Kent & Medway - Cancer

The Management of Lymphoma

Oncological Treatment Guidelines for the Management of Lymphoma & Pathway of Care

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1.0 General Haematology Overview

This document has been written to provide guidance on the treatment of lymphoma in Kent & Medway.

These guidelines describe the process for ensuring that all lymphoma cases diagnosed within the Kent & Medway region are managed by the designated Haematological Cancer MDTs, achieving a coordinated seamless patient pathway in accordance with the best possible evidence based practice and to facilitate advancement in the specialty in the field of haematological cancer management.

Radiotherapy schedules are as defined in the *Kent Oncology Centre Quality System Clinical Protocols.* For further details on indications for radiotherapy see appendix A.

- See chemotherapy prescribing proformas for details on chemotherapy / anti-cancer regimens.

- All patients should be considered for entry into a clinical trial (see appendix C).

- All patients should be discussed within a multidisciplinary team meeting before commencing treatment. Prognostication using the tools below is mandatory prior to discussion in the MDMs.

- All 16-24 year olds must be notified to the TYA MDT. All young people aged 16-18 must be referred to the TYA Principle Treatment Centre (PTC) which for Kent & Medway is based at the Royal Marsden Hospital. Referral to a TYA PTC does not necessarily mean that treatment will be undertaken at that centre; shared care management protocols may allow some treatments to be delivered locally. Young people aged 19-24 have the option of being referred to the Royal Marsden Hospital for treatment but may choose to be treated locally however they should have their treatment discussed with the TYA PTC.

Notes:

- The Kent & Medway – Cancer, Haematology Tumour Site Specific Group (TSSG) is responsible for agreeing all of the guidance
- The TSSG should consult with primary care members of the Kent & Medway Clinical Commissioning Groups (CCGs) regards the development of the pathway
- The purpose of the document is to provide a framework for the management of patients with suspected/confirmed haematological cancer
- The overall management details are largely reflected in the updated flow charts
- Information on MDT "functioning" is confined to the MDT Operational Policies based on the TSSG agreed "High Level Operational Policy" which is located on the Kent & Medway – Cancer website: http://www.kmcn.nhs.uk/home/resource-library

2.0 Scope

This Standard Operating Procedure (SOP) applies to all cases and suspected cases of Haematological Cancer within Kent & Medway and haematological cancer specification of delivery of care requires all Trusts within Kent & Medway to adopt an agreed policy for the delivery of care. The policy relates to the expected pathway of care / treatment regimes for patients diagnosed with haematological cancer.

The policy covers the following:
- Access
- Initial Assessment
- Investigations
- Colorectal cancer multidisciplinary meeting (MDM)
- Surgical and non-surgical treatment
- Recurrent disease
- Follow up

3.0 Process and Terminology

3.1 Tumours

- B-Cell lymphoproliferative disorders including myeloma
- Chronic myeloproliferative disorders
- Acute lymphoblastic leukaemia
- Acute myeloid leukaemia
- Myelodysplastic syndromes
- Chronic myeloid leukaemia

3.2 Referral guidelines and process

- The incidental finding of haematological malignancy on specimens sent for routine examination is common. In these circumstances the haemato-oncologist will often be the clinician advising the GP that the patient requires an urgent appointment. Delays should NOT be built into the system by insisting on the use of a rapid access proforma.
- In the unlikely event that a GP receives a blood count/film reported as acute leukaemia (0r any of the conditions outlined above) and not directly contacted by a haematologist – the patient should be referred to a specialist immediately.
- Patients with spinal cord compression or renal failure suspected of being caused by myeloma require immediate referral to a haematologist.
- Patients with unexplained splenomegaly should be referred urgently to a haematologist.
- Patients referred to head & neck lump clinics who are found to have a haematological malignancy should be fast tracked to a haematologist. (The Head & Neck Pathway of Care reflects this)
- Patients with a “lump” referred to a surgeon and subsequently diagnosed with a haematological malignancy should be fast tracked to a haematologist.

3.3 GP alert (NICE: Referral guidelines for suspected cancer – June 2005)

- Combinations of the following signs and symptoms should alert GPs to perform a full examination, further investigations (including FBC and film) and possible referral:
    - Abdominal pain
    - Alcohol induced pain
    - Bleeding
    - Breathlessness
    - Bruising
    - Drenching night sweats
    - Fatigue
    - Fever
    - Lymphadenopathy
    - Recurrent infections
    - Splenomegaly
    - Weight loss
- GP investigations in patients with:
    - Persistent unexplained fatigue:
      Carry out an FBC, ESR & C-reactive protein. Repeat at least once if the patients condition remains unexplained and does not improve.
    - Unexplained lymphadenopathy:
      Carry out an FBC, ESR, & C-reactive protein.
- Any of the following additional features of lymphadenopathy:
    - Persistence for 6 weeks or more
    - Lymph nodes increasing in size
    - Lymph nodes greater than 2 cm in size
    - Widespread nature
    - Associated splenomegaly, night sweats or weight loss: Investigate further and/or refer.
    - Unexplained bruising, bleeding and purpura or symptoms suggesting anaemia:
      Carry out FBC, Film, Clotting screen, ESR, C-reactive protein.
    - Persistent and unexplained bone pain:
      Carry out FBC, X-ray, U&Es, LFTs, Bone profile, PSA (in males), ESR, C-reactive protein.

4.0 Imaging

Imaging guidelines for haematological cancer can be located on the Kent & Medway – Cancer website: http://www.kmcn.nhs.uk/home/resource-library/diagnostics-ccag/

5.0 Pathology

All Kent & Medway reporting pathologists follow The Royal College of Pathologists Histopathology Reporting on Cancers guidelines – a copy of which is available through the Kent & Medway – Cancer website:- http://www.kmcn.nhs.uk/home/resource-library/pathology-ccag/

http://www.rcpath.org/publications-media/publications/datasets/datasets-TP

6.0 Specialist Palliative Care and Support

All patients with a Haematological Cancer will have access to specialist palliative care and support at every stage of the patient journey.

Open and frank discussions with patients should take place with patients at all stages of their journey so that patients are not confused about their prognosis or have unrealistic expectations of any of the forms of treatment offered to them.

Relatives and carers will need to be appropriately supported and given appropriate information. However, in accord with the recommendations set out in various revised Improving Outcomes Guidance, relatives and carers should not be given information different to that given to the patient.

Frail and terminally ill patients with a Haematological Cancer should always be discussed with the specialist palliative care team.

Patients with end stage disease may choose to end their days at home and therefore the options should always be discussed openly with them and their relatives/carers.

Effective communication with primary care is essential.

All patients should have unlimited access to a Haematology Cancer nurse specialist who is a member of the specialist Haematology Cancer team

7.0 Follow Up

To be reviewed by Haematology TSSG during the period 2013/14.

8.0 Data

Collection of data at each stage of the pathway is the responsibility of the team looking after the patient at that time. The minimum dataset agreed by the TSSG will be a combination of those data items that meet national requirements, and additional items as agreed by the TSSG.

National data requirements will include:

- Cancer Waiting Times monitoring, including Going Further on Cancer Waits. The data items required will be as defined in ISB0147 at the time of referral and/or treatment.
  Details of the Cancer Waiting Times dataset are available from:
  http://nww.connectingforhealth.nhs.uk/nhais/cancerwaiting/documentation
  Cancer Waiting Times data will be submitted according to the timetable set out in the National Contract for Acute Services.
- The Cancer Outcomes and Services Dataset. The data items will be as defined in ISB1521, and any subsequent versions, at the time of diagnosis and/or treatment. The requirement will include those fields listed in the "Core" section of the dataset, and any additional tumour site specific sections, as applicable.
  Details of the COSD are available from:
  http://www.ncin.org.uk/collecting_and_using_data/data_collection/cosd.aspx
  Cancer Registration and Cancer Outcomes and Services (COSD) data will be submitted according to the timetable set out by Thames Cancer Registry.
- Where applicable, teams will also collect additional data items as defined in any corresponding National Clinical Audit Support Programme (NCASP) audit dataset.
  Details of these datasets are available from:
  http://www.ic.nhs.uk/services/national-clinical-audit-support-programme-ncasp/cancer
  Data for NCASP audits will be submitted, where applicable, according to timetables as agreed by the TSSG, and within the overall submission deadlines for each audit.

Submission of data to meet these national requirements will be the responsibility of each individual Trust.

Note that these standards are subject to variation from time to time, and where these requirements change, the data items required to be collected by the team will also change in line with national requirements.

Local data requirements will include any additional data items as agreed by the TSSG. These must be selected to avoid overlap with any existing data items, and where possible must use standard coding as defined in the NHS Data Dictionary.

Where possible and applicable, InfoFlex will be used for the collection and storage of data.

Additional areas of the COSD, relating to pathology, radiotherapy, SACT, diagnostic imaging and basic procedure details will feed into the dataset from other nationally mandated sources. It is the responsibility of each team to ensure that the whole of the relevant dataset is collected, and it is acknowledged that this may come from a variety of sources.

9.0 Personnel and Contact Information

A comprehensive, up to date list of MDM contact details can be found on the Kent & Medway - Cancer website via the following link: http://www.kmcn.nhs.uk/home/resource-library

10.0 Management of Lymphoma

10.1 WHO Classification - Lymphoma

Classification of NHL World Health Organisation (WHO) / Revised European and American Lymphoma (REAL) classification and Working Formulation (WF) equivalent

Proposed WHO Classification

B-cell neoplasms

Precursor B-cell neoplasms

1. Precursor B-lymphoblastic leukaemia/lymphoma (precursor B-cell acute lymphoblastic leukaemia)

Mature (peripheral) B-cell neoplasms

1. B-cell chronic lymphocytic leukaemia/small lymphocytic lymphoma
2. B-cell prolymphocytic leukaemia
   Lymphoplasmacytic lymphoma
3. Splenic marginal zone B-cell lymphoma
   (+/- villous lymphocytes)
4. Hairy cell leukaemia
5. Plasma cell myeloma/plasmacytoma
6. Extranodal marginal zone B-cell lymphoma of
   MALT type
7. Nodal marginal zone B-cell lymphoma
   (+/- monocytoid B cells)
8. Follicular lymphoma
   Grade 1, 0-5 centroblasts/hpf
   Grade 2, 6-15 centroblasts/hpf
   Grade 3, > 15 centroblasts/hpf
   Grade 3a, > 15 centroblasts - centrocytes present
   Grade 3b, centroblasts solid sheets - no centrocytes
9. Mantle cell lymphoma
10. Diffuse large B-cell lymphoma
    Mediastinal large B-cell lymphoma
    Primary effusion lymphoma
11. Burkitt's lymphoma

REAL Classifcation (WF equivalent)

B-cell neoplasms

Precursor B-cell neoplasms

1. Precursor B-lymphoblastic leukaemia/lymphoma (I)

Peripheral B-cell neoplasms

1. B-cell CLL / prolymphocytic leukaemia / small lymphocytic lymphoma (A)
2. Lymphoplasmacytoid lymphoma / immunocytoma (A)
3. Mantle cell lymphoma (E)
4. Follicle centre lymphoma, follicular
   Cytological grades: I (small cell) (B)
   II (mixed cell) (C)
   III (large cell) (D)
5. Marginal zone B-cell lymphoma (A-C)
   Extranodal (MALT ± monocytoid B cells) (U)
6. Splenic marginal zone lymphoma (A)
7. Hairy cell leukaemia (U)
8. Plasmacytoma / myeloma (U)
9. Diffuse large B-cell lymphoma (F,G)
10. Burkitt's lymphoma (J)
11. High grade B-cell lymphoma, Burkitt-type (U)

T-cell and putative NK cell neoplasms

Precursor T-cell neoplasm

1. Precursor T-lymphoblastic lymphoma/leukaemia (I)

T-cell and NK cell neoplasms

Precursor T-cell neoplasm

1. Precursor T-lymphoblastic lymphoma/leukaemia

2. (precursor T-cell acute lymphoblastic leukaemia)

Mature (peripheral) T-cell neoplasms

1. T-cell prolymphocytic leukaemia
2. T-cell granular lymphocytic leukaemia
3. Aggressive NK-cell leukaemia
4. Adult T-cell lymphoma/leukaemia (HTLV1+)
   Extranodal NK/T-cell lymphoma, nasal type
5. Enteropathy-type T-cell lymphoma
   Hepatosplenic gamma-delta T-cell lymphoma
6. Subcutaneous panniculitis-like T-cell lymphoma
7. Mycosis fungoides/Sezary syndrome
8. Anaplastic large-cell lymphoma, T/null cell,
   Primary cutaneous type
9. Peripheral T-cell lymphoma, not otherwise
10. Characterized
    Angioimmunoblastic T-cell lymphoma
11. Anaplastic large-cell lymphoma, T/null cell,
    Primary systemic type

Hodgkin's lymphoma (Hodgkin's disease)

1. Nodular lymphocyte-predominant Hodgkin's lymphoma

2.Classical Hodgkin's lymphoma

3. Nodular sclerosis Hodgkin's lymphoma Grades 1 & 2

4. Lymphocyte-rich classical Hodgkin's lymphoma

5. Mixed cellularity Hodgkin's lymphoma

6. Lymphoctye depletion Hodgkin's lymphoma

WHO classification fully described in – Harris N L., et al. Journal of Clinical Oncology. 1999, Vol 17, 12: 3835-3849

10.2 The International Non-Hodgkin's Lymphoma Prognostic Factors Index

Prognostic Factors identified

Age (< or > 60)
Ann Arbor Stage (I/II v III/IV)
Performance Status (0/1 v ≥ 2)
Serum LDH (Normal v abnormal)
Number of Extranodal Disease Sites (≤ 1 v > 1)

Number of factors	5 Year DFS	5 Year OS
0 or 1	70%	73%
2	50%	51%
3	49%	43%
4 or 5	40%	26%

Age-Adjusted index in patients below 60 years:

0	86%	83%
1	66%	69%
2	53%	46%
3	58%	32%

IPI=International Prognostic Index
DFS=Disease Free Survival
LDH=Lactate Dehydrogenase

Risk analysis

0-1	low
2	Intermediate
3	High Intermediate
4-5	High

1993. "A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project [see comments]", N Engl J Med, vol. 329, no. 14, pp. 987-94.

10.3 Initial assessment of lymphomas

- **Full history and clinical examination**, with particular reference to clinically assessable disease (eg lymph nodes, spleen, liver etc.), co-morbid conditions and the presence or absence of "B" symptoms (weight loss of $\geq$ 10% over the preceding 3 months, night sweats and fevers).

- **Baseline bloods** - FBC, U+E, LFT,Ca++/PO4, LDH, □2M, ESR,SPE and Ig levels. Consider HIV test, with appropriate counselling and consent to stages IB-IV of aggressive B-NHL, in particular patients in high risk category.

- **Baseline imaging:** CT thorax abdomen and pelvis is standard but may not be needed for CLL/ lymphocytic NHL with bone marrow infiltration particularly in elderly patients and in the palliative setting. PET scanning is becoming more useful particularly in young patients with apparent low bulk/limited stage disease but significant "B" symptoms. MRI scanning should be used in pregnancy, if patient is allergic to iodine based contrast media, in spinal disease/suspected spinal cord compression, in CNS lymphoma and in the assessment of the extent of marrow infiltration.

- **Bone marrow aspirate and trephine** for all patients with NHL and in HD stages IB-IV or cytopenia on FBC. Marker analysis, FISH and cytogenetics should be considered in selected cases such as Burkitt's and mantle cell lymphoma.

- **Lumbar puncture** (see also CNS lymphoma section):
  - Immunoblastic lymphoma, lymphoblastic lymphoma, Burkitt's, Burkitt-like lymphoma
  - Diffuse large cell lymphoma involving a high risk site (bone marrow, peripheral blood, orbit, base of skull, testes & sinus) or in a high risk group.
  - Clinical evidence of CNS infiltration.

- Review of histology by designated haematopathologist, radiology and treatment options by the MDT as per IOG guidance.

- Review of previous treatment/scans/histology if referred from elsewhere.

- For relapsed lymphoma, re-biopsy is usually necessary as part of re-staging and need to be compared to original histology (not necessary if in leukaemic phase as in CLL, MCL)

- Consider whether patient suitable for any current studies.

- Arrange Echocardiogram if there is a cardiac history or previous anthracycline therapy regardless of dose given in a patient due anthracycline based therapy or if age > 65. Similarly do **PFTs** prior to high dose chemotherapy or mantle RT or if patient has history of respiratory impairment/previous pulmonary toxic drugs. **Do not start treatment until these results are available**.

- **Fertility counselling.** Arrange sperm banking in males if appropriate and collection of ovarian tissue/oocytes for cryopreservation in females if appropriate. HIV/hepatitis screening mandatory.
- Complete **consent forms** for chemotherapy, radiotherapy or clinical trials.

- Check standard **additional medications** prescribed.

- Provide appropriate disease and treatment leaflets. Discuss possible treatment side effects. Refer chemotherapy nurses for further counselling and explanation.

10.4 Primary Management of Hodgkin's Lymphoma (excluding Lymphocyte Predominant Disease)

A modern therapy that depends on risk assessment and prognostic factors. The following risk assessments should always be used to determine therapy in lymphoma:

Hodgkin's Disease BNLI/EORTC
Male vs Female
ESR > 40 mm /Hr
Age > 40
"B" symptoms
Advanced stage (III & IV vs I & II)
MC and LD histology

International Prognostic Index (IPI) in NHL:

- Age (<60 years of age versus >60 years of age),
- Serum lactate dehydrogenase-LDH (normal versus elevated),
- Performance status (0 or 1 versus 2-4), (see definition below)
- Stage (I or II versus III or IV),
- Extranodal site involvement (0 or 1 versus 2-4).

In the pre-Rituximab era patients with 2 or more risk factors have less than a 50% chance of relapse-free and overall survival at 5 years. However the proposed revised IPI indicates since the including of Rituximab with CHOP there are three distinct prognostic risk groups.

- 0 risk factors, very good - 90% progression free survival @ 5 years
- 1-2 risk factors, good - 80% progression free survival @ 5 years
- 3-5 risk factors, poor - 50% progression free survival @ 5 years

German Limited Stage Hodgkin's Disease Prognostic index (stages 1 – 2):

- Number of nodal sites: 1-2 vs >2
- Size of largest node: <5cms vs ≥5 cms
- Presence or absence of B symptoms

German (Hasenclever) Hodgkin's Disease prognostic index in advanced stage disease (stages 3-4):

- Hb at presentation (≤ 10g/dl)
- Albumin at presentation (< 40g/l)
- Lymphocyte count at presentation (< 1.0 x 10^9/l)
- Age >40
- Male sex
- Stages III & IV

Follicular Lymphoma International Prognostic Index (FLIPI):

- Age (< 60 years of age versus >60 years of age)
- Ann Arbor Stage III or IV
- Haemoglobin level < 120 g/L
- Elevated LDH
- Greater than 4 nodal sites

Mantle Cell Lymphoma International Prognostic Index

- The MIPI identifies four risk factors for overall survival. For each factor your get points from zero up to 3. The maximum score is 11 points

Points	Age	ECOG PS	LDH (ULN)	WBC, 10^9/L
0	<50	0-1	<0.67	<6.700
1	50-59	-	0.67 - 0.99	6.700 - 9.999
2	60-69	2-4	1.0 - 1.49	10.000 - 14.999
3	≥ 70	-	≥ 1.5	≥ 15.000

- ECOG PS = Eastern Cooperative Oncology Group performance status
- LDHULN = lactic acid dehydrogenase institutional upper limit of normal
- WBC = white blood cell count from the complete blood count

Low risk (0-3 points)
Intermediate risk (4-5 points)
High risk (6-11 points)

10.5 Primary Management of Hodgkin's Lymphoma (1.1-1.4 Classical Hodgkin's Disease, 1.5 Lymphocyte Predominant Hodgkin's Disease)

10.5.1 1st Line – Curative Intent

Stage IA, IB, IIA (favourable)
2 ~~3~~ x ABVD and 20Gy involved field radiotherapy
Note: If radiotherapy is deemed toxic for the above (e.g. risk of breast cancer in young women or ischaemic heart disease), perform PET after 2 cycles of ABVD and complete 6 cycles if PET negative. If PET positive, radiotherapy or escalation of chemotherapy will be important.

Stage IIA unfavourable, IIB:
Option 1: Consider PET to define true stage.
Treat with ABVD, perform PET after 2 cycles : if negative continue ABVD total ~~6-8~~ 4 followed by 30Gy IFRT
If PET positive: switch to alternative therapy, e.g. escBEACOPP.
Option 2: esc BEACOPP x 2, ABVD x 2 then 30Gy IFRT

Stages IIIA favourable:
Treat with ABVD, perform PET after 2 cycles : if negative continue ABVD total 6-8
If PET positive: switch to alternative therapy, e.g. escBEACOPP.

poor prognosis, IIIB and IV
Escalated BEACOPP or BEACOPP14 x 8.
For older patients or those with comorbidities, standard BEACOPP (50% less anthracyclines than ABVD) or ABVD x 2 followed by a PET scan. If negative PET continue for total of 6-8 cycles. For patients with cardiomyopathy consider same approach with non-anthracycline containing regimen or Brentuximab through a clinical trial where available or following funding approval.

10.5.2 1st Line – Non Curative Intent

For unfit elderly patients. Consider palliative therapy, e.g: ChlVPP, VEEP, Radiotherapy, Gemcitabine with or without Platinum and steroids (GEM-P). Brentuximab can be considered following funding approval.

10.5.3 Primary Refractory Disease (<50% response) and 2nd Line

For patients refractory to ABVD after 2 courses consider salvage chemotherapy with BEACOPP14 or escalated BEACOPP otherwise, CAIP, ESHAP or DHAP with or without Gemcitabine or Brentuximab (through clinical trial or following funding approval, then discuss transplant options with transplant centre in eligible patients. Consolidation radiotherapy in limited stage disease should be considered.

10.5.4 3rd Line

Gemcitabine or a non-cross resistant combination depending on initial therapy or Brentuximab (clinical trial or following funding approval) with option of radiotherapy to bulky/symptomatic areas.

Discuss transplant options with transplant centre for eligible patients.

10.5.5 Management of Lymphocye Predominant Hodgkin's Lyphoma

Most present at stage I-II disease, progression beyond this is rare and should be histologically questioned. 2-10% transform to DLBCL.

Stages I –II (favourable)
Surgical resection, observe or IFRT

Stages I –II (unfavourable)
ABVD x 2-4 depending on PET response followed by IFRT

Stages III – IV
Treat with R-CHOP or R-ABVD x 6-8 cycles option of consolidation RT to bulky sites

High grade transformation
Treat as DLBCL. Discuss transplant options with transplant centre.

10.6 Management of Diffuse Large B-Cell Lymphoma (DLBCL)

Management depends on:

1. International prognostic Index (IPI)
2. Risk of CNS Disease
3. Proliferation Index (Ki-67)

All patients should have screening virology for hepatitis B and C and HIV prior starting therapy. This should be documented on the drug chart for cycle 1.

10.6.1 Stage 1A, Low IPI, Low Bulk (<7cm)

CHOP x 3 followed by involved field radiotherapy (IF-RT)

10.6.2 Stage 1A, Low IPI, High Bulk (<7cm)

- R-CHOP x 6; alternative R-CHOP x 3 followed by IF-RT if chemotherapy is not well tolerated. Recent GELA data suggest R-CHOP x 6 to be superior.
- Funding approval required for Rituximab in stage I disease.

10.6.3 Stage IIA, Low IPI, Low Bulk (<7cm)

R-CHOP x 6 (+/- 2 additional R), Radiotherapy to initial bulk if PET/CT positivity remains.

10.6.4 Stage IIB-IV

R-CHOP x 8. Standard treatment is R-CHOP given every 21 days but R-CHOP 14 x 6 and 2 additional Rituximabs may be considered as an equally effective treatment (Recently proven by NCRI study).

If MIB-1 $\geq$90% or C-MYC oncogene rearranged in patients <65 years consider R-CODOX-M/R-IVAC, Dose adjusted R-EPOCH or R-HyperCVAD/R-high dose Methotrexate and Cytarabine for 4-6 cycles depending on response.

Elderly patients: Consider the NCRI Study or the GELA elderly R-CHOP Protocol

Impaired cardiac function: Enrol in NCRI clinical trial or otherwise consider Liposomal Doxorubicin (Caelyx) following funding approval. RGCVP with Gemcitabine (NCRI Data) or R-CEOP with Etoposide (Canadian data).

Other protocols may be considered following MDT discussion and applied for through off-protocol and CDF process.

Is Rituximab funded when not used with CHOP (NICE TA 65)

10.6.5 Residual PET positive adenopathy

Residual disease/PET positivity end of therapy consider rebiopsy (high risk of false positivity). If positive salvage therapy discussed through MDM and ASCT. Otherwise, radiotherapy to residual disease site(s) if unfit for ASCT.

10.6.6 Relapse

Late Relapse (>6 months) First-line treatment is R-ESHAP, R-ICE,~~or~~ DHAP or R-Gem-DHAP. (rituximab funded for patients suitable for consolidation with an autograft transplant).

Early Relapse (<6 months): Same as above without Rituximab

Other treatment options include:
CAIP, GEMP, GEMOX, PMitCEBO, CHOP, CNOP, CODOX-M/IVAC, HyperCVAD/R-high dose Methotrexate and Cytarabine, or miniBEAM

Auto or allograft options should be discussed with the transplant centre for fit patients. Otherwise consider radiotherapy to sites of residual disease.

10.6.7 CNS prophylaxis and treatment

See CNS disease guidance document.

10.7 Management of Aggressive NHL other than DLBCL

10.7.1 Testicular B-NHL

Even with localised presentation, this is usually a systemic disease with a high incidence of CNS relapse. Treatment should be with R-CHOP (4-8 courses), adding appropriate systemic CNS prophylaxis (see CNS guidelines). Radiotherapy should be considered to contralateral testis in selected patients following discussions regarding fertility and male menopause.

Intensification with R-CODOX-M/IVAC or R-HyperCVAD/R-high dose Methotrexate and Cytarabine should be considered for young high MiB-1 and International ~~p~~ Prognostic Index (IPI) patients.

10.7.2 Bone High Grade NHL

R-CHOP (6-8 courses) with radiotherapy to localised disease. CNS prophylaxis needed if $\geq$2 sites of disease.

Intensification with R-CODOX-M/IVAC or R-HyperCVAD/R-high dose Methotrexate and Cytarabine should be considered for young high MiB-1 and International Prognostic Index (IPI) patients.

10.7.3 Mantle Cell Lymphoma

Usually presents with stage IV/leukaemic phase and carries poorer prognosis. Management depends on MIPI (see above), age, stage and histological subtype (nodular vs. blastoid).

Diagnostic Criteria
Typical Cases
1. Monomorphic population of small to intermediate sized B-cells
2. Phenotype: sIg++/+++ (IgM & IgD), CD5+, CD23-, CD20+
3. BCL-1 expression/ t(11;14); Cyclin D1
Variants
Blastic or large cell variant associated with an aggressive clinical course
An indolent form is seen in about 20% of cases and a watchful policy may be appropriate initially in asymptomatic patients, particularly those with advancing age.

Essential Investigations
- Bone marrow aspirate and trephine
- FISH analysis for the t(4,11) from marrow or blood lymphocytes
- CT scan of thorax, abdomen and pelvis (and neck if clinically involved)
- Calculation of MIPI
- Gastrointestinal investigations e.g. Upper GI endoscopy/ sigmoidoscopy and biopsy, if symptomatic

Primary Treatment
Trial participation is strongly encouraged. Outside of trial:

- Young and fit patients: should NOT receive FC (Fludarabine and cyclophosphamide) or FCR because of toxicity and stem cell depletion. R-maxi-CHOP/R-high dose Cytarabine or R-HyperCVAD /R-high dose Methotrexate and Cytarabine are established treatments usually followed by consolidation autologous stem cell transplant (ASCT). R-high dose Cytarabine is being investigated by the HOVON and NCRI groups as a treatment option. If used, entry into trial is essential as it remains currently investigational. However, it can be used for patients with contra-indications for anthracycline usage. Consideration of allogeneic transplant at time of presentation if high MIPI and fit patients.
- Older patients with asymptomatic and nonprogressive disease should be observed.
- Patients who are unfit for ASCT should be considered for R-CHOP followed by R maintenance based on the recently published German study. Those who cannot receive anthracyclines should receive a combination of Rituximab and Bendamustine (funding approval required) based on the Rummel data. FCR should be avoided because of toxicity and high mortality rates particularly in older patients.
- Chlorambucil can be used for the unfit patient as a palliative treatment particularly those with slow pace disease.
- Radiotherapy for localized symptomatic or bulky disease is effective and should be considered for quick relief of symptoms particularly in patients with reduced performance status.

Relapse Treatment
- Biologically young and fit patients who didn't have a transplant in the primary treatment should be discussed with the transplant centre.

- A Rituximab and Bortezomib (funding approval required) containing regimen should be used, either with Bendamustine (funding approval required) or with high dose Cytarabine and Dexamethasone. .

- The Bruton Kinase Inhibitors (BTKI) are highly effective with minimal toxicity and are currently only available as part of clinical trials. Entry is encouraged for those who fail 2 courses of a Bortezomib containing regimen.

Palliative options: Lenalidomide has significant activity, Thalidomide, ~~possibly~~ particularly combined with Rituximab has a potential action. Both require funding approval.

10.7.4 Burkitt's and Burkitt-like Lymphoma

Highly aggressive disease with high CNS relapses. Treat with R-CODOX-M/R-IVAC or R-HyperCVAD/R-high dose Methotrexate and Cytarabine. Discuss transplant options with transplant centre in first CR for patients <65 years of age and advanced disease.

10.7.5 Lymphoblastic NHL

Refer for UKALL 14 study, treat as ALL using UKALL 12 or equivalent protocol. B-Lymphoblastic NHL can be treated as in Burkitt's lymphoma. Discuss transplant options with transplant centre.

10.7.6 Mediastinal Sclerosing B-Cell Lymphoma

Genetically distinct from DLBCL. Typically presents in females with stage I-II mediastinal disease, local extension with SVC occlusion and no "B" symptoms. Bone marrow and CNS disease are rare. Residual radiological masses common and PET is essential at diagnosis to determine later response.

Treatment options include R-CHOP, R-DA-EPOCH, and R-MACOP-B. PET evaluation is important as radiotherapy and/or ASCT should be considered especially in those patients receiving R-CHOP where 80% need consolidation and the 5 year PFS is 60-80%. Data with R-DA-EPOCH show that all become PET negative with chemotherapy alone and none of the patients require radiotherapy with 93% 5 year PFS.

10.7.7 T-cell Rich B-cell Lymphoma

Prognosticate and treat as DLBCL.

10.7.8 Anaplastic Large Cell Lyphoma (CD30 Positive)

Stratify risk using IPI, phenotype (T vs. null) and ALK [t (2;5)] expression.

T-cell phenotype and ALK positivity confers good prognosis and these cases should be managed according to stage and site of disease. Primary skin disease can be treated with radiotherapy, mustine cream or systemic chemotherapy (e.g. CHOP, MACOP-B).

Null phenotype and ALK negativity carries poor prognosis and advanced disease should be treated aggressively (CHOP14, HyperCVAD/High dose Methotrexate and Cytarabine, CODOX-M/IVAC, MACOP-B, ESHAP, DA-EPOCH, DHAP). For younger patients, consider transplant options with transplant centre in first remission.

10.7.9 Peripheral T-cell Lyphoma

This is a group of largely incurable malignancies where no standard therapies exist and trial entry is encouraged. Please refer to KMCN Pathway of Care for Cutaneous Lymphoma: section 10.

Indolent T-NHL: alpha-Interferon, pentostatin, CVP, CHOP, alemtuzumab (funding approval required) +/- chemotherapy (eg CHOP, MACOP-B), Gemcitabine, Platinum containing regimen and Thalidomide (funding approval required). Consider consolidation RT for limited stage disease. (off protocol)

Aggressive T-NHL: **Includes Sezary syndrome**. Gemcitabine, Platinum containing regimens, CHOP, Liposomal Doxorubicin (funding approval required), MACOP-B, IVE, high dose Methotrexate, Thalidomide funding approval required). Otherwise alemtuzumab (funding approval required), or Romidepsin (Named Patient Basis).

Consider transplant options with transplant centre for fit patients.

10.8 Management of Plan for Follicular B-NHL

10.8.1 Management Depends on FLIPI

- Age (≥ 60)
- Stage 4
- Male gender
- Raised LDH
- Hb <120 g/l
- >4 nodal areas

Risk factors for high grade transformation include bulky, particularly abdominal disease with heavy marrow infiltration and raised LDH.

10.8.2 Grade 3 FL

Grade 3B should be treated as DLBCL. There is no consensus about how grade 3A should be treated. It is recommended that the high FLIPI and young patients be treated as for DLBCL with R-CHOP followed by 2 monthly Rituximab maintenance for 2 years. The localised ones with low FLIPI and in older age groups can be treated as low grade disease.

10.8.3 Stage I-IIA, Grades 1-2

Radical radiotherapy to be considered. Curable in 50% of carefully selected patients. Advisable: PET scanning, bone marrow molecular genetics for the 14;18 translocation.

10.8.4 Stage IIB, III and IV, Grades 1-2

Observation unless impaired organ function, symptomatic adenopathy or constitutional symptoms. Outside of trial consider Rituximab containing induction chemotherapy followed by Rituximab maintenance (funding approval required for stage IIB disease).

10.8.5 Systemic Therapy, Grades 1 and 2

1st Line

Patients with low-intermediate 1 FLIPI R-CVP

Patients with intermediate 2-high FLIPI: Rituximab with CHOP or Bendamustine (funding approval required) if unfit/cardiomyapathy. Discuss transplant options with transplant centre at 1st CR for poor prognosis disease and fit patients.

Zevalin® (where exceptional circumstances can be evidenced or funding has been approved) may be considered for incomplete remissions particularly in poor prognosis / younger patients.

Maintenance treatment

Rituximab maintenance therapy is recommended as an option for treatment of people with follicular non-Hodgkin's lymphoma that has responded to first line induction therapy with Rituximab in combination in chemotherapy. Patients must have achieved at least a partial response with Rituximab in combination with chemotherapy. Treatment should start 2 months after the last dose of first-line induction therapy and will be given every 2 months until disease progression or for a maximum of 2 years.

2nd and 3rd Line

R-CVP, R-CHOP, R-DHAP, R-ESHAP, RICE, R-FMD/FAD, FCR (standard or lite), R-Bendamustine (funding approval required), Gemcitabine. Followed by 3 monthly Rituximab maintenance starting 3 months after completion of therapy for a total of 2 years.

Elderly/palliative: Chlorambucil, CVP, FC Lite, Bendamustine (funding approval required) with or without Rituximab.

Consider transplant option with transplant centre for fit patients in 2nd or 3rd CR for poor prognosis disease.

Other Treatments

Zevalin® (where exceptional circumstances can be evidenced).

Splenectomy for hypersplenism.

Radiotherapy (24GY preferable to 4Gy) to unsightly, painful or threatening adenopathy.

10.8.6 High Grade Transformation

High grade transformation of grades 1-2 has aggressive behaviour. Treatment is as for DLBCL (R-CHOP) with CNS prophylaxis if high risk. If proliferation index is>90%, consider R-CODOX-M /R-IVAC with CNS prophylaxis. Eligible patients should be discussed with the transplant centre. Radiotherapy should be considered for localised high grade transformation following systemic induction therapy or for sites of bulk.

10.9 Management of Marginal Zone Lymphoma (MZL) and Lymphoplasmacytoid Lymphoma (LPL/Waldnstroms Macroglobulinaemia)

10.9.1 Low Grade (Indolent) Gastric MZL (MALT)

Commonly patients are *Helicobacter pylori* positive. All cases should receive H. pylori eradication therapy regardless of their histology/serology. Those who test positive should have a breath test performed after at least two weeks without treatment with Proton Pump Inhibitors, as proof of eradication.

Stages $TisN_0M_0$ and $T_1N_0M_0$ could respond with only H Pylori eradication therapy. Repeat endoscopy is required after course with repeat H Pylori screening and biopsies. Responses can take up to one year to show.

More advanced stages

Patients with recurrent disease after 1 year, stage greater than 1E or persistent and symptomatic disease with visible bulky disease after Helicobacter eradication; options include:

Radiotherapy which is effective in majority of cases and remissions are long-lived.
Chemotherapy (Chlorambucil, CVP, CHOP or Fludarabine and Cyclophosphamide) preferably with Rituximab.

Surgery: Total gastrectomy should not be routinely performed unless radiotherapy &/or chemotherapy is not possible in locally advanced disease.

10.9.2 Low Grade (Indolent) lacrimal/salivary MZL (MALT)

Localised disease appears to have high and durable remission rates with localised radiotherapy which is the gold standard. Chlorambucil or CVP considered otherwise. Widespread disease should be treated as per low grade NHL. 6 week course of Doxycycline Chlamydia eradication can be considered with remission seen in up to 30% of cases.

10.9.3 High Grade (aggressive) MZL (MALT)

Patients should be managed as per DLBCL with H pylori/Chlamydia eradication.

10.9.4 Splenic Lymphoma with Villous Lymphocytes

Watchful waiting in asymptomatic patients with no cytopenia.

Splenectomy is often effective as first line treatment. Chlorambucil, Fludarabine +/- Cyclophosphamide, , CHOP and Rituximab are other effective modalities.

10.10 Lymphoplasmacytoid Lymphoma (LPL/Waldnstroms Macroglobulinaemia)

Treat symptomatic disease, ~~or~~ marrow failure, plasmacytic over-differentiation with myeloma like signs or associated neuropathy (usually anti-MAG positive), cryoglobulinaemia or amyloid.

Chlorambucil +/- Prednisolone produces 20-40% short response rates and should only be used for the very frail patients. Adding Rituximab to Chlorambucil improves responses.

Bendamustine (funding approval required), CVP, CHOP, Cladribine,~~/~~ Fludarabine alone or in combination with Cyclophosphamide ~~may~~ should be considered as alternative treatments. Rituximab use is advisable (BSH Guidelines, in press) as it deepens and prolongs response. Bortezomib containing regimens are also currently being evaluated in an NCRI study (R2W), entry to which is highly recommended.

Flare phenomenon (rise in IgM paraprotein following Rituximab) can occur in high paraprotein disease and can lead to stroke. It is recommended that patients with IgM of 40g/l or more should have plasmapheresis before starting R containing regimens. Otherwise it would be advisable to give the first course without Rituximab. Giving Rituximab a day or two following chemotherapy also appears to reduce the incidence of flare.

Poor risk fit patients should be considered for autologous or allogeneic BMT.

For relapsed disease, same regimens can be used as for first line treatment. Rituximab may be used in patients who have not received prior rituximab base treatment. An NCRI study (OBOE) will evaluate Bendamustine and Ofatumumab for induction with a following randomisation to either observation or 2 year maintenance programme with Ofatumumab. Until the role of maintenance is tested, routine use of Rituximab maintenance should not be encouraged and entry into the study is highly recommended.

Other salvage regimens include Thalidomide (funding approval required) or Bortezomib (funding approval required)with or without Rituximab. Lenalidomide should not be used because of the high incidence of pure red cell aplasia in this disease.

10.11 Cutaneous Lymphoma

- Refer to Kent & Medway - Cancer Pathway of Care – Cutaneous Lymphoma.

11.0 Appendices

11.1 Appendix A: Radiotherapy

11.1.1 Radiotherapy in Hogkin's Disease

Roles	
Curative	
a	**Early stage Hodgkin's Disease (Ia, Ib, non-bulky IIa)**
i	Extended field radiotherapy eg Mantle *or*
ii	Involved field radiotherapy after 2 – 4 cycles of chemotherapy Note: NLPHD : Involved field radiotherapy only
b	**Advanced stage Hodgkin's Disease (IIb onwards, or bulky disease)**
	Radiotherapy is given in the context of trial or as involved field to site of initial bulk disease only or on basis of post-chemotherapy PET scan
Salvage	
a	To consolidate response to second line chemotherapy
b	Following high dose regimens
c	Total or subtotal irradiation (plus spleen) may cure up to 20% of chemorefractory patients
Palliative	
a	In chemorefractory patients

11.1.2 Radiotherapy in low grade lymphomas

Curative	
a	Stages I & II as involved field radiotherapy
b	Skin lymphomas
Palliative	
a	Stage III/IV patients
b	Chemorefractory patients
c	Hypersplenism
d	Skin lymphomas
Experimental/System Radiotherapy	
a	Radioimmunotherapy may induce high (often durable) response rates
Salvage	
a	As part of high dose regimens

11.1.3 Radiotherapy in Diffuse Large B Cell Lymphomas

Curative	
a	**Early stage disease (Ia, Ib, IIa non-bulky)**
i	Involved field radiotherapy alone is less commonly used now
ii	Combined modality therapy following limited chemotherapy
b	**Other stage I/II disease (eg bulky or involving extra nodal sites)**
i	Involved field radiotherapy to sites of bulky disease following chemotherapy
ii	Consolidate chemotherapy response in sanctuary sites eg primary bone lymphoma

Palliative	
a	Chemorefractory patients
b	Chemotherapy sanctuary sites such as meningeal disease
Salvage	
a	Total body irradiation or radiation to sites of bulky disease as part of high dose regimens
b	Chemorefractory patients with stage I or II disease
Other Indications	
a	Consolidate partial response to chemotherapy in patients with stage III/IV disease, in sites of initial bulky disease (particularly if this is second line chemotherapy or PET show limited residual active disease
b	Consolidate response to chemotherapy in sanctuary sites such as primary cerebral lymphoma, site of spinal cord compression

11.1.4 Radiotherapy Fields

i	Total nodal irradiation (TNI) or total lymphoid irradiation (TLI): Sequential treatment with mantle and inverted Y fields (including spleen).
ii	Sub total nodal irradiation (STNI): Mantle field with a sub diaphragmatic field that does not include the pelvis
iii	Extended field irradiation: Irradiation to all nodal sites either above (mantle field) or below (inverted Y plus or minus spleen) the diaphragm.
iv	Involved field radiotherapy: Irradiation to involved nodal groups only, with a small margin of adjacent normal tissue.

11.1.5 Radiotherapy post chemo in NHL

No Radiotherapy

If patient in **CR** defined by CT criteria as $\leq$ 2cm mass (regardless of size of disease at presentation)

Exceptions

1. Epidural mass with cord compression
2. Leptomeningeal - adjuvant cranio-spinal radiotherapy
3. PET positive residual mass in Stage III/IV intermediate High Grade NHL (discuss with consultant)
4. Stage I/II non-bulky disease, short course chemo followed by RT

11.2 Appendix B: Staging of Lymphoma

11.2.1 Hodgkin's and non-Hodgkin's Lymphoma – Ann Arbour classification

Stage I
Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (I_E)

Stage II
Involvement of two or more lymph node regions (number to be stated) on the same side of the diaphragm (II) or localised involvement of extralymphatic organ or site and of one or more lymph node regions on the same side of the diaphragm (II_E).

Stage III
Involvement of lymph node regions on both sides of the diaphragm (III) which may also be accompanied by localised involvement of extralymphatic organ or site (III_E) or by involvement of the spleen (III_S) or both (III_{SE})

Stage IV
Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node enlargement. Organ should be identified by symbols:
L : Lung, H : Liver, P : Pleura, O : Bone, M : Marrow, S : Spleen, D : Skin.

B Symptoms: Weight loss $\geq$10 % over 3 months, night sweats and fever. Skin rash not B symptom.

11.2.2 CLL – Binet Classification

Stage	Organ enlargement*	Hb** (g/dl)	Platelets** ($X10^9/1$)
A	0,1 or 2 areas	$\geq$ 10	$\geq$ 100
B	3, 4 or 5 areas	$\geq$ 10	$\geq$ 100
C	not considered	< 10 and/or	< 100

*Each of the following counts as one area : (i) lymph nodes >1cm in the neck, axillae or groins (ii) spleen (iii) liver. **Other causes of anaemia (e.g. iron/folate/B12 deficiency) must be identified and treated before staging. A^0 clonal lymphocytosis $\leq$ 5 x 109/L with no adenopathy/organomegaly.

11.2.3 Gastrointestinal Lymphoma – TNM Classification

Primary Tumour (T)

TX Primary tumour cannot be assessed

T0 No evidence of primary tumour

Tis Carcinoma *in situ*: intraepithelial tumour without invasion of the lamina propria

T1 Tumour invades lamina propria or submucosa

T2 Tumour invades muscularis propria or subserosa

T3 Tumour penetrates serosa (visceral peritoneum) without invasion of adjacent structures

T4 Tumour invades adjacent structures

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastases

N1 Metastases in regional lymph nodes (<3cm from primary in gastric lymphoma)

N2 (Gastric only) Metastases in regional lymph nodes >3cm from primary

Distant Metastases (M)

MX Presence of distant metastases cannot be assessed

M0 No distant metastases

M1 Distant metastases

11.2.4 Sezary Syndrome

The TNMB classification agreed at the NCI in 1978 is recommended as below:

Stage	Definition
T0	Clinically and/or histologically suspicious – premycotic syndrome
T1	Limited plaques or patches less than 10% skin surface
T2	Generalised plaques or patches greater than 10% skin surface
T3	One or more skin tumours
T4	Generalised erythroderma
N0	No nodal enlargement
N1	Clinically enlarged nodes – histologically negative
N2	Nodes not enlarged but sampled and found histologically positive
N3	Clinically enlarged nodes – histologically positive
B0	Atypical circulating cells not present or less than 5%
B1	Atypical circulating cells present and greater than 5%
M0	No visceral involvement
M1	Visceral involvement – biopsy proven

The BAD/UKCLG guidelines use the Bunn Lamberg staging system(Wood and Greenberg 2003):

Stage 1A	T1 N0
Stage 1B	T2 N0
Stage IIA	T1/2 N1 but nodes dermatopathic
Stage IIB	T3 N0/1 but nodes if enlarged dermatopathic
Stage III	T4 N0/1
Stage IVA	Any T N2/3
Stage IVB	Any T Any N, M1

11.3 Appendix C: Clinical Trials

Suitability for entry into Kent & Medway - Cancer agreed clinical trials should be a standard component of the MDM discussion on each patient with a Haematological Cancer.

Refer to the local research team who will provide on request an orientation handbook, list of current trials and associated trial protocols and summaries.

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12.0 Glossary

Acronyms in common usage throughout Kent & Medway – Cancer documentation:

CNB	Cancer Network Board
CYP	Children & Young People (in relation to the IOG)
DCCAG	Diagnostic Cross Cutting Advisory Group
TSSG	Tumour Site Specific Group (DOG/NSSG/TWG)
DVH	Darent Valley Hospital
EK	East Kent
EKHUFT	East Kent Hospitals University Foundation Trust
HoP	High Level Operational Policy
IOSC	Improving Outcomes: A Strategy for Cancer
K&C	Kent & Canterbury Hospital, Canterbury, (EKHUFT)
KMCN	Kent & Medway Cancer Network
KMCRN	Kent & Medway Cancer Research Network
LSESN	London & South East Sarcoma Network
MFT	Medway Foundation Trust
MTW	Maidstone & Tunbridge Wells NHS Trust
NOG	Non Surgical Oncology Group *(Permanent oncologist sub group of the TSSGs with a specific responsibility for chemo/rad pathways and advice to the TSSG, Network and geographical locations on new drugs)*
PoC	Pathway of Care *(Network agreed disease site specific clinical guidelines)*
QEQM	Queen Elizabeth the Queen Mother Hospital, Margate (EKHUFT)
QoL	Quality of life
RAT	Research and Trial Group *(Permanent sub-group of the TSSGs with a specific responsibility for taking forward the clinical trials agenda)*
RMH	Royal Marsden Hospital
RNOH	Royal National Orthopaedic Hospital
QVH	Queen Victoria Foundation Trust Hospital East Grinstead
UCLH	University College Hospital London
WHH	William Harvey Hospital, Ashford (EKHUFT)
WK	West Kent
CCG	Clinical Commissioning Groups

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