

# Greater Manchester Cancer Pathway Lymphoma Guidelines 2019

## **Fifth Edition**

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## Introduction

Greater Manchester Cancer Pathway Lymphoma Guidelines were first published in 2004. There have been significant and exciting advances in the understanding of the pathophysiology of lymphoproliferative disorders since the last published guidelines, this has translated to improvements in the management of patients.

These guidelines are updated from 2011 and outline best practice based on the current evidence and management options within the NHS. To enable continued improvement in patient outcomes it is critical that, wherever possible, patients are entered into national clinical trials.

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## Initial Assessment in Patients with Suspected Lymphoma

### Clinical Evaluation

History including ECOG performance status and presence of B symptoms.  
Examination, with particular attention to nodal areas.

### Initial investigations

#### Blood Tests

FBC, blood film and cell markers as appropriate to exclude B-CLL or acute leukaemia.

Consider reticulocytes, ESR, group and save/antibody screen, haematinics, coagulation profile.

Biochemistry including LDH, urate

Viral serology (Hepatitis B, C, HIV, (HTLV-1 in selected T cell lymphoma)), consider Monospot test, EBV PCR.

Immunoglobulins, serum electrophoresis and beta-2-microglobulin

#### Imaging

CXR is recommended if any concern regarding mediastinal disease

CT neck, chest, abdomen and pelvis in patients with high clinical suspicion of lymphoma.

Echocardiogram is recommended in patients prior to receiving anthracyclines or those with suspected or known cardiac disease.

#### Biopsy

Wherever possible a lymph node excision biopsy is recommended.

Core biopsy may be appropriate if surgical biopsy cannot be readily obtained.

Fine needle aspirate should be avoided.

Major surgery should be avoided if at all possible.

Request forms accompanying the specimen must include relevant clinical and laboratory information, including previous pathological diagnoses.

## Staging Investigations in Patients with Confirmed Lymphoma

CT neck, chest, abdomen and pelvis (if not performed in investigational work-up)

PET/CT scan is recommended in all high grade NHL, Hodgkin's lymphoma and suspected stage 1 low grade NHL. See appendix 1 for Deauville scoring.

Bone marrow examination is recommended in low grade NHL or unexplained cytopenias in other lymphoma.

Cerebrospinal fluid examination if clinical signs of CNS disease. Cytological assessment by cytospin and immunophenotyping if cells seen. Consider administration of intrathecal chemotherapy at the same time as diagnostic lumbar puncture if high clinical suspicion.

MRI head scan if neurological involvement suspected. MRI if stage I/II nasopharyngeal/para-nasal sinus as this will help radiotherapy planning.

See appendix 2 for Ann Arbor staging classification for lymphoma

## Multi-disciplinary Approach

All new diagnoses of lymphoma should be subject to central review by a specialist haematopathologist, and should be discussed alongside imaging at the appropriate MDT meeting.

All patients should have written information on diagnosis and proposed treatment

All patients should have contact with a clinical nurse specialist.

## Young Adults

The designated primary treatment centre (PTC) for Teenage and Young Adolescents (TYA's) with Cancer is the TYA Centre at Christie Hospital (Young Oncology Unit).

The PTC should be notified of all 16 - 24 year olds. All 16 - 18 year olds should be referred to the PTC so that treatment is delivered in age appropriate facilities and with appropriate staff and support.

Patients aged 19- 24 year olds should be fully informed of the facilities available at the PTC and offered referral.

## **Fertility preservation**

Semen cryopreservation must be offered to all male and oocyte/embryo storage considered for pre-menopausal women concerned about fertility and treatment may cause permanent sterility.

## Indolent Non-Hodgkins Lymphoma

(Small lymphocytic lymphoma/chronic lymphocytic leukaemia are discussed in alternative guidelines)

### Mantle cell lymphoma (MCL)

All patients at diagnosis and relapse should be considered for a suitable clinical trial. In asymptomatic patients it is acceptable to watch and wait in patients with indolent disease.

Staging should be performed using CT scan and bone marrow biopsy. Prognostication can be aided using the MIPI score (appendix C).

*In autoSCT eligible patients:* induce remission by an induction regimen including high dose cytarabine (either a NORDIC protocol (1) or alternating R-CHOP with R-DHAP) and consolidate with BEAM/LEAM autoSCT. Allogeneic stem cell transplant can be considered in high risk patients following discussion with a transplant centre.

Maintenance rituximab can be offered to patients after autoSCT (2).

Ibrutinib can be administered at relapse and discussion with a transplant centre regarding allogeneic transplant if eligible.

*In patients ineligible for autoSCT:* treatment options include R-CHOP, bortezomib containing regimens (3), R-Bendamustine or R-CVP. Maintenance rituximab can be offered to patients who have responded to first line induction therapy with rituximab in combination with chemotherapy. (4).

Ibrutinib can be administered at first relapse(5).

### Follicular lymphoma (FL)

All patients at diagnosis and relapse should be considered for a suitable clinical trial.

Staging should be performed using CT scan and bone marrow biopsy. Prognostication can be aided using the FLIPI score (appendix C).

*Patients with stage 1A FL* should be offered radiotherapy. PET/CT can be useful to distinguish stage 1 from more advanced stage FL.

#### *Patients with advanced stage FL*

For asymptomatic patients without bulky disease a watch and wait approach can be taken. Single agent intravenous rituximab can be offered to selected patients.

*Patients who have a FLIPI score >2, obinutuzumab and CVP/CHOP/bendamustine can be offered followed by obinutuzumab maintenance for two years in patients with at least a documented PR (6).*

*Patients who have a FLIPI score <2, rituximab and CVP/CHOP/bendamustine can be offered followed by rituximab maintenance for two years in responding patients.*

### **Relapsed Disease**

At relapse or in refractory disease, options will depend on previous treatment, performance status, co-morbidity and patient preference.

Any patient with symptoms suggestive of high-grade transformation should have repeat biopsy.

If the patient is asymptomatic a watch and wait approach can be taken

*Patients eligible for an autoSCT:* an autoSCT can be considered in patients who relapse especially if relapse is within 24 months of first line therapy (7). Remission can be induced by a rituximab and chemotherapy (different to first line chemotherapy) containing regimen prior to stem cell collection and a BEAM/LEAM autoSCT. Patients who relapse <6 months following rituximab and CVP/CHOP, or during/within 6 months of completing rituximab maintenance, obinutuzumab with bendamustine can be given. Allogeneic stem cell transplant can be considered either at first relapse in high risk patients or following relapse after autoSCT following discussion with a transplant centre

*Patients who are ineligible for an autoSCT:* if a patient relapses <6 months following rituximab and CVP/CHOP, or during/within 6 months of completing rituximab maintenance, obinutuzumab with bendamustine can be given followed by obinutuzumab maintenance in responding patients or those with stable disease (8).

Patients who either receive obinutuzumab first line or relapse > 6 months following first line therapy should be offered rituximab and chemotherapy (different to first line chemotherapy).

### **Marginal Zone Lymphoma (MZL)**

All patients at diagnosis and relapse should be considered for a suitable clinical trial.

Staging should be performed using CT scan and bone marrow biopsy.

### **Gastric mucosal associated lymphoid tissue (MALT)**

*Patients with gastric MALT stage 1A/E; If Helicobacter Pylori (H.Pylori) positive treat with 'triple eradication therapy' (antibiotics and proton pump inhibitor) and repeat H. Pylori testing and gastroscopy. Surveillance by gastroscopy every 6 months for 2 years and 12-18 monthly should be considered.*

*Patients with gastric MALT stage 2-4A/BE: treatment should include H.Pylori eradication and either a watch and wait approach or rituximab with chemotherapy (CVP, CHOP, bendamustine, chlorambucil).*

### **Extranodal and nodal MZL**

*Patients with stage 1A extranodal or nodal MZL: should be offered radiotherapy or a watch and wait approach.*

*Patients with stage 2-4 A/B extranodal or nodal MZL: should be offered a watch and wait approach (if asymptomatic) or rituximab and chemotherapy (CVP, CHOP, bendamustine, chlorambucil).*

*Patients with splenic marginal zone lymphoma: options include watch and wait, rituximab and chemotherapy (CVP, CHOP, bendamustine, chlorambucil), in selected patients splenectomy can be utilised.*

Maintenance rituximab can be offered to responding patients with MZL following rituximab and chemotherapy.

In relapsed MZL, treatment options include radiotherapy (for localized disease), further rituximab containing regimens and stem cell transplantation.

### **Waldenstrom's macroglobulinemia/lymphoplasmacytoid lymphoma (LPL)**

All patients at diagnosis and relapse should be considered for a suitable clinical trial.

Staging should be performed using CT scan and bone marrow biopsy. LPL is associated with a IgM paraprotein which should be monitored through observation periods and treatment.

Treatment options include a watch and wait approach, rituximab with chemotherapy (bendamustine, cyclophosphamide and dexamethasone, CHOP, chlorambucil). Maintenance rituximab can be offered to responding patients with LPL following rituximab and chemotherapy.

Patients with a IgM paraprotein of over 40g/l caution should be taken with rituximab as can cause a flare of paraprotein.

Patients who present with signs or symptoms of hyperviscosity should be treated as a haematological emergency and treated initially with plasma exchange and steroid.

At relapse, treatment options include ibrutinib (9), a rituximab containing regimen (which the patient had not previously been exposed to) and consideration of transplantation options.

### **Hairy Cell Leukaemia (HCL)**

All patients at diagnosis and relapse should be considered for a suitable clinical trial.

Staging should be performed using CT scan and bone marrow biopsy.

Asymptomatic patients with low-level disease with no significant cytopenias can be observed.

First line treatment for HCL is with purine analogues, cladribine or pentostatin; both agents have been shown to be equally effective. End of treatment assessment with bone marrow +/- CT should be performed 4-6 months after initial therapy.

Patients with suboptimal response to first line therapy or at relapse can be treated with cladribine or pentostatin and the addition of rituximab.

## Aggressive Non Hodgkin's Lymphoma

All patients at diagnosis and relapse should be considered for a suitable clinical trial.

Staging and end of therapy imaging should be performed using PET/CT scan. Bone marrow biopsy is often not required. Prognostication can be aided using the R-IPI score.

### Diffuse Large B Cell Lymphoma (DLBCL)

*Stage 1 DLBCL (including variants) and follicular lymphoma, grade 3B;* patients should be treated with 3 cycles of RCHOP followed by involved field radiotherapy.

Patients with high risk disease (bulk disease, extra-nodal involvement, IPI risk factors) may be more appropriately treated with 6 cycles R-CHOP followed by consideration of radiotherapy.

*Stages 2-4 DLBCL (including variants) and follicular lymphoma, grade 3B;* patients should receive 6 cycles of R-CHOP followed by consideration of radiotherapy to sites of previous bulk disease/residual abnormality.

In patients with a high R-IPI score or double/triple hit lymphoma alternative regimens to R-CHOP may be considered, DA-EPOCHR or RCODOXM- RIVAC. There is paucity of evidence in this area and enrollment of patients in suitable clinical trials should be considered where possible.

Central nervous system prophylaxis is an area of uncertainty. Patients who are deemed high risk for CNS relapse should receive CNS prophylaxis. This can be administered as intrathecal methotrexate and IV high dose methotrexate or IV high dose methotrexate. Local practices may differ (see below for Burkitts lymphoma and testicular lymphoma).

In less fit patients and those with cardiac disease, alternative regimens such as RCVP and RGCVP can be used.

### High Grade Transformation of Low Grade NHL

If the diagnosis of high grade transformation is made concurrently with low grade lymphoma the patient should be treated as per DLBCL guidelines and transplantation is not recommended in first remission.

Patients with high grade transformation of low grade NHL who have either previously received treatment or have been actively monitored should receive 6 cycles of RCHOP (salvage regimens can be considered if patient has previously received R-CHOP). AutoSCT should be offered to eligible patients in first remission.

## Primary Mediastinal B Cell Lymphoma

Treatment options include RCHOP and DA-EPOCHR, it is not clear which patients should receive radiotherapy consolidation and this should ideally be assessed by enrolling patients in clinical trials.

## Testicular Lymphoma

Testicular lymphoma has a propensity for CNS involvement. Treatment should be with 6 cycles of RCHOP and prophylactic intrathecal methotrexate given with cycles 1-4 and 2-3 cycles of high dose IV methotrexate following completion of R-CHOP. Radiotherapy to the contralateral testis should also be undertaken in addition to consideration or radiotherapy to sites of initial bulky disease or residual abnormality.

## Relapsed/Refractory High Grade B Cell Lymphoma

Relapse should be confirmed with biopsy wherever possible.

All patients should be considered for clinical trials due to the poor prognosis in this group.

Patients fit for autoSCT should receive 2 cycles of salvage treatment with rituximab (ESHAP, ICE, DHAP, IVE, IGEV, GDP and miniBEAM) and remission status should be evaluated with a PET/CT scan.

If the patient is in a complete metabolic remission (CMR) or near CMR, the patient should undergo stem cell collection following further salvage chemotherapy + GCSF prior to BEAM/LEAM autoSCT. Allogeneic transplantation can be considered in selected patients and should be discussed with a transplant centre.

Fit patients not responding to salvage chemotherapy should be considered for CAR-T therapy (contact Jane Norman or John Radford/Adrian Bloor).

Patients who relapse post autoSCT should be considered for a clinical trial, CAR-T cell therapy and/or allogeneic transplantation .

Palliative options for patients unfit for stem cell transplantation/CAR T therapy or who have poor response to salvage chemotherapy/experimental therapies include gemcitabine based regimens, single agent pixantrone, rituximab with oral chemotherapy and palliative radiotherapy to sites of disease causing symptoms.

## Burkitt and Burkitt-like lymphoma

In fit patients treat as per LY10 protocol (10) with addition of rituximab, for low risk patients (stage 1 or 2, low LDH, site of disease < 10cm, good performance status) offer 3 cycles RCODOXM.

For high risk patients (those who do not fit the low risk criteria) give alternating R-CODOXM-R-IVAC to a maximum of 4 cycles.

For less fit patients alternative regimens can be considered (DA-EPOCHR).

Relapsed or refractory Burkitts has a poor prognosis experimental therapies or palliation should be considered.

### **Primary CNS lymphoma (PCNSL)**

Treatment of PCNSL should be managed in a specialist centre with established links to a neurosurgical/oncology MDT (Dr Kim Linton at Christie).

Based on outcomes from IESLG32 (11) fit patients should be treated on a MATRix protocol and consolidated with autoSCT using thiotepa/BCNU conditioning.

Other treatment options include whole brain radiotherapy and ifosfamide containing regimens.

Patients not fit enough for such intensive therapy should be considered for repeated courses of high dose methotrexate, intrathecal decocyte if meningeal disease, dexamethasone, temozolomide or experimental approaches.

### **Secondary CNS lymphoma**

Treatment options depend on whether CNS lymphoma is detected at diagnosis (e.g systemic lymphoma co-presenting with CNS involvement) or relapse in CNS without evidence of systemic lymphoma.

The former, R-CODOX-M-R-IVAC is recommended in fitter patients and the latter (if eligible) can be treated as per PCNSL.

### **Lymphoblastic lymphoma (B and T cell types)**

An acute lymphoblastic leukaemia protocol is recommended.

### **Peripheral T-cell Lymphomas (PTCL)**

Overall the prognosis is poor for this group of tumours and patients should be offered clinical trials wherever possible.

6 cycles of CHOP followed by a BEAM/LEAM autoSCT or allogeneic haemopoietic stem cell transplant in eligible patients. Consolidation radiotherapy should be considered. See below (specific PTCL for differences to this approach).

### **Specific PTCL**

Anaplastic large cell lymphoma (ALCL), alk positive; 6 cycles of CHO(E)P can be considered and in young patients stem cell transplantation is not recommended

in first remission as the prognosis is better than other PTCL. Relapse should be treated with a salvage regimen and stem cell transplantation.

Adult T cell lymphoma (HTLV-1); treatment should include zidovudine and interferon alpha and specialist advice should be sought. Risk of infection is high in these patients. Allogeneic transplant should be used in first remission in eligible patients.

Extranodal NK/T Cell Lymphoma, nasal type; treatment should include early radiotherapy and an asparaginase containing regimen (SMILE).

### **HIV associated Lymphoma**

Anti-lymphoma therapy should be administered in combination with HIV treatment and these patients should be treated in centres with HIV expertise (Dr Martin Rowlands at Pennine Acute Trust or Dr Jane Norman at MRI).

### **Post Transplant Lymphoproliferative Disorders (PTLD)**

Treatment will depend on histology of lymphoma, in polymorphic PTLD reduction of immunosuppression can often induce remission.

In more aggressive (monomorphic PTLD) reduction of immunosuppression and treatment with either rituximab or a rituximab containing chemotherapy regimen is recommended.

Consider referral of PTLD to a specialist centre (Dr Sarah Burns at MRI).

### **Cutaneous Lymphoma**

Refer to supra-regional cutaneous lymphoma service for initial assessment and management plan (Dr Richard Cowan/Dr Eileen Parry at Christie).

## Hodgkin's Lymphoma

All patients at diagnosis and relapse should be considered for a suitable clinical trial.

Staging should be performed using PET/CT scan. All patients should receive irradiated blood products.

### Classical Hodgkin's Lymphoma (cHL)

*Early stage (favourable risk):* Patients can be treated with 3 cycles of ABVD and if a PET/CT demonstrates CMR involved field radiotherapy can be considered (12).

*Early stage (unfavourable risk) or advanced stage:* Patients should receive 2 cycles of ABVD followed a PET/CT scan. If this shows response graded as Deauville 1 to 3 the patient should receive a further 4 cycles of AVD (13).

If the interim PET/CT scan shows Deauville score 4 to 5, patients should receive a further 3 cycles of escalated BEACOPP or 4 cycles of BEACOPP 14 with a PET/CT scan after 2 of these cycles. If patient not in remission after 2 cycles of BEACOPP 14 or escalated BEACOPP consider treating as per relapsed/refractory cHL.

End of treatment PET/CT scans are not needed if patient is in remission on an interim PET/CT scan.

In frailer patients with co-morbidities, options include attenuated ABVD (avoid bleomycin in those patients with lung disease), CHVPP and VEMEPB.

### Relapsed/Refractory Classical Hodgkin's lymphoma

Relapse should be confirmed with biopsy wherever possible.

#### *Patients eligible for stem cell transplantation*

Patients should receive salvage chemotherapy, regimens include ESHAP, ICE, DHAP, IVE, IGEV, GDP and miniBEAM. Patients should receive 2 courses of salvage chemotherapy and restaged with a PET/CT scan.

If the patient is in a complete metabolic remission (CMR) or near CMR, the patient should undergo stem cell collection following further salvage chemotherapy + GCSF prior to BEAM autoSCT. Reduced intensity allogeneic transplantation can be considered in selected patients and should be discussed with a transplant centre.

Brentuximab vedotin (BV) can be considered if the patient does not reach remission and therefore not suitable for transplantation (14). Pembroluzimab can be offered to patients who do not have an adequate response to BV (15).

### *Relapse after autoSCT*

The treatment aim should be to reach a complete metabolic remission with BV and consideration to proceed to allogeneic transplantation with discussion with transplant centre.

Nivolumab can be used following BV if a patient does not reach remission (16).

*Patients ineligible for stem cell transplantation:* therapy in this setting is likely to only offer disease control rather than cure. Options include radiotherapy to localised disease or further chemotherapy (ChVPP, VEPEMB, etoposide). BV can be used in the third line setting. Pembroluzimab can be used following treatment with BV at relapse or disease progression.

### **Nodular Lymphocyte Predominant Hodgkin's Lymphoma (NLPHL)**

*Patients with stage 1A NLPHL;* treatment options include surgical excision, involved field radiotherapy and a watch and wait approach can be considered

*Patients with advanced disease;* options include, watchful waiting, rituximab and chemotherapy regimens (RCVP, RCHOP, R-ABVD) or rituximab monotherapy in frailer patients.

*Patients with relapsed NLPHL;* a biopsy to ensure there is no evidence of high grade transformation should be carried out and further rituximab containing regimen can be offered in symptomatic patients.

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