2. HODGKIN’S & NON-HODGKIN’S LYMPHOMA

[A] Diagnosis and Staging

Patients with either Hodgkin’s lymphoma (HL) or non-Hodgkin’s lymphoma (NHL) must first have a tissue diagnosis (usually from an excisional lymph node biopsy). Investigations then proceed to allocate a clinical/radiological Ann-Arbor stage to the patient. Document ‘B’ symptoms (fever > 38°C; drenching night sweats; loss of >10% body weight over 6 months). Lymphoma (NHL) patients are allocated an International Prognostic Index score (high grade) or FLIPI score (for follicular lymphoma), and HL patients allocated a Hasenclever score.

Note: All final histological reporting is done at Hammersmith Hospital.

Diagnostic investigations

- Excisional lymph node biopsy (or other tissue biopsy)
- Immunohistochemistry on the LN biopsy
- Immunoglobulin levels and serum protein electrophoresis

If the bone marrow or blood is thought to have NHL involvement, then further diagnostic information may be obtained from:
- Cytogenetics: BM and/or peripheral blood in culture medium.
- Immunophenotyping: unstained BM or peripheral blood slides, plus peripheral blood and/or bone marrow in preservative-free heparin.
- Gene rearrangement studies: BM and/or PB.

Staging investigations

- CXR
- CT scan: neck, chest, abdomen and pelvis
- FBC and film, ESR
- Biochemistry profile (including LDH)
- Bone marrow aspirate morphology, +/- immunophenotyping and gene rearrangement studies as above
- Bone marrow trephine biopsy histology
- Lumbar puncture in some cases - e.g. Burkitt’s lymphoma and some other aggressive lymphomas. Send for haematological cytology; occasionally immunophenotyping and/or gene rearrangement studies may also be required (Refer to Intrathecal Chemotherapy section).
Other important investigations

- Establish HIV status (lymphoma treatment may differ – see B.2.e below)
- Group and screen (EDTA sample)
- ECG (& ECHO for LV function, if any cardiac history) Culture of blood, urine, sputum etc (if patient febrile)

Ann-Arbor Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Involvement of a single lymph node region or a single extra lymphatic site (IE)</td>
</tr>
<tr>
<td>II</td>
<td>Involvement of two or more lymph node regions on the same side of the diaphragm; may include localised extra lymphatic involvement in the area drained by the involved lymph node region (IIE)</td>
</tr>
<tr>
<td>III</td>
<td>Involvement of lymph node regions on both sides of the diaphragm; may include spleen (IIIS)</td>
</tr>
<tr>
<td>IV</td>
<td>Diffuse extra-lymphatic disease (e.g. liver, bone marrow, lung, skin)</td>
</tr>
</tbody>
</table>

[If any ‘B’ symptoms are present, then classify as ‘B’ (e.g. IIB); otherwise classify as ‘A’ (e.g. IIA). Stage II can also be divided into ‘Bulky II’ (if any tumour mass = 10cm+ in diameter), or ‘Non-bulky II’ (largest tumour mass < 10cm)]

International Prognostic Index (IPI)

(NEJM 1993; 329:987)

One point is allocated for each of:

- Age > 60 years
- Ann-Arbor stage III or IV
- More than one extranodal site of involvement
- ECOG Performance Status 2-4 (i.e. non-ambulatory)
- LDH higher than the normal range

* ECOG Performance Status
  0 Asymptomatic
  1 Symptomatic but ambulatory
  2 Bedridden < Half of day
  3 Bedridden > Half of day
  4 Bedridden, requiring assistance with activities of daily living

Thus a score (the IPI) can be derived, which ranges from 0-5. For patients with aggressive NHL the prognosis with previous standard treatment (i.e. not containing rituximab) is as follows:
<table>
<thead>
<tr>
<th>Risk Group</th>
<th>IPI score</th>
<th>Complete remission</th>
<th>5 year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;60 yrs</td>
<td>&gt;60 yrs</td>
<td>&lt;60 yrs</td>
</tr>
<tr>
<td>Low risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low/intermediate risk</td>
<td>0</td>
<td>92%</td>
<td>91%</td>
</tr>
<tr>
<td>High/intermediate risk</td>
<td>1</td>
<td>78%</td>
<td>71%</td>
</tr>
<tr>
<td>High risk</td>
<td>2</td>
<td>57%</td>
<td>56%</td>
</tr>
<tr>
<td></td>
<td>3 or 4</td>
<td>46%</td>
<td>36%</td>
</tr>
</tbody>
</table>

**Age-adjusted IPI**

*Age adjusted international prognostic index for aggressive non-Hodgkin's lymphoma (NEJM 1993)*

**Score one point for each factor present**

<table>
<thead>
<tr>
<th>LDH raised</th>
<th>Performance status ≥2</th>
<th>IPI score</th>
<th>Complete remission</th>
<th>5 year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt;60 yrs</td>
<td>&gt;60 yrs</td>
<td>&lt;60 yrs</td>
</tr>
<tr>
<td>Low</td>
<td>0</td>
<td>92%</td>
<td>91%</td>
<td>83%</td>
</tr>
<tr>
<td>Low</td>
<td>1</td>
<td>78%</td>
<td>71%</td>
<td>69%</td>
</tr>
<tr>
<td>Low</td>
<td>2</td>
<td>57%</td>
<td>56%</td>
<td>46%</td>
</tr>
<tr>
<td>Low</td>
<td>3 or 4</td>
<td>46%</td>
<td>36%</td>
<td>32%</td>
</tr>
</tbody>
</table>

**FLIPI score (for follicular NHL)**

*Score one for each of the following factors (Solal-Celigny et al. Blood 2004)*

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>No of factors</th>
<th>% patients</th>
<th>5yr OS %</th>
<th>10yr OS %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0-1</td>
<td>36%</td>
<td>91%</td>
<td>71%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2</td>
<td>37%</td>
<td>78%</td>
<td>51%</td>
</tr>
<tr>
<td>High</td>
<td>≥3</td>
<td>27%</td>
<td>53%</td>
<td>36%</td>
</tr>
</tbody>
</table>
Hasenclever Score (Hasenclever 1998)

Score one point for each factor present

<table>
<thead>
<tr>
<th>Score</th>
<th>FFP at 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>84%</td>
</tr>
<tr>
<td>1</td>
<td>77%</td>
</tr>
<tr>
<td>2</td>
<td>67%</td>
</tr>
<tr>
<td>3</td>
<td>60%</td>
</tr>
<tr>
<td>4</td>
<td>51%</td>
</tr>
<tr>
<td>5+</td>
<td>42%</td>
</tr>
</tbody>
</table>

Age ≥ 45 years
Male sex
WCC >15 x10^{9}/L
Lymphocytes <0.6 x10^{9}/L
Albumin <40g/L
Haemoglobin <10.5g/dL
Stage IV disease (Ann Arbor)

Definitions

Bulky disease is defined as a tumour mass more than 5 cm in any dimension.

Complete response (CR) is defined as complete disappearance (with confirmation after a period of at least 4 weeks) of all palpable and radiologically demonstrable disease as well as bone marrow disease judged by iliac crest bone marrow biopsy (if initially positive). Residual masses of uncertain significance in areas of previous known disease should be clarified by histology whenever possible. Patients achieving a CR but relapsing within 4 weeks are defined as having PR only.

Residual masses remaining in areas of previous non-bulky disease which are not amenable to excision will be considered to be uninvolved if they measure ≤ 1.5 cm in diameter.

Residual masses remaining in areas of previous bulky disease which are not amenable to excision will be considered to be uninvolved if they measure ≤ 2.5 cm in diameter.

If the liver and/or spleen are enlarged prior to start of treatment, they must return to normal size. Furthermore, negative liver biopsy is required to document complete remission if a positive liver biopsy, palpable hepatomegaly, or abnormal liver function studies existed prior to initiation of therapy.

Partial response (PR) - Those patients with a ≥50% reduction in the sum of the products of the dimensions of the measurable lesions, will be considered to have a partial response. PR must be confirmed after a period of at least 4
weeks. Patients achieving a PR but progressing within 4 weeks are defined as having SD.

1. If the liver and/or spleen are enlarged prior to therapy, the palpable disease-related organomegaly must decrease in size by >30% for the patient to be classified as a partial responder.

**Stable disease (SD)**
A response status, which does not satisfy the criteria of complete response, partial response, or progressive disease, will be categorised as stable disease.

Progressive disease must not occur for a period of at least 4 weeks.

**Progressive disease (PD)**
Progressive disease is defined as an increase in size of >25% of the sum of the products of the pre-treatment measurements or appearance of new lesions.

**Relapse**
Relapse is defined as the re-appearance of any clinical or histological evidence of lymphoma in a patient who has had a CR. Relapse for partial responders is defined as progressive disease relative to disease status during the partial remission.

**Treatment failure**
Treatment failure is defined as any event leading to discontinuation of the trial treatment, relapse, progressive disease, or death. In addition, treatment failure includes response to treatment which is less than PR after 3 cycles of the CHOP regimen, or after phase II of the sequential high-dose regimen, respectively in areas with non-bulky disease at diagnosis: Response to treatment which is less than CR after 6 cycles of the CHOP regimen, or after phase IV of the sequential high-dose regimen, respectively in areas with bulky disease at diagnosis: Reduction of the bulky area to > 2.5cm after 6 cycles of the CHOP regimen, or after phase IV of the sequential high-dose regimen, respectively.
**[B] Non-Hodgkin’s Lymphoma (NHL)**

First line therapy

<table>
<thead>
<tr>
<th>Stage IA, indolent/low-grade</th>
<th>1. Current recommendations are for involved field radiotherapy to be used alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IA, Non-indolent/low-grade</td>
<td>2. Radiotherapy. Many authorities advise using initial shortened chemotherapy (e.g. R-CHOP x 3) prior to radiotherapy</td>
</tr>
<tr>
<td>Stage II, indolent/low-grade</td>
<td>3. Therapy may not be required. Chlorambucil or CVP. Radiotherapy is an option depending on bulk of disease</td>
</tr>
<tr>
<td>Stage III/IV, indolent/low-grade</td>
<td>4. Therapy may not be required. Chemotherapy with either chlorambucil or CVP. Addition of rituximab to CVP (R-CVP) is gaining favour as first-line therapy</td>
</tr>
<tr>
<td>Stages IB,II,III,IV,Non-indolent/low-grade</td>
<td>5. Chemotherapy is indicated. Rituximab with chemotherapy (R-CHOP) has become standard initial therapy in the UK. COP/COPADM (UKALL XII for T-cell disease) should be used for the most aggressive lymphomas (B-lymphoblastic, T-lymphoblastic, Burkitt’s).</td>
</tr>
</tbody>
</table>

**B.1 Treatment of indolent/low-grade NHL**

**B.1.a.** Early stage disease is potentially curable with radiotherapy, advanced stage disease may require no treatment depending on the age of the patient and his/her symptoms. First line chemotherapy regimens for low-grade NHL include single-agent chlorambucil and CVP (usually given with rituximab). Fludarabine with rituximab may be another option.

**2.01 Chlorambucil**
2.02 CVP

2.02 CVP Version
1.2.doc (65 K...}

2.03 Rituximab

2.03 Rituximab
Version 2.2 Jul...

2.24 R-CVP

2.24 R-CVP version
2.1 Jul08....

2.04 CHOP

2.04 CHOP Version
2.0 Jul08.do...

2.07 R-CHOP

2.07 R-CHOP
Version 2.0 Jul08....

2.05 Fludarabine

2.05 Fludarabine
v2.1 Jul08.do...

2.27 R-Fludarabine

2.27 R-Fludarabine
version 1.0, Oct07.do
**Anti-CD20 (Rituximab)** is a monoclonal antibody that targets the CD20 surface marker expressed on almost all B-cell lymphomas. CD20 is a suitable target for immunotherapy and induces cell death of CD20-positive cells by a combination of mechanisms including antibody-directed cytotoxicity, and the induction of apoptosis. Rituximab sensitises cells to the action of conventional cytotoxic drugs.

### Precaution when using Rituximab

Rituximab has been associated with potentially serious Hepatitis ‘flare’ in patients with chronic hepatitis B infection. All patients should have hepatitis B serology checked before therapy, and in those who have positive serology lamivudine 100mg daily should be commenced 1-2 weeks prior to rituximab. Currently it is recommended that lamivudine is continued for 6 months after rituximab is discontinued.

### Indications

Rituximab is currently recommended by NICE for: (see [www.nice.org.uk](http://www.nice.org.uk))

1- For treatment of patients with stage 3 or 4 advanced follicular lymphoma when all other treatment options have been exhausted - **as last line therapy**.

2- The treatment of patients with CD20-positive diffuse large B-cell non-Hodgkin’s lymphoma in combination with CHOP chemotherapy (as first line treatment).

3- It is also licensed for maintenance therapy after first-line treatment of follicular lymphoma (375mg/m² every 3 months)

### Schedule of treatment

- Follicular NHL, weekly for 4 weeks. Cycle may be repeated.
- Diffuse Large B-cell Non-Hodgkin’s Lymphoma DLBL; administered prior to chemotherapy on day 1 - **for 6-8 cycles**.

### B.1.b. Marginal zone/gastric MALT lymphoma

All patients should have their *H. pylori* status assessed. Early gastric MALT lymphomas show low regression over 6–18 months following removal of underlying stimulus i.e. *H. pylori* infections.

**H. pylori eradication: triple therapy**

Lansoprazole 30mg BD (or omeprazole 20 mg) for 7 days†

Clarithromycin* 500mg BD for 7 days

Amoxycillin* 1g BD for 7 days

* Substitute metronidazole 400mg BD for 7 days (for amoxicillin) if allergic to penicillins and substitute metronidazole 400mg BD for 7 days if patient is allergic to macrolides.

† Continue as a once a day dose for 4 weeks for large ulcers
The treatment for patients failing eradication and those not able to be entered into the IELSG Trial is unclear.

The accepted first line option is chlorambucil 10mg/day for 14 days, repeated every 28 days for 6-12 cycles. The combination of chlorambucil with rituximab has been used.

Second line- Radiotherapy to stomach and adjacent lymph nodes.

Transformation to large cell lymphoma (DLBL) may occur.

These patients then should go on to receive combination chemotherapy with R-CHOP or a second-generation regimen.

The role of surgery is controversial and it is recommended that it is reserved as salvage therapy in those who do not achieve a CR with chemotherapy alone.

Stage III/IV – treatments are as for follicular lymphoma with single agent or combination chemotherapy.

**B.1.c. Treatment of Mantle Cell Lymphoma (MCL)**

All patients should be considered for the NCRI Mantle Cell Lymphoma Trial of fludarabine/cyclophosphamide +/- rituximab (LY-05).

Patients not on the trial: options are R-CHOP, Fludarabine/cyclophosphamide or HyperCVAD. Patients receiving fludarabine/cyclophosphamide or R-CHOP should be restaged after 4 cycles. Those patients responding should be treated to maximum response, with 2 cycles beyond CR or a maximum of 8 cycles. Some centres would perform stem cell transplantation in CR1.

**1.13 HyperCVAD-MTX/AraC**

2.07 R-CHOP
**2.06 Fludarabine/ Cyclophosphamide +/- 2.03 Rituximab**

Non responders/those who progress or relapse should be treated with

**ESHAP +/-Rituximab**

or **DHAP +/- Rituximab**, followed by High Dose Therapy and PBSC rescue.

Co-trimoxazole/Pentamidine prophylaxis is essential and needs to continue up to 6 months post therapy. All blood products to be irradiated following Fludarabine.

**B.2 Treatment of aggressive NHL**

In relation to this guideline, treatment for aggressive NHL has been subdivided into the following categories:

- **B.2.a. DLBL**
- **B.2.b. Burkitt and Burkitt-like Lymphomas**
- **B.2.c. T-cell Lymphoblastic Lymphoma**
- **B.2.d. Primary CNS Lymphomas**
- **B.2.e. HIV related Lymphomas**
- **B.2.f. Treatment of relapsed aggressive NHL**

- **B.2.a. DLBL**

Outside of trials, all patients with high grade NHL should have Rituximab with CHOP. Should be offered 6-8 cycles of R-CHOP, re stage after 3 and 6 courses.
2.04 CHOP (BNLI)

2.07 R-CHOP

2.11 CIDex (adapted Riverside version)

Patients with indolent lymphomas with high-grade transformation should be treated according to DLBL guidelines depending on the patient's previous chemotherapy.

- **B.2.b. Burkitt and Burkitt-like Lymphomas**

COP/COPADM has been studied in Lyon (protocol no: 903) with promising results in B-lymphoblastic and Burkitt's lymphomas. Shown below is a modified version of Lyon 903, and is a 23-week protocol consisting of 9 separate courses including high-dose MTX, high-dose Ara-C, and intrathecal therapy. In selected patients it may be advisable to give a shortened course of therapy (e.g. omit last 3 courses, from week 17) followed by up-front high-dose therapy with stem cell support.

**UKCCSG (LYON 902/903)**

**Protocol 2.08 COP/COPADM**

A brief outline of the protocol is shown below:

<table>
<thead>
<tr>
<th>Week 1</th>
<th>COP</th>
<th>(Cyclophos., vinc., pred.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 2</td>
<td>COPADM (1)</td>
<td>(Cyclophos., vinc., pred., doxo., HD-MTX)</td>
</tr>
</tbody>
</table>
Week 5 COPADM (2) (Cyclophos., vinc., pred., doxo., HD-MTX)
Week 8 HD-Ara-C / etoposide
Week 11 HD-Ara-C / etoposide
Week 14 COPADM (3) (Cyclophos., vinc., pred., doxo., HD-MTX)
Week 17 Ara-C / etoposide
Week 20 COPAD (Cyclophos., vinc., pred., doxo.)
Week 23 Ara-C / etoposide

There is some evidence both in Burkitt’s lymphoma and ALL-L3 that cranial irradiation does not improve outcome in protocols such as this in which intrathecal therapy and high-dose systemic methotrexate/Ara-C are administered, for which reason prophylactic radiation is not included. However, there is an option in patients who present with CNS disease to give 18 Gy cranial irradiation at week 17, thus delaying the timing of the final 3 courses by 3 weeks.

Another option is CODOX-M/IVAC (Magrath) as in LY10

1.28 CODOX-M/IVAC

- **B.2.c. T-Lymphoblastic Lymphoma**

**MRC UKALL XII**

UKALL XII is the current MRC protocol for adult acute lymphoblastic leukaemia. This protocol is suitable for patients with T-lymphoblastic lymphoma. In selected patients it may be advisable to give a shortened course of therapy followed by up-front high-dose therapy with stem cell support.

- **B.2.d.1 CNS prophylaxis**

The purpose of Central Nervous System (CNS)-directed prophylaxis in patients with lymphoma is to prevent CNS relapse, a development which is associated with a very poor outcome (a median survival of a few months in most studies).

The risk of CNS relapse varies with the type of lymphoma and other factors. These guidelines do not present the available data in detail but relevant references are given for further reading.
Hodgkin’s Lymphoma

Less than 0.5% of patients with HL develop CNS disease. CNS prophylaxis is not justified.

Very aggressive NHL

The risk of CNS disease in patients with Burkitt lymphoma, lymphoblastic lymphoma and lymphoblastic leukaemia is in the order of 30-50%, and CNS-directed prophylaxis is a well-established part of therapy.

Aggressive NHL

A. Mantle Cell Lymphoma (MCL)

CNS disease in MCL is nearly always associated with relapsed systemic disease, and usually in patients with the blastic type of disease. However, little data exist on the use of CNS prophylaxis or any benefit that may be associated with this. At the present time it may be reasonable to consider CNS prophylaxis in patients with blastic disease in whom therapy with curative intent is being given.

B. Diffuse Large B-cell Lymphoma (DLBL)

The overall risk of CNS relapse for all patients with DLBL is approximately 5%. There have been many studies which have attempted to identify which patient groups are at sufficiently higher risk of CNS relapse to justify CNS prophylaxis. Multivariate analyses suggest that the following patients should receive this therapy:

(1) General

The evidence suggests that patients who have both a raised LDH and more than one extranodal site of disease have an approximate 20% risk of CNS relapse. Giving CNS prophylaxis to patients without both of these criteria would expose many patients to the potential toxicity of this therapy when there is insufficient risk.

(2) Site-specific extranodal disease

(i) Testicular lymphoma
(ii) Breast lymphoma

[(iii) Epidural/extradural lymphoma]
[(iv) Sinonasal lymphoma]

The data for the first two (testicular and breast) are relatively strong. They are less strong for the latter two (epidural/extradural and sinonasal). Other extradural sites, such as bone marrow and lung,
appear to lose their influence on CNS relapse risk in multivariate analysis other than being one site of extranodal disease (see 1. above).

It should be noted that currently there is very little data showing benefit for CNS-directed prophylaxis in any group of patients with DLBL.

Indolent NHL

The overall risk for CNS relapse in patients with indolent NHL (in most studies these have been mainly follicular NHL) appears to be less than 5%, and in the majority of reported cases the CNS relapse has followed transformation of the lymphoma into a more aggressive grade of disease. There is currently no evidence of benefit for CNS prophylaxis in any group of patients, although such therapy could be justified in patients with transformed disease fulfilling the criteria as for DLBL (see B. above).

Peripheral T-cell Lymphoma (PTCL)

There is almost no data on the risk of CNS relapse in patients with PTCL, and currently CNS-directed prophylaxis is not advocated in these patients.

Summary of recommendations

CNS prophylaxis is not required

Hodgkin’s Lymphoma
Untransformed indolent NHL
PTCL

CNS prophylaxis is required

Lymphoblastic lymphoma
Lymphoblastic leukaemia
Burkitt and Burkitt-like lymphoma

CNS prophylaxis is controversial but justifiable

Mantle cell lymphoma of blastic type
DLBL with:
  Raised LDH and more than one extranodal site of disease or Testicular lymphoma/breast lymphoma/epidural-extradural lymphoma/sinonasal lymphoma
Transformed indolent NHL meeting criteria as for DLBL
CNS prophylaxis
As in the relevant chemotherapy regimen.

References


- **B.2.d.2 Primary CNS Lymphoma**

  Must be treated using this regimen.

  **2.29 CNS HD-MTX**

  ![2.29 CNS HD-MTX](file)

  2.29 CNS HD-MTX
  Version 2.0 Jul08...

- **B.2.d.3 Aggressive Systemic & CNS Lymphoma**

  Where there is aggressive systemic lymphoma e.g. DLBL with parenchymal CNS involvement at presentation or relapse, suitable treatments are:

  **2.30 CHOMP**

  ![2.30 CHOMP](file)

  2.30 CHOMP
  Version 2.0 Jul08...

  **2.31 IDARAM**

  ![2.31 IDARAM](file)

  2.31 IDARAM
  Version 2.0 Jul08...
B.2.e. HIV-associated Lymphoma

Pre-treatment assessment

Full history of HIV, OIs & antiretroviral therapy
Clinical examination
CT thorax, abdomen & pelvis
Bone marrow aspirate & trephine
Lumbar puncture & CSF cytology, protein & glucose with 12.5 mg methotrexate given intrathecally
Serum LDH & Beta2 microglobulin
CD4 cell count & HIV RNA viral load
Performance status (ECOG or Karnovsky)

Staging

Ann Arbor staging of non-Hodgkin's lymphoma is used as for other non-Hodgkin's lymphomas.

Prognostic Modelling

Prognostic modelling for AIDS-NHL has been developed from the IPI (International Prognostic Index):
The International Prognostic Index (IPI) predicts the risk of disease recurrence and overall survival in aggressive NHL not associated with HIV infection by taking into account 5 factors:
1. Age over 60 years
2. Late-stage disease (Stages 3 and 4)
3. More than one extranodal site
4. High LDH
5. Poor performance status

New prognostic scoring weightings for systemic AIDS-NHL in HAART era. Calculate total prognostic score by adding weightings.

<table>
<thead>
<tr>
<th>Score</th>
<th>CD4 count</th>
<th>IPI score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score</td>
<td>CD4 count</td>
<td>IPI score</td>
</tr>
<tr>
<td></td>
<td>&lt;100/mm³</td>
<td>High</td>
</tr>
<tr>
<td>1.34</td>
<td>2.9</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>1.84</td>
<td>Intermediate</td>
<td></td>
</tr>
<tr>
<td>1.0</td>
<td>Low intermediate</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Low</td>
<td></td>
</tr>
</tbody>
</table>
Prognostic Risk Score

<table>
<thead>
<tr>
<th>Risk Score</th>
<th>Likelihood ratio value</th>
<th>HR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total=111</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1.00</td>
<td>0.23</td>
<td>0.15 (0.06 to 0.33)</td>
</tr>
<tr>
<td>1.00-1.83</td>
<td>0.74</td>
<td>0.44 (0.22 to 0.88)</td>
</tr>
<tr>
<td>1.84-2.90</td>
<td>3.32</td>
<td>1.17 (0.64 to 2.17)</td>
</tr>
<tr>
<td>&gt;2.90</td>
<td>7.90</td>
<td>1</td>
</tr>
</tbody>
</table>

Score | 1 year overall survival |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>82%</td>
</tr>
<tr>
<td>1-1.83</td>
<td>47%</td>
</tr>
<tr>
<td>1.83-2.90</td>
<td>20%</td>
</tr>
<tr>
<td>&gt;2.90</td>
<td>15%</td>
</tr>
</tbody>
</table>


Treatment

All patients should be referred to and discussed at Network Haematology MDT

HAART

- All patients receive 12.5mg methotrexate intrathecally with diagnostic lumbar puncture.

- All patients receive anti-PCP, anti-fungal and anti-mycobacterial prophylaxis (usually Co-trimoxazole 960mg od, Fluconazole 100mg od and Azithromycin 1250mg once a week).

- All patients receive concomitant HAART therapy in accordance with accepted BHIVA guidelines. Potential drug interactions between antiretrovirals and chemotherapy should always be considered.

**Burkitt’s Lymphoma**

**1.28 CODOX-M/IVAC**

**Diffuse Large B Cell Lymphoma**

**2.07 R-CHOP**

**Intrathecal therapy for DLBL**

All patients have a diagnostic staging lumbar puncture and on this occasion methotrexate 12.5mg should be given intrathecally.

In addition, patients with Testicular, Breast with paranasal or epidural disease will receive meningeal prophylaxis as will patients with >1 extradural site. Patients with raised serum LDH should also receive intrathecal prophylaxis of fortnightly intrathecal methotrexate 10mg for 6 doses. (Ref: Central nervous system – directed preventative therapy in adults with Lymphoma. McMillan A. Br J Haem 2005 131:13-21).

Patients with meningeal lymphoma present at diagnosis will be treated with one of two intrathecal chemotherapy schedules:

1. Liposomal cytarabine (DepoCyte) 50mg intrathecal every fortnight for 2 months followed by monthly injections for 6 months (total 10 intrathecal installations). Each intrathecal injection will be accompanied by Dexamethasone 4mg bd po or iv for 5 days.

**2.21 Depocytte protocol**

2. Alternating intrathecal methotrexate 12.5mg and intrathecal cytarabine 50mg, given twice a week for four weeks, once a week for four weeks, once a fortnight for eight weeks and then monthly until systemic chemotherapy is completed.


**Antiinfection Prophylaxis**
Throughout the entire duration of the chemotherapy patients will also receive
1. Allopurinol 300mg orally od,
2. Cotrimoxazole 960mg od orally, (dapsone or pentamidine if allergic)
3. Fluconazole 100mg od,
4. Azithromycin 1250mg orally once a week.

**HIV - associated Primary Cerebral NHL**
Treatment options depend on performance status and patient preference, and include;
- Best supportive care
- Whole brain radiotherapy -20Gy in 5 daily fractions
- Systemic Methotrexate

Note: Methotrexate assays are measured at St Thomas’, send 10ml clotted blood to clinical chemistry at CWH who will send it on. First sample 2 days after methotrexate then on alternate days. The schedule is repeated every 14 days until complete remission on CT scan up to a maximum of 6 cycles. CT scan should be performed every other cycle. Stop if there is radiological evidence of disease progression and offer palliative whole brain radiotherapy.

**2.22 Methotrexate High Dose (HIV)**

B.2.f. Treatment of relapsed aggressive NHL

Patients with relapsed high-grade lymphoma should be treated with appropriate chemotherapy and considered for high dose chemotherapy and stem cell rescue. Rituximab may be added to these protocols.

Indications

- Relapsed lymphomas
- Mantle cell lymphoma
- Burkitt’s lymphoma
- Lymphoblastic lymphoma

2.12 DHAP or 2.25 R-DHAP

2.13 ESHAP or 2.26 R-ESHAP

1.13 HyperCVAD


Patients >65 years receive 8 cycles, while patients ≤ 65 years are consolidated after 4 cycles with high dose chemotherapy and PBSC transplant.

HCVAD: cycles 1, 3, 5, 7
MTX-ARAC: Cycles 2, 4, 6, 8

2.28 F-GIV is also suitable for relapsed HL

2.30 CHOMP
C. Hodgkin’s Lymphoma

The optimal treatment of HL is uncertain, with a balance to be struck between disease control/cure and the risk of long-term side effects. To best manage this all patients require careful staging and assessment of risk factors. At diagnosis staging is by CT and if possible pre-treatment PET scan, BM biopsy is undertaken where appropriate and laboratory data is collected. All new patients are discussed at the Lymphoma MDT where histology, stage, risk factors and IPS are reviewed and an individual treatment plan formulated.

Using the “Cotswold staging” classification and the following risk factors: LMM, extra nodal disease, >3 nodal areas, age >50 years, elevated ESR >50mm/hr in stage A disease, >30mm/hr in stage B disease, the aim is to delineate three patient groups. Although it is as yet unclear whether there is value in defining an Intermediate group for the purpose of therapy, this may prove to be helpful in auditing outcome and in future determine treatment strategy.

Classical HL (cHL)

1. Early Favourable: Stage I or II, no risk factors.
2. Intermediate (Early Unfavourable): Stage I or II with 1 or more risk factors (excluding LMM or bulky disease >10cm, see advanced)
3. Advanced: Stage II with LMM or bulk >10cm., Stage III or IV.

Early Favourable and Intermediate cHL

Current management of this stage is either combined modality treatment (CMT) or chemotherapy alone. It should be noted that this choice leads to a trade off with CMT providing potentially superior disease control but with an increased risk of long-term side effects.

Combined Modality Treatment:
ABVD 4 cycles followed by Involved Field (IF) Radiotherapy (for details see radiotherapy section of this protocol)

Chemotherapy Alone:
ABVD 4 cycles (if CR by restaging after 2 cycles) ABVD 6 cycles (if no CR after 2 cycles.)

Advanced cHL

As with the above patients, the role of chemotherapy alone versus combined modality treatment is unclear. Meta analysis does not provide support for the use of consolidation radiotherapy. In contrast excellent results (in a single centre non-randomised study) were obtained using Stanford V, a regimen in which most patients receive radiotherapy. Two approaches for advanced HL can be considered: ABVD and Stanford V.
ABVD 6-8 cycles: on completion of chemotherapy a CT/PET scan is performed. Consolidation radiotherapy may be considered for residual active disease is demonstrated.

Stanford V: a 12 week regimen with the addition of IF radiotherapy to LMM, bulk disease > 5cm, or macroscopic splenic nodules visible on CT.

Lymphocyte Predominant Hodgkin’s Lymphoma (LPHL)

Stage 1: surgical excision followed by radiotherapy.

Advanced stage: treat as cHL. (LPHL patients may respond to Rituximab)

Relapsed or Refractory HL

Patients with a long first remission and persistent or relapsed localised disease may be cured by further standard chemotherapy or localised radiotherapy. However the majority of relapsed patients particularly if treated adequately at first presentation will require high dose chemotherapy and autologous stem cell transplant.

Standard therapy is 2 cycles of DHAP chemotherapy to demonstrate chemosensitivity (although failure to formally demonstrate a response in a stable cHL patient does not necessarily exclude SCT). Etoposide (or cyclophosphamide) mobilised peripheral blood stem cell collection is undertaken, followed by autologous SCT. For details of the chemotherapy regimens see links below:

HIV-associated Hodgkin’s Lymphoma

Staging

The staging and treatment for HL is the same as for the HIV negative population, although there are a number of clinico-pathological differences outlined in the table.

<table>
<thead>
<tr>
<th>HIV associated HL</th>
<th>Non-HIV associated HL</th>
</tr>
</thead>
<tbody>
<tr>
<td>High incidence of EBV in HL tissues</td>
<td>Low incidence of EBV in HL tissues</td>
</tr>
<tr>
<td>Mixed cellularity &amp; lymphocyte depleted histologies predominate</td>
<td>Nodular sclerosis histology predominates</td>
</tr>
<tr>
<td>Advanced stage at presentation (75-85% Stage III/IV)</td>
<td>Earlier stage at presentation</td>
</tr>
<tr>
<td>B symptoms common</td>
<td>B symptoms less common</td>
</tr>
<tr>
<td>Extranodal disease common</td>
<td>Extranodal disease less common</td>
</tr>
<tr>
<td>Lower CR rate (45-60%)</td>
<td>Higher CR rate (80-95%)</td>
</tr>
<tr>
<td>High relapse rate</td>
<td>Low relapse rate</td>
</tr>
<tr>
<td>Median survival 8-18 months</td>
<td>Median survival &gt;12 years</td>
</tr>
</tbody>
</table>
Treatment

HAART
All patients to receive concomitant HAART therapy in accordance with accepted BHIVA guidelines. Potential drug interactions between antiretrovirals and chemotherapy should always be considered. Please refer to full prescribing guidelines within the HIV antiretroviral policy for the HIV/GUM Directorate when prescribing HAART.


Chemotherapy

2.14 ABVD

2.15 ChIVPP (substitute for MOPP)

2.16 PABIOE

2.17 STANFORD V

ABVD is used first line.
Antiinfection Prophylaxis (for HIV patients)
Throughout the entire duration of the chemotherapy patients will also receive
Allopurinol 300mg orally od,
Cotrimoxazole 960mg od orally, dapsone or pentamidine if allergic,
Itraconazole 200mg od, fluconazole if drug interactions, and
Azithromycin 1250mg orally once a week.

D. High-Dose Therapy For Hodgkin and Non-Hodgkin’s Lymphoma

High-dose therapy (HDT) with autologous stem cell support (SCT) is an established treatment for specific categories of NHL and HL patients. Both autologous and allogeneic transplants for NHL or HL are performed at the Hammersmith Hospital.

The upper age limit is normally 65 years for autologous and 50-55 years for allogeneic transplantation. Unless there are exceptional circumstances, patients with refractory disease will not be considered for HDT. Allogeneic SCT, however, may be considered in appropriate patients with an HLA-matched donor. Younger patients with BM involvement and/or with low-grade lymphoma may be considered for allogeneic BMT.

Relapsed patients will be restaged after initial chemotherapy (CT scan, LDH, BM if relevant) to confirm responsiveness and will be restaged immediately prior to commencement of HDT.

Post-transplant staging investigations will be performed at 3, 6, and 12 months and annually thereafter.

INDICATIONS FOR HIGH-DOSE THERAPY

Hodgkin Lymphoma
Patients relapsing after chemotherapy with a hybrid regimen or equivalent.

Intermediate and High-Grade NHL
Patients relapsing after an anthracycline-containing regimen.

- Patients in 1st CR at high risk as defined by the International Prognostic Index (IPI) have previously been considered as candidates for HDT; however, the IPI has not yet been validated in patients who have received rituximab as part of first-line therapy, and so currently it may be reasonable to just observe such patients.
Indolent/Low-grade NHL

- Patients relapsing after 2nd-line therapy.
- Allogeneic SCT should be considered especially if the bone marrow is involved.

AUTOLOGOUS OR ALLOGENIC SCT

All patients felt to be eligible for HDT should be referred to the appropriate consultant for outpatient review, prior to formal transplant work-up by the relevant transplant co-ordinator.

Scheduling of High-Dose Therapy

‘Aggressive’ high-risk NHL in 1st CR

Mobilise and proceed to HDT (but see above).

Relapsed ‘aggressive’ NHL

Two courses of DHAP or R-DHAP to establish chemosensitivity are given prior to stem cell mobilisation.

Relapsed Hodgkin’s Lymphoma

Two courses of DHAP or ChlVPP (or equivalent) to establish chemosensitivity and then mobilise stem cells with cyclophosphamide or etoposide.

Low-grade (indolent) lymphoma

Give two-three courses of CVP or R-CVP or fludarabine (depending on previous therapy) to establish chemosensitivity and then proceed to mobilisation and HDT.

PBSC Mobilisation

Chemotherapy and instruction in the administration of G-CSF can be given at the Hammersmith Hospital or at the referring hospital, depending on local facilities. Stem cell collection takes place in the Haematology Day Care Unit at Hammersmith Hospital usually on two consecutive days, as an outpatient. Arrangements for the measurement of the white cell count and CD34+ cell estimation will vary according to local facilities and the distance that the patient has to travel.

Prior to the administration of mobilisation chemotherapy estimation of cardiac and renal function by MUGA / echocardiogram and creatinine clearance respectively should be performed.
At present etoposide for PBPC mobilisation is preferred, however cyclophosphamide may be considered an option.

### 2.18 Etoposide Mobilisation

2.18 Etoposide Mobilisation

### 2.19 Cyclophosphamide Mobilisation

2.19 Cyclo Mobilisation

---

**Stem cell transplantation**

Hammersmith Hospital uses a high-dose combination chemotherapy protocol called LACE. Prior to this procedure the patient is restaged and pulmonary function tests performed.

---

**Revised by:** Dr George Hughes, Dr Ed Kanfer, Donald Macdonald and Pauline McCalla

**Authorised by:** WLCN Haematology TWG November 2007

**Date for review by Haematology TWG:** November 2009