **Mustine** 6mg/m² iv weeks 1,5,9
- **Doxorubicin** 25mg/m² iv weeks 1,3,5,7,9,11
- **Vinblastine** 6mg/m² iv weeks 1,3,5,7,9,11
- **Prednisone** 40mg/m² alternate days po days 1-63, taper days 64-84
- **Vincristine** 1.4mg/m² iv weeks 2,4,6,8,10,12
- **Bleomycin** 5000IU/m² iv weeks 2,4,6,8,10,12
- **Etoposide** 60mg/m² x 2 iv weeks 3,7,11
  (given for 2 consecutive days)
* *dose should be capped at 2mg

**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
**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.

**Escalated dose BEACOPP**
Esc BEACOPP
Cycles of BEACOPP are 22 days each

<table>
<thead>
<tr>
<th>Letter</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>Bleomycin</td>
<td>10,000IU/m²</td>
<td>iv/im</td>
<td>day 8</td>
</tr>
<tr>
<td>E</td>
<td>Etoposide</td>
<td>200mg/m²</td>
<td>iv</td>
<td>days 1-3</td>
</tr>
<tr>
<td>A</td>
<td>Adriamycin</td>
<td>35mg/m²</td>
<td>iv</td>
<td>day 1</td>
</tr>
<tr>
<td>C</td>
<td>Cyclophosphamide</td>
<td>1250mg/m²</td>
<td>iv</td>
<td>day 1</td>
</tr>
<tr>
<td>O</td>
<td>Vincristine</td>
<td>1.4mg/m² (max 2mg)</td>
<td>iv</td>
<td>day 8</td>
</tr>
<tr>
<td>P</td>
<td>Procarbazine</td>
<td>100mg/m²</td>
<td>po</td>
<td>days 1-7</td>
</tr>
<tr>
<td>P</td>
<td>Prednisone</td>
<td>40mg/m²</td>
<td>po</td>
<td>days 1-14</td>
</tr>
</tbody>
</table>

First day of next cycle = day 22

4 cycles of escalated dose BEACOPP are to be given, and treatment is to be continued by 4 cycles of baseline dose BEACOPP

**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 courses of rituximab with each course of salvage chemotherapy (if not received rituximab in last 6 months).
**ESHAP +/-R**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etoposide (VP16)</td>
<td>40mg/m²</td>
<td>IV</td>
<td>1-4</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>500mg</td>
<td>iv</td>
<td>1-5</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>2000mg/m²</td>
<td>iv</td>
<td>1</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>25 mg/m² (continuous infusion)</td>
<td>iv</td>
<td>1-4</td>
</tr>
</tbody>
</table>

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.

**IGEV**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vinorelbine</td>
<td>20mg/m²</td>
<td>IV infusion</td>
<td>1</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>800mg/m²</td>
<td>IV infusion</td>
<td>1 and 4</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>2000mg/m²</td>
<td>IV infusion</td>
<td>1 to 4</td>
</tr>
<tr>
<td>Mesna</td>
<td>2600mg/m²</td>
<td>IV infusion</td>
<td>1 to 4</td>
</tr>
<tr>
<td>Mesna</td>
<td>2600mg/m²</td>
<td>IV infusion</td>
<td>12 hours</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>100mg OD</td>
<td>PO</td>
<td>1 to 4</td>
</tr>
</tbody>
</table>

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

For mobilisation, refer to local mobilisation policy.

**IVE +/-R**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ifosfamide</td>
<td>3000mg/m²</td>
<td>iv</td>
<td>1-3</td>
</tr>
<tr>
<td>VP16 (etoposide)</td>
<td>200mg/m²</td>
<td>iv</td>
<td>1-3</td>
</tr>
<tr>
<td>Epirubicin</td>
<td>50 mg/m²</td>
<td>iv</td>
<td>1</td>
</tr>
</tbody>
</table>

Mesna 1600mg/m² iv 15 mins prior to ifosfamide infusion, then 2400mg/m² mesna in 1lit 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.
Mini-Beam +/- R
30 minutes prior to Carmustine give anti-emetics and chlorphenamine 10mg iv.

Day 1  Carmustine  60mg/m²  od iv over 1 hour
Days 2, 3, 4, 5  Cytarabine  100mg/m²  bd iv over 30 minutes
Days 2, 3, 4, 5  Etoposide  75mg/m²  od iv over 1 hour
Day 6  Melphalan  30mg/m²  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/m² Lomustine equivalent to 60mg/2 Carmustine in Mini-Beam or 200mg/m² Lomustine equivalent to 300mg/m² Carmustine in BEAM Auto). This dose has been used as part of the LACE protocol, which is similar to BEAM (REF Perz JB, Giles C, Szydlo R, et al. LACE-conditioned autologous stem cell transplantation for relapsed or refractory Hodgkin's lymphoma: treatment outcome and risk factor analysis in 67 patients from a single centre. (Bone Marrow Transplantation 2007; 39: 41-47).

R-ICE +/- 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, 2, 3  Etoposide  100mg/m²  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/m²  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)
**R-DHAP +/-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**  
Cisplatin 100mg/m$^2$ 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/m$^2$ 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 MgSO$_4$ over 2hrs  
Mannitol 10% 500ml over 1hr

Cisplatin given as described above.

Post hydration:  
1L 0.9% saline + 20mmol KCl + 1gram MgSO$_4$ over 4 hrs  
1L glucose 4%, saline 0.18% + 20mmol KCl + 1gram MgSO$_4$ over 6 hrs

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

**Bendamustine**

Cycle to be repeated at 28-day intervals

Bendamustine 90mg/m² over 60minutes in 500mls N/S on days 1 and 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.
**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)

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

**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

**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
**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).

Lenograstim should be prescribed from day 6 until completion of harvesting.

**May be repeated after 28 days or on full haematological recovery.**
Appendix 5: Suggested regimen for CNS prophylaxis

Methotrexate 12.5 mg IT fortnightly (or with each cycle of CHOP) x 6
High dose methotrexate as per UKALL XII protocol
Systemic treatments including high dose Cytarabine or Ifosfamide
Craniospinal irradiation

All patients with Burkitt Lymphoma or lymphoblastic 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 and UK ALL XII respectively, both of which contain 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

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 standard staging procedure. There is a 10x increase in incidence of patients with CNS disease by flow cytometry than conventional cytometry.
Appendix 6: 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>Daunorubicin$^1$</td>
<td>600</td>
</tr>
<tr>
<td>Doxorubicin$^{2,3}$</td>
<td>450</td>
</tr>
<tr>
<td>Epirubicin$^4$</td>
<td>900</td>
</tr>
<tr>
<td>Idarubicin – IV$^5$</td>
<td>150</td>
</tr>
<tr>
<td>Idarubicin – PO$^6$</td>
<td>400</td>
</tr>
<tr>
<td>Mitoxantrone$^7$</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/m$^2$ doxorubicin
            = 300mg/m$^2$ doxorubicin
            = ~ $2/3$ cumulative anthracycline allowance

2 x IVE   = 2 x 50mg/m$^2$ epirubicin
            = 100mg/m$^2$ 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>
<tr>
<td>AML 17 AIDA 1st Consolidation</td>
<td>Idarubicin (IV)</td>
<td>20</td>
<td>AML 17</td>
</tr>
<tr>
<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>
</tr>
<tr>
<td>Baseline BEACOPP</td>
<td>Doxorubicin</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>CHOP</td>
<td>Doxorubicin</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>CODOX-M</td>
<td>Doxorubicin</td>
<td>40</td>
<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>
</tr>
<tr>
<td>DA 3+8</td>
<td>Daunorubicin</td>
<td>150</td>
<td>AML 17</td>
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<tr>
<td>DA 2+5</td>
<td>Daunorubicin</td>
<td>100</td>
<td>AML 18</td>
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<tr>
<td>DAE</td>
<td>Daunorubicin</td>
<td>150</td>
<td>AML 18</td>
</tr>
<tr>
<td>DCio</td>
<td>Daunorubicin</td>
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<td>AML 17 &amp; 18</td>
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<tr>
<td>FMD</td>
<td>Mitoxantrone</td>
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<tr>
<td>Hyper-CVAD</td>
<td>Doxorubicin</td>
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<td></td>
</tr>
<tr>
<td>Ida/Ara-c</td>
<td>Idarubicin (IV)</td>
<td>30</td>
<td>AML 18</td>
</tr>
<tr>
<td>IDARAM</td>
<td>Idarubicin (IV)</td>
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<tr>
<td>IVE</td>
<td>Epirubicin</td>
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<tr>
<td>MAXI-CHOP</td>
<td>Doxorubicin</td>
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<td>Nordic MCL-2</td>
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<tr>
<td>MIDAC</td>
<td>Mitoxantrone</td>
<td>50</td>
<td>AML 17</td>
</tr>
<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>UKALL 14 Phase I induction</td>
<td>Daunorubicin</td>
<td>120</td>
<td>UKALL 14</td>
</tr>
<tr>
<td>UKALL 14 Cycle 3 Consolidation</td>
<td>Daunorubicin</td>
<td>100</td>
<td>UKALL 14</td>
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<td>UKALL 2011 Regimen A Delayed Intensification</td>
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<td>UKALL 2011</td>
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<tr>
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<tr>
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<td>Z-DEX</td>
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</tr>
</tbody>
</table>

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