Guideline for the Management of Non Hodgkin’s Lymphomas (NHL) in Adults

Version History

<table>
<thead>
<tr>
<th>Version</th>
<th>Date Issued</th>
<th>Brief Summary of Change</th>
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Changes made between version 1 and version 2

There have been developments in clinical practice since the publication of version 1. In particular, these refer to the use of Rituximab and NICE approval. These have been incorporated into this document.
1. **Scope of the Guideline**

   This guidance has been produced to support:
   a. The diagnosis and staging of patients with suspected Non Hodgkin’s Lymphoma (NHL).
   b. The management of patients with NHL.

2. **Guideline Background**

2.1 This document aims to combine up to date research, current thinking, and local expert opinion to generate Network Guidelines. In updating the previous guidelines there has been incorporation of a number of recent publications:

   a. BCSH guidelines 2010: Best Practice in Lymphoma Diagnosis and Reporting & Specific Disease Appendix.
   b. BCSH guidelines 2007: Guidelines on the diagnosis and management of adult patients with primary CNS lymphoma (PCNSL) and primary intra-ocular lymphoma (PIOL);

2.2 Local Services

2.2.1 In Pan Birmingham Cancer Network two hospitals are designated transplant centres for haematological malignancies - University Hospital Birmingham Foundation Trust and Heartlands Hospital (part of Heart of England Foundation Trust [HEFT]). These two hospitals treat patients with haematological malignancies at BCSH levels I-IV. In addition to this Good Hope Hospital (part of HEFT) practises to level 1 and Worcester Acute Hospitals NHS Trust and Sandwell and West Birmingham Hospitals NHS Trust, Sandwell site practise to level 2.

2.2.2 For patients with neck lumps (some of whom may have NHL) rapid diagnosis is required and Head & Neck Improving Outcomes Guidance recommends a multidisciplinary neck lump clinic, to fast track patients and ensure appropriate staging and investigations (see Pan Birmingham Cancer Network Guideline for the Management of Neck Lumps). Within the Pan Birmingham Cancer Network a local agreement has been reached that where possible these patients will be assessed in the first instance by the ENT Team

**Guideline Statements**

3. **Referral**

   Patients with the following symptoms and signs warrant full examination,
further investigation (including a blood count film) and urgent referral:

- Fatigue
- Bone pain
- Fever
- Weight loss
- Generalised itching
- Breathlessness
- Bruising
- Bleeding
- Recurrent infections
- Drenching night sweats
- Alcohol induced pain
- Abdominal pain
- Lymphadenopathy
- Splenomegaly

4. Diagnosis

4.1 Patient Pathway

4.1.1 All patients, whether referred as a 2 week wait patient, routine or other should be discussed at a specialist multidisciplinary team prior to the commencement of treatment, unless waiting is clinically contraindicated.

4.1.2 Initial diagnostic tests should be carried out in a manner that ensures minimal hospital visits for the patient and enables the maximum waiting times targets to be adhered to (usually tests should be completed within 2 weeks of urgent clinic appointment).

4.1.3 Where lymphoma is strongly suspected (for example in young patients with B symptoms or splenomegaly) a surgical excision biopsy should be carried out without a prior FNA in order to reduce delay in diagnosis. Neck lump referrals should be seen in a specified clinic with access to both Head & Neck and Haematology specialist opinion.

4.1.4 In the remaining patients, where the nature of the disease is uncertain, an FNA should be carried out for isolated lymphadenopathy. For multiple enlarged nodes, excision biopsy should be carried out as the primary investigation. Results of FNA should be reported and reviewed promptly and a decision made quickly to proceed direct to open biopsy as soon as possible if NHL is suspected.

4.1.5 If haematological cancer has been confirmed or suggested by a FNA then excision biopsy is necessary to determine its type.

4.1.6 Excision biopsy should be carried out by the designated surgeon in the trust for lymph node excision.

4.1.7 Where the enlarged nodes are cervical the lymph node excision should be carried out by a surgeon who specialises in surgery of the neck (e.g. ENT, Thyroid, Head and Neck).

4.2 Histological Diagnosis

The lymph node biopsy should be sent to a dedicated histopathologist(s) specialising in lymphoma diagnosis with access to all the necessary investigations i.e. immunohistochemistry, and genetic studies (PCR, FISH). Similar panels for investigation should be available for other tissue biopsies and peripheral blood,
marrow and trephines. The reporting haematopathologist should attend at least 50% of MDT meetings and be on a list of named haematopathologists. Recommendations:

a. The final report should integrate all investigations carried out on a sample.
b. Specialist areas, such as neuropathology, paediatrics and hepatopathology, should refer lymphoma cases for review by specialist haematopathologists.
c. Consent for laboratory investigations, including DNA analysis should be part of the initial consultation as should consideration of testing for viral factors (hepatitis, HIV and HTLV). Consent for excess sample to be directed for research investigations should also be considered at presentation (West Midlands Regional Tissue Bank – LRF funded resource).
d. FNA should not normally be used as sole tissue for diagnosis

e. Fresh tissue should be submitted to laboratories where a diagnosis of lymphoma is suspected. Samples should be sent immediately to the labs.
f. Samples requiring transport from remote locations should be sent in appropriate tissue media/temperature control.
g. Request forms should include all relevant clinical and laboratory information.
h. Cytogenetics or FISH analysis is essential for the diagnosis of Burkitt’s Lymphoma. These techniques should be used as adjuncts to diagnosis, not as a routine request on all samples. PCR results should not form the sole basis for a diagnosis.
5. **Staging investigations**

These should include the following

b. *Immunophenotyping* of peripheral blood if abnormal or excess lymphocytes present, to permit the diagnosis of B-CLL, thus avoiding unnecessary lymph node biopsy in some patients.
c. *Routine biochemistry* including LDH and urate.
d. *Virology* including, Hep B and Hep C. It is recommended to perform a monospot in all patients under the age of 30 with lymphadenopathy, after discussion with the patient to determine risk factors an HIV test should be considered.
e. *Protein electrophoresis* looking for paraprotein and/or immune paresis
f. *Bone Marrow Aspirate* for morphology and immunophenotyping. Cytogenetics can be helpful in certain cases such as suspected mantle cell lymphoma or Burkitt’s lymphoma.
g. *Bone Marrow Trephine* for histological examination, immunohistochemistry and if necessary genetic studies (PCR and FISH).
h. *Imaging*: CXR to assess mediastinum. As part of staging, all patients with newly diagnosed lymphoma currently have a CT scan of neck, thorax, abdomen and pelvis. If clinically indicated, imaging of other areas may be required.
i. *A lumbar puncture* is indicated if there is clinical suspicion of CNS involvement or if the patient is at high-risk of CNS disease (paranasal sinus, testicular, parameningeal, orbit disease or BM involvement in high-grade disease).

6. **Treatment – all patients**

6.1 Treatment options should be discussed and agreed by the multidisciplinary team. This should take place prior to the commencement of treatment unless this is likely to compromise the patient’s outcome.

6.2 A clinic slot of up to one hour should be allocated for the first visit which should be with the consultant and clinical nurse specialist.

6.3 All patients being offered chemotherapy that can result in fertility problems should be informed about sperm banking / oocyte and ovarian cryopreservation and carefully counselled prior to starting chemotherapy. Those wishing further information/treatment should be referred to the Assisted Conception Unit at Birmingham Women’s NHS Foundation Trust (http://www.bhamivf.org.uk/)

6.4 Patients being considered for anthracycline based chemotherapy aged >60, or with coexistent cardiovascular risk factors should be referred for Echocardiogram or MUGA scan.

6.5 All patients should be offered treatment in a clinical trial where they are eligible.
6.6 The patient’s GP should be notified by fax within 24 hours of the patient being told their diagnosis.

6.7 All cases should be reported to the West Midlands Cancer Intelligence Unit.

6.8 Patients that present to other teams such as ENT, Head and Neck, Plastics and Dermatologists should have access to the Haematology/Lymphoma CNS as soon as they are informed of their diagnosis, and be referred urgently to the haematologists. Local policies should be in place to ensure that the patients are treated within 31 days and that the breaking bad news policy is followed.

6.9 Patient Information and Counselling

6.9.1 All patients, and with their consent, their partners will be given access to appropriate written information during their investigation and treatment, and on diagnosis will be given the opportunity to discuss their management with a clinical nurse specialist who is a member of the relevant MDT. The patient should have a method of access to the haematology team at all times.

6.9.2 Access to psychological support will be available if required. All patients should undergo an Holistic Needs Assessment and onward referral as required.

7 Diffuse Large B-Cell Lymphoma (DLBCL)

7.1 Stage I disease:

7.1.1 Non-bulky disease (<10cm nodal disease or a mediastinal mass <1/3 of the maximum transverse diameter of the chest on plain CXR):

Patients with non-bulky disease and no adverse risk factors (elevated LDH, PS <2) should receive combined modality therapy of 3-4 cycles of R-CHOP followed by involved site radiotherapy (ISRT) unless pre chemotherapy cross sectional imaging is not available when involved field radiotherapy (IFRT) should be used. These volumes are as defined in “Guidelines for the use of radiotherapy in nodal lymphoma” produced on behalf of the NCRI Radiotherapy and Lymphoma Clinical Study groups

a. ISRT (or IFRT) radiotherapy should be to a dose of 30 Gy in 15 fractions.
b. In view of increased breast cancer risk, younger female patients may receive a chemotherapy only regimen if breast tissue is within the proposed field of radiation e.g. R-CHOP 6-8 courses.

7.1.2 Bulky disease (>10cm nodal disease or a mediastinal mass >1/3 of the maximum transverse diameter of the chest on plain CXR)
Patients with bulky disease should receive 6-8 cycles of R-CHOP. Radiotherapy (ISRT or IFRT) should be considered for residual mass at the completion of treatment.

7.2 Stage II-IV Disease

Following the GELA study and subsequent NICE guidance, patients with CD20 positive DLCBL stage II-IV disease should now be offered 6-8 cycles of R-CHOP as first line treatment (NICE TA65). Patients with high/intermediate and high-risk disease have a higher (>50%) risk of relapse. There is however currently no evidence to support the use of ‘up-front’ high dose therapy (HDT) and stem cell rescue. Tumour lysis is a risk in occasional patients with bulky and aggressive disease and should be managed as described for Burkitt’s lymphoma. The first infusion of rituximab should be used with extreme caution and closely monitored when treating patients with ≥ 25x10⁹/l circulating malignant cells or high tumour burden (higher risk of severe cytokine release syndrome (CRS)) and some consideration should be given to delaying the first dose in this situation.

7.3 Radiotherapy

In addition to those patients mentioned above, radiotherapy is indicated in patients with primary mediastinal large B cell lymphoma. Radiotherapy may be indicated in other patients with localised areas of previously bulky disease. PET-CT is indicated for patients with residual tumour masses at the end of chemotherapy and may be used in decision making regarding requirement for radiotherapy or salvage therapies. Radiotherapy should again be to an involved site (or field if no pre chemotherapy cross sectional imaging is available). A dose of 30 Gy in 15 fractions is used.

7.4 Relapse/Progression

Salvage chemotherapy followed by HDT and stem cell rescue is now the standard of care in patients considered suitable. Allogeneic transplantation (reduced intensity) may be considered in suitably fit candidates who relapse after HDT and stem cell rescue or who fail to mobilise sufficient autologous stem cells or who have had extensive marrow involvement. Radiotherapy (ISRT or IFRT) should be considered after these procedures to sites of residual disease or initial bulky disease. Again PET-CT is often helpful in these decisions.

7.5 Trials for which patients may be suitable: Aggressive NHL

Newly Diagnosed
a. PET substudy for RCHOP 21 trial
b. Phase II: R-CODOX-M/IVAC for aggressive high grade NHL
c. R-GCVP: for patients unsuitable for CHOP based induction chemotherapy

Peripheral T cell lymphoma
a. CHOP Campath - Phase II dose escalation study
8. Clinical Management of Burkitt’s Lymphoma

8.1 High-intensity chemotherapy regimens have been developed for Burkitt’s lymphoma resulting in a 60-70% long-term survival rate. Current recommended regimens include the modified BFM NHL86 or the BNLI-LY 10 protocol: CODOX-M / IVAC. There is no proven benefit for an ‘up-front’ autograft in such patients in first response. Tumour lysis syndrome is a particular risk in Burkitt’s lymphoma. The risk of this is reduced by;

a. the pre-phase chemotherapy inherent in the regimen
b. aggressive hydration (3L/m²/day)
c. urinary alkalisation with sodium bicarbonate
d. rasburicase (except where contraindicated e.g. G6PD deficiency) followed by allopurinol

8.2 Patients with Burkitt’s lymphoma are at a high risk of CNS disease/relapse and intrathecal treatment is included in the protocol as standard. There is evidence that addition of Rituximab to chemotherapy may improve response rates and survival, this is the subject of ongoing studies.

8.3 Relapse/Resistant Disease

The outlook in patients with relapsed Burkitt’s disease is poor (<20% 5 year survival). Reinduction should be with a non-cross-resistant regimen followed by HDT and autologous or allogeneic transplant.

8.4 There are no current UK NCRN trials addressing relapsed Burkitt’s lymphoma.

9. Clinical Management of Lymphoblastic Lymphoma\Leukaemia

9.1 This disease requires aggressive ALL-type treatment. Currently the UKALLXII regimen is used but consideration of the new UKALL14 protocol is appropriate. The risk of tumour lysis syndrome is high and requires an approach as outlined for Burkitt’s lymphoma. CNS prophylaxis is also required.

9.2 The role of transplant is not completely defined. Patients at high-risk of relapse (such as high WCC) do benefit from a transplant procedure. Otherwise, HDT and transplant has not been shown to confer an improvement in overall survival. However, relapse-free survival is better and the overall length of treatment is much shorter. The current BCSH guidelines recommend ‘consideration of HDT and ASCT’ and this should be assessed on a case-by-case basis.

9.3 Relapsed Disease
Reinduction should be attempted if the patient is fit enough. HDT therapy followed by autologous/allogeneic transplant should then be considered.

9.4 **Resistant Disease**

Alternative non-cross-resistant regimens should be considered. These patients may be suitable for clinical trials if they become available.

10. **Clinical Management of Mantle Cell Lymphoma**

10.1 Mantle cell lymphoma is a distinct subtype of B-cell NHL. The majority of patients are over the age of 60 usually presenting with advanced stage disease. Conventional CHOP chemotherapy offers 75% overall response rate (ORR), 7% complete response (CR) rate but most patients relapse within 2 years. In randomised data, R-CHOP improved ORR and CR rates to 94% and 34% respectively and prolonged TTP but did not improve overall survival. Recent meta-analysis of randomised trials has demonstrated overall survival advantage for patients receiving R-chemotherapy versus chemotherapy alone (Cochrane review 2008).

10.2 If fit, patients should be considered for treatment with the BNLI FC v FCR study. However younger patients fit enough for autologous transplantation may be best treated with the NORDIC protocol. R-HyperCVAD is another aggressive regimen that has been reported for younger patients. There is a lack of randomised data to recommend any single regimen for younger patients although the data from the NORDIC study is impressive with a plateau in disease free survival after 5 years. Autologous stem cell transplantation has been shown in a randomised trial to prolong disease free survival in first response.

10.3 **Relapsed Disease**

If fit enough, reinduction should be attempted with a non-cross-resistant regimen. If a donor is available, reduced-intensity transplantation should be considered or an autologous stem cell transplant of not performed in CR1. Patients may be eligible for Bortezomib trial (NCRN phase II).

10.4 **Resistant Disease**

Such patients have a very poor prognosis and may be considered as candidates for experimental therapy/clinical trials.

10.5 **Trials for Which Patients May be Suitable**

Randomised study comparing Fludarabine + cyclophosphamide (FC) vs. FC and Rituximab in newly diagnosed patients. (Mantle Cell P3).

Bortezomib study for patients with relapsed mantle cell lymphoma.

Mini-allo MCL study (level 4 centres only)
11. **Small Lymphocytic Lymphoma**

Small lymphocytic lymphoma is regarded as the same disease entity as chronic lymphocytic leukaemia, requiring the same investigational and treatment approach. See CLL guidelines.

12. **Follicular Lymphoma (not including histological grade 3b)**

12.1 15-20% of patients presenting with stage I/II may be suitable for radiotherapy if disease is small volume. Prolonged disease-free survival up to 50-70% is reported in such patients. Radiotherapy should be involved site (or involved field if cross sectional imaging prior to biopsy is not available) to a dose of 24 Gy in 12 fractions depending upon adjacent critical structures. The recent BNLI study (FORT study) comparing 2 different dose schedules is open. In the elderly observation alone following an excision biopsy may be appropriate.

12.2 80-85% of patients present with stage III/IV disease. Stage III/IV disease is incurable for the majority of patients and thus the decision to treat should take into account:

a. Symptoms and disease bulk
b. Compromise of one or more organ functions (particularly bone marrow)
c. The wishes of the patient

12.3 Current policy for asymptomatic patients is ‘watchful waiting’ i.e. monitoring of the clinical state, typically every 3 months.

12.4 When treatment is commenced, the aim is to achieve ‘remission’ and to treat to maximal response. Subsequent surveillance is performed to detect recurrent disease at which point further treatment is indicated once restaging +/- re-biopsy is performed. By cycling through treatment and surveillance, a median survival of 10 years can be expected.

12.5 **Options for Initial Treatment**

12.5.1 Randomised trial data has shown a highly significant improvement for patients treated with R-CVP compared to CVP alone in ORR, CR rates 81% v 57%, 41% v 10%, respectively and median time to treatment failure 27 v 7 months (Marcus et al, Blood 2005, 105 1417). Further literature now indicates that Rituximab chemoimmunotherapy prolongs overall survival for patients with follicular lymphoma, however at the present time it is not clear at which stage of treatment this impact from Rituximab on OS is seen, (i.e. induction, re-induction, maintenance).

12.5.2 Patients with poor performance status or at patient/physician preference may be treated with oral alkylating agents such as chlorambucil. Alternative includes
CVP or CHOP or CMD, no survival advantage has been shown for the addition of an anthracycline.

12.5.3 Purine analogues have been extensively reported and FCR is a highly effective induction or salvage regimen. Other purine analogue regimens that are effective include FMD. Bendamustine has reported efficacy in relapsed low-grade NHL and has been licensed for this indication.

12.5.4 Maintenance Rituximab following first-line R-chemo was found to be beneficial in terms of PFS for responding patients, in the PRIMA trial. This led to licensing and NICE approval for relapsed patients following induction chemotherapy. Rituximab (375mg/m2) is given every 2 months for 2 years and this has been shown to prolong progression free survival.

12.6 Options for Subsequent Treatment

12.6.1 Careful consideration should be given to re-biopsy at time of disease relapse/progression to exclude high grade transformation.

12.6.2 Patients are frequently treated with a similar regime to induction if response has been long (>18-24 months). Alternatively they may be treated with a non-cross resistant regime, such as purine analogues.

12.6.3 Maintenance Rituximab: is now licensed and NICE approved for relapsed patients following re-induction chemotherapy. Rituximab (375mg/m2) is given every 3 months for 2 years and this has been shown to prolong progression free survival.

12.7 Transplantation

12.7.1 Autologous
The use of HDT and stem cell rescue can increase DFS with little effect on overall survival. Thus, although not curative, it may allow patients to remain free of treatment for a prolonged period of time.

12.7.2 Allogeneic
Allogeneic transplantation may potentially offer a cure for indolent NHL. However, as the median survival for this disease is so long, there is no significant (i.e. large cohort) data demonstrating an overall benefit for allogeneic transplantation and no randomised trials. In those patients considered fit for transplant, allogeneic transplantation may be considered in second or third CR, and for patients with short responses to suitable induction or high-risk FL-IPI. Reduced intensity conditioning may reduce the transplant related toxicity and should be considered for older patients.

Trials for Which Patients May be Suitable:

a. PACIFICO - Alkylator Combination In Follicular lymphoma Immuno-Chemotherapy for Older patients: a phase III comparison of first-line R-CVP versus R-FC (previous acronym: RiCH FLO).
b. **FORT Trial.**
c. Radical radiotherapy in stage 1A follicular NHL, radiation dose trial.
d. **Radiopharmaceutical treatment options.**
   Ibritumomab tiuxetan (Zevalin) is licensed for the treatment of rituximab relapsed or refractory CD20+ follicular lymphoma. Patients may be referred to Dr Andrea Stevens at the Queen Elizabeth Hospital for consideration of ibritumomab provided they fulfil the safety eligibility criteria and funding is established.

13. **Marginal Zone\Gastric MALT Lymphoma**

13.1 **Extra-Nodal Marginal Zone Lymphoma (low-grade B cell lymphoma of MALT type)**

Non-bulky gastric disease (stage IE-II) should be treated with *H. pylori* eradication therapy for 3 weeks and then restaged at 3 months post-therapy (earlier if symptomatic). This treatment can be followed up with chlorambucil for up to 6 courses but evidence supporting this as a definitive approach is still lacking. Whether further treatment is given or not, follow-up is mandatory and should include a schedule of endoscopy. BCSH recommends repeat at 3 months after completion of treatment, then 6-monthly for 2 years then annually for 5 years. Patients with more widespread disease should be treated as per patients with follicular lymphoma.

14. **Splenic Marginal Zone Lymphoma**

14.1 This disease overlaps to a great extent with splenic lymphoma with villous lymphocytes. Marrow and peripheral blood involvement is common. Monoclonal gammopathy can occasionally be found and lymphadenopathy is usually absent or minimal.

14.2 This disease is incurable and usually follows an indolent course. A policy of observation is appropriate for early asymptomatic disease. Historically, many patients have undergone splenectomy resulting in prolonged ‘control’ of their disease. If unfit for splenectomy, splenic irradiation is an option. Chemotherapy/antibody therapy may be indicated for those where surgery is not appropriate and for patients with predominantly marrow or lymph node disease. Single agent rituximab has shown encouraging results or alternatively a fludarabine based regimen may be used.

14.3 **Trials for Which Patients May be Suitable**

Those patients with splenic lymphoma with villous lymphocytes may be considered for the *Waldenstrom's study* - a randomised trial of Chlorambucil vs. Fludarabine as initial therapy of Waldenström’s macroglobulinaemia & splenic lymphoma with villous lymphocytes.
15. **Primary CNS Lymphoma**

*Please note BCSH guidelines for the diagnosis and treatment of CNS lymphoma (2007)*. *These should be used to guide diagnosis and therapy.*

15.1 Primary CNS or primary intraocular lymphoma is rare, it has a significantly increased incidence in HIV positive individuals.

15.2 Poor prognostic factors at presentation include age>60, Karnofsky score<70%, involvement of deep structures, CSF protein >0.6g/l and positive CSF cytology. Full staging should be performed to exclude occult systemic disease. Relapse is usually within the CNS.

15.3 There is now good evidence that drugs which cross the blood-brain barrier, such as methotrexate and cytosine, significantly improve survival.

15.4 In patients fit enough for treatment: consider high dose methotrexate ≥3g/m² i.v. on days 1, 8 and 22 with folinic acid rescue. An EDTA clearance is required before commencement of therapy and between days 8 and 22. A multi-drug regimen based on high dose methotrexate is an alternative – IDARAM has shown good results in patients with CNS only and systemic and CNS lymphoma.

15.5 There is no evidence supporting the need to give adjunctive intrathecal methotrexate when high dose IV methotrexate has been used.

15.6 Chemotherapy based treatment may be consolidated with whole brain radiotherapy (WBRT - dose determined by response to chemotherapy). There is a risk of neurotoxicity, in particular, leuco-encephalopathy which increases significantly for patients >60 years in age. WBRT should therefore be considered for all patients aged < 60. In older patients risks and toxicities may outweigh benefits.

15.7 For patients who are non-responsive or who relapse, salvage can be attempted using high dose cytosine followed by an autograft.

16. **Peripheral T-Cell lymphoma (ALK negative)**

This is a heterogeneous group of lymphomas with a poor outlook if ALK protein negative. There is a lack of data about optimal treatment but CHOP chemotherapy for 6-8 courses is often given as first line treatment. The incorporation of alemtuzumab is interesting but currently only in the setting of clinical trials. In younger patients there is a rationale for considering peripheral blood stem cell transplant options.

17. **Other Lymphoma Sub-Types**
17.1 There are a large number of rare lymphoma sub-types including the following: adult T-cell leukaemia/lymphoma, enteropathy-type T-cell lymphoma, adult T-cell leukaemia/lymphoma, angioimmunoblastic T-cell lymphoma, hepatosplenic T-cell lymphoma NK related lymphomas, methotrexate associated lymphomas, post transplant lymphoproliferative disorders, HIV related lymphomas, lymphomas related to primary immune disorders and skin lymphomas.

17.2 These rarer conditions are beyond the scope of the current guideline.

18. Non-Hodgkin’s Lymphoma During Pregnancy

18.1 NHL in pregnancy is a rare event. Effective liaison between the Haematology team, obstetrician and mother is required to ensure optimal outcome. MRI can replace staging CT but is not advisable in the first trimester. Patients with aggressive NHL usually have stage II-IV disease and present at a median of 23 weeks of gestation. Prolonged delay in treatment is likely to have serious consequences for the patient. If the patient is diagnosed in the first trimester, termination prior to the commencement of chemotherapy should be offered. For those patients diagnosed after 32 weeks, it may be possible to delay treatment until safe delivery of the child is possible. For those patients that fit into neither of the above categories, a decision will have to be made as to when treatment should start.

18.2 Preferred treatment for high grade NHL is R-CHOP. There are case reports of Rituximab being given uneventfully in pregnancy but its license does not cover this group of patients. Anthracyclines and steroids have been used in the second and third trimester of pregnancy with one group reporting normal child development with a follow-up of several months to 11 years after anthracycline therapy. Ectrodactylia was reported in 2 of 3 cases exposed to cyclophosphamide in utero. One case report describes cardiac abnormalities. The risks appear higher in the first trimester. Vincristine has been linked with abnormalities in 2 children, both born to mothers receiving combination chemotherapy. In 14 infants born to mothers treated only with Vincristine, no abnormalities were reported. It is thus difficult to calculate the risk to the foetus and ultimately the decision on when to treat must rest with the patient.

18.3 For patients diagnosed with indolent NHL during pregnancy, there is usually very little requirement to treat at the time of diagnosis. If treatment becomes necessary, the same considerations as above need to be given.

19. Follow-up

19.1 Patients who have been treated in a clinical trial should be followed up in accordance with the trial protocol.

All other patients should be followed up as follows:
- Following chemotherapy usually every 12 weeks for the first year. More frequently if clinically indicated.
- monthly for the second year.
- Discharge after 2 years follow up for patients with high grade disease treated with curative intent and no evidence of relapse. Patients should be discharged with an “information prescription” which covers the diagnosis, treatment received and what to look out for. These are currently being developed.

19.2 For all patients open access to the service is essential. Patients who develop signs or symptoms suggestive of relapse should be able to see their specialist within 2 weeks. Patients and GP should be made aware of this open access to the service.
20. **Clinical Trials**

20.1 Wherever possible, patients who are eligible should be offered the opportunity to participate in National Institute for Health Research portfolio clinical trials and other well designed studies.

20.2 Where a study is only open at one Trust in the Network, patients should be referred for trial entry. A list of studies available at each Trust is available from Pan Birmingham Cancer Research Network. Email: PBCRN@westmidlands.nhs.uk.

20.3 Patients who have been recruited into a clinical trial will be followed up as defined in the protocol.

21. **Monitoring of the Guideline**

Compliance with the guidance will be reviewed in March 2013.

**References**

a. [www.bcshguidelines.com](http://www.bcshguidelines.com)
b. BCSH guidelines 2008: Best Practice in Lymphoma Diagnosis and Reporting & Specific Disease Appendix
c. BCSH guidelines 2007: Guidelines on the diagnosis and management of adult patients with primary CNS lymphoma (PCNSL) and primary intra-ocular lymphoma (PIOL);
e. Medical Treatment Portfolio, The Cancer Centre, University Hospital Birmingham NHS Foundation Trust

**Authors**

Fiona Clark  Consultant Clinical Haematologist
Andrea Stevens  Consultant Clinical Oncologist
Lara Barnish  Deputy Director of Nursing
Matthew Lumley  Consultant Clinical Haematologist
Guy Pratt  Consultant Clinical Haematologist
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Approval Date by the Clinical Governance Team  
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Approval Signatures

Pan Birmingham Cancer Network Governance Committee
Name:  Doug Wulff
Signature  Date  May 2011

Pan Birmingham Cancer Network Manager
Name:  Karen Metcalf
Signature  Date  May 2011

Network Site Specific Group Clinical Chair
Name:  Fiona Clark
Signature  Date  May 2011