

**GREATER MANCHESTER AND CHESHIRE CANCER
NETWORK**

HAEMATO-ONCOLOGY CLINICAL SUBGROUP

GUIDELINES FOR MANAGEMENT OF LYMPHOMA

Fourth edition, June 2011

FOREWORD

These guidelines were written by a group of oncologists, haematologists and nurses on behalf of the Haemato-oncology sub-group of the Greater Manchester and Cheshire Cancer Network (GMCCN) and first published in November 2004. **They are intended for use by consultant led teams in the management of patients with Hodgkin and non-Hodgkin lymphoma in the setting of the various multi-disciplinary teams operating in the GMCCN.** They should not be used without the approval of the patient's consultant.

These guidelines although detailed are not fully comprehensive and have evolved in line with the availability of new data since they were first published in 2004. This is the third edition and our intention is for reviews to continue on an approximately annual basis.

For further information please contact any member of the Lymphoma Guidelines Group listed below:

Dr. Adrian Bloor, Consultant Haematologist, The Christie
0161 446 3869

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0161 446 3332

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0161 206 4983/4984

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Dr Martin Rowland, Consultant haematologist, Pennine Acute Trust
contact no

Dr.Kate Ryan, Consultant Haematologist, Manchester Royal Infirmary
0161 276 6448

The guidelines group wish to acknowledge and thank the following for their contributions to these guidelines:-

Dr. Adam Gibb, SPR in Medical Oncology, The Christie

Dr. Kim Linton, SPR in Medical Oncology, The Christie

Dr. Ed Smith, Consultant Clinical Oncology, The Christie

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BASELINE INVESTIGATIONS AND STAGING

- Lymph node biopsy (avoid inguinal region if alternative sites available) with central pathology review performed by the GMCCN haemato-malignancy diagnostic service 0161 446 3279. Consider fresh tissue for tumour bank and cytogenetic analysis. **Do not perform FNA cytology**; the technique does not provide sufficient information on which to base a treatment decision in lymphoma, the results may be misleading and, because a lymph node biopsy is always required, its use causes delay.
- Clinical history and examination to include assessment of performance score, presence of B symptoms (night sweats, fever, $\geq 10\%$ weight loss) and assessment of bulk (see below)
- Standard PA chest radiograph with assessment of mediastinal bulk (see below)

Notes:

In the mediastinum bulk is defined as a ratio of the maximum transverse diameter of mass to internal thoracic diameter at T5/6 interspace ≥ 0.33 on a pa chest Xray. **At other sites** bulk comprises nodal masses with a maximum transverse diameter $\geq 10\text{cm}$.

- CT scan neck, thorax, abdomen, pelvis
- MR scan in NHL of Waldeyer's ring, sinuses, orbits and brain
- Baseline PET scan should be performed in HL and DLBCL
www.christie.nhs.uk/pro/cs/radiology/pet_ct.aspx
In follicular lymphoma discuss with radiologist
- Bone marrow trephine **in all cases of NHL** with additional aspirate if elevated lymphocyte count for morphology/flow cytometry/cytogenetics
- Bone marrow trephine **in HL stages IB, IIB, III and IV (not required in CS IA/IIA)**. Aspirate not required in any circumstances for staging purposes
- Full blood count (and ESR in HL), serum biochemical profile including LDH, immunoglobulins and electrophoresis (in NHL)
- HIV, hepatitis B and C serology in all new patients

- Semen cryopreservation must be offered to all males \leq 55yrs and oocyte/embryo storage considered for pre-menopausal women concerned about fertility and treatment likely to cause permanent sterility please refer to NICE guidelines – (National Institute for Clinical Excellence (2004) Fertility: assessment and treatment for people with fertility problems (NICE guidelines CG11), London: NICE. www.nice.org.uk)
For further information/discussion please contact Dr. Cheryl Fitzgerald, sub-fertility lab, ST. Mary's Hospital, Manchester
- Cardiac assessment (MUGA or echocardiography) for patients \geq 70yrs requiring anthracycline containing therapy or patients of any age with a history of cardiac disease/hypertension. Normal reference ranges will vary
- Record height and weight
- Provide contact details for Clinical Nurse Specialist for further information and support, and inform re new patients if CNS not available in clinic.
- Provide contact details for the Lymphoma Association, CancerBACUP Leukaemia and Lymphoma Research and Cancer Research UK as appropriate (see below). These organisations are able to provide patients with high quality information about lymphoma and its treatment.

Lymphoma Association

PO Box 386
Aylesbury
Bucks HP20 2GA
0808 808 5555

CancerBACUP

3 Bath Place
Rivington Square
London EC2A 3JR
0808 800 1234

Leukaemia and Lymphoma Research

Eagle Street
London WC1N 3JJ
020 7405 0101

MDT meetings

MDT meetings are held on a regular basis (usually weekly).

The central purpose of the MDT meeting is to review every new case on a prospective, multi-disciplinary basis, identify missing data and those investigations requiring further analysis, assign clinical stage, prognostic scores (IPI, Hasenclever, EORTC) and determine appropriate management/eligibility for trial entry according to network guidelines.

In addition patients with recurrent disease can also be discussed, particularly where management decisions may be difficult or complex

Restaging after completion of treatment

At completion of all planned treatment, patients should have all previously abnormal baseline investigations repeated to assess remission status (see below). The need for further treatment should then be discussed.

Radiotherapy should take place within 2 months of completing chemotherapy and therefore post-treatment CT scan should ideally be within 2 weeks of completing therapy to allow for timely referral to the clinical oncologist. Given the time required for modern computer planning, referrals for consolidation radiotherapy should be made within 4 weeks of completing chemotherapy at the latest.

Requirements for imaging

At Baseline

- CXR for assessment of mediastinal mass (?bulk disease) in all cases
- CT scan neck, thorax, abdomen and pelvis in all cases
- MR scan if suspected oro-pharyngeal, naso-pharyngeal, nasal, facial sinus or central nervous system involvement
- FDG-PET scan in patients with Hodgkin lymphoma and diffuse large B cell lymphoma
- Ultrasound examination if advised by radiologist (assessment of pelvic masses, liver abnormalities identified by CT scan)
- MUGA scan or echocardiography to assess left ventricular function if age 70 plus or at any age if history of hypertension, myocardial infarction, angina or heart failure and anthracycline based chemotherapy likely to be recommended

During chemotherapy

- For patients with mediastinal mass, CXR after every second cycle to assess response.
- Where no mediastinal mass or other means of assessing response, CT scan neck, thorax, abdomen and pelvis after 3 cycles.

After chemotherapy

- CT scan neck, thorax, abdomen and pelvis in all cases (except if normal pre-treatment)
- Any of the other baseline investigations if abnormal at that time
- FDG-PET scan (Hodgkin lymphoma and diffuse large B cell lymphoma) to assess potential residual masses. This may inform the treatment volume of any consolidation radiotherapy required.

After consolidation radiotherapy

- CT scan neck, thorax, abdomen and pelvis where residual abnormalities present after chemotherapy
- Any of the other baseline investigations if abnormal at that time

During follow-up

Apart from thyroid function tests for patients who have received radiation to the neck, no routine bloods or imaging is required in patients with Hodgkin lymphoma or DLBCL once patients reach annual follow up

Investigate new symptoms as appropriate

Ann Arbor staging

Stage I - Involvement of only one lymph node region

Stage II - Two or more lymph node areas involved confined to one side of the diaphragm

Stage III - Involvement of lymph nodes above and below the diaphragm

Stage IV – Multi-focal involvement of an extranodal site

A = No constitutional symptoms

B = Constitutional symptoms present ($\geq 10\%$ weight loss; night sweats; unexplained fever – but not pruritis)

E = Extra-nodal disease at a single site with or without adjacent adenopathy (IE or IIE; by convention IIIIE is stage IV)

X = Bulk disease

Evaluation of response.

Cheson et al. J Clin Oncol 25:579-586, 2007

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

Abbreviations: CR, complete remission; FDG, [¹⁸F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

Refer to SLL/CLL section for response criteria for SLL (page 53)

Indications for referral for transplant opinion

Referral for stem cell transplantation should be considered for the following indications (based on the current BSBMT criteria – see http://www.bsbmt.org/pages/64-Indications_Table)

Disease and Status	Transplant Type		Notes
	Autologous	Allogeneic	
Follicular Lymphoma (FL)			
CR/PR 1	No	No	Reduced intensity allogeneic transplant may be considered at CR/PR > 1 in younger patients (< 60) esp those with short remission following chemotherapy
CR/PR > 1	Yes	Clinical Opinion	
Chemorefractory	No	No	
Relapse post autograft	No	Yes	
Transformed disease	Yes	No	
Diffuse Large B-Cell Lymphoma			
CR 1	No	No	Autologous transplantation in PR1 may be considered in patients with high risk disease that is responsive to salvage chemotherapy
PR 1	Clinical Opinion	Investigational	
CR/PR > 1	Yes	No	
Chemorefractory	No	No	
Relapse post autograft	No	Clinical Opinion	
Mantle Cell Lymphoma			
CR/PR 1	Yes	Investigational	Reduced intensity allogeneic transplant may be considered at CR/PR > 1 in younger patients (< 60) esp those with short remission following chemotherapy
CR/PR > 1	Yes	Clinical Opinion	
Chemorefractory	No	No	
Relapse post autograft	No	Yes	
T-Cell lymphoma			
CR/PR 1	Yes	No	Young patients with ALK-1

CR/PR \geq 1	Yes	Clinical Opinion	+ve ALCL have a good prognosis with chemotherapy and transplant in CR1 is not recommended
Chemorefractory	No	No	
Relapse post autograft	No	Clinical Opinion	
Hodgkin Lymphoma			
CR/PR 1	No	No	
CR/PR > 1	Yes	Investigational	
Chemorefractory	No	Investigational	
Relapse post autograft	No	Yes	
Chronic Lymphocytic Leukaemia / Small Lymphocytic Lymphoma			
CR/PR 1	No	Yes	Del (17p), or Richter's Transformation only
CR/PR 2	No	Yes	Purine analogue refractory (relapse within 6 months)
CR/PR \geq 2	No	Clinical Opinion	Selected high risk cases (eg relapse within 2 years of chemo-immunotherapy)
PLL	Clinical Opinion	Clinical Opinion	

Recommendations

Yes:	Generally recommended
No:	Generally not recommended
Clinical Opinion:	May be considered on a case by case basis
Investigational:	Only recommended as part of a Clinical Trial

Required Clinical Parameters for Stem Cell Transplantation

The following parameters are generally required for patients to be eligible for stem cell transplantation:

- Age < 65 (up to 70 years in selected cases)
- Good performance status (Karnofsky Performance Score \geq 80%)
- Adequate cardiac and renal function (creatinine clearance \geq 50 ml/min, left ventricular ejection fraction \geq 50%)
- Chemotherapy sensitive disease
- For allogeneic transplantation either an HLA identical sibling or for unrelated donor transplants, a 9/10 or 10/10 match at HLA A, B, C, DQ and DR loci.

- Allogeneic Transplantation will generally be performed using non-myeloablative (reduced intensity) conditioning.

Additional Information

For additional information regarding eligibility for transplantation, it is suggested that cases are discussed with either:

- Dr Adrian Bloor (Christie Hospital) 0161 446 3869
- Professor John Yin (Manchester Royal Infirmary) 0161 276 4802

Guidelines for referral pathway of adolescents (access to YOU)

In the two Cancer Networks (GMCCN and LSCCN), 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).

According to IOG the PTC should be notified of all 16 - 24 year olds so that they can be registered with the National Cancer Information Network.

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. In some cases treatment delivery can be shared.

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

Logistics

Leukaemia/Transplants/Burkitt Lymphoma/Lymphoblastic Lymphoma

	Telephone	Fax
Key Contact: Dr Adrian Bloor, Consultant Haematologist	0161 446 3657	0161 446 8565
Tracey Blinkhorn, Secretary to Dr Adrian Bloor	0161 446 3869	0161 446 3940

In his absence contact the on call consultant haematologist. The Christie
0161 446 3000

Lymphoma (HD/DLBCL/ FL and other Low Grade NHL)

	Telephone	Fax
Key Contact: Dr Ed Smith, Consultant Clinical Oncologist	0161 918 7205	0161 446 8565
Liz McElvey, Secretary to Dr Smith	0161 446 3952	0161 446 3092

In his absence contact Professor John Radford. The Christie
0161 446 3753

Other enquiries

	Telephone	Fax
Key Contact: Dr Michael Leahy, Consultant Medical Oncologist	0161 446 8602	
Gwyn Mattimore, Secretary to Dr Michael Leahy	0161 446 8384	0161 446 3478

HODGKIN LYMPHOMA

Adverse features for early stage Hodgkin lymphoma (EORTC)

Very favourable; females <40 years with stage IA with NS or LP histology

Unfavourable; males and females >50 years or 4/5 involved nodal sites or elevated ESR/B symptoms or bulky mediastinal involvement

Favourable; all other patients with stages I/II

Prognostic scoring for advanced Hodgkin lymphoma

Hasenclever et al., NEJM 1998:1506-1514

Male Sex

Age \geq 45 years

Clinical stage IV

Hb < 10.5g/dl

WCC \geq $15 \times 10^9/l$

Lymphocytes $<0/6 \times 10^9/l$ or $<8\%$ of total WCC

Albumin <40g/l

Score	5 year PFS %	5 year OS %
0	80-88	88-91
1	74-80	88-92
2	65-69	79-83
3	57-63	75-81
4	47-55	57-65
≥ 5	37-47	51-61

Treatment of Hodgkin lymphoma

Consider clinical studies

a. Early stage, low risk Hodgkin lymphoma (stages I or II with no B symptoms or mediastinal bulk)

3 cycles ABVD followed by involved field RT. **These patients must be seen by a clinical oncologist before the start of chemotherapy** so that the full

extent of disease can be ascertained and an appropriate Radiotherapy Planning Target Volume prescribed upon completion of chemotherapy.

b. Stage IA nodular lymphocyte predominant Hodgkin lymphoma

Involved field RT alone should be discussed with a radiation oncologist or consider observation only.

c. Advanced Hodgkin lymphoma (stages III or IV, or stage I or II with 'B' symptoms and/or mediastinal bulk)

6 cycles ABVD. If bulk disease at presentation or PR at completion of chemotherapy, RT to residual radiographic abnormalities should be discussed with a radiation oncologist*. A PET scan may help treatment decisions but caution should be exercised when de-escalation of treatment (no consolidation radiotherapy) is being considered. This requires discussion at an MDT meeting with a radiation oncologist in attendance.

* In order to prevent delay to start of RT, inform radiation oncologist about patient with bulk disease as soon as possible and certainly no later than cycle 4 of chemotherapy.

d. Recurrent Hodgkin lymphoma after previous CT/RT for advanced disease

If 5 years or more since previous treatment and disease confined to a single nodal site discuss RT with radiation oncologist. Otherwise after ABVD, give 3-4 cycles ChIVPP or 2 cycles of platinum based therapy (preferred option), or RIC allotransplant if chemorefractory,

For disease resistant to the above regimens, consider a gemcitabine based combination such as GDCVP

e. Recurrent Hodgkin lymphoma after high dose chemotherapy

Consider phase II trials available at the time, gemcitabine based combinations such as GDCVP, allogeneic or mini-allogeneic transplantation (discuss with Dr Adrian Bloor, The Christie) or palliative approaches such as single agent vinblastine (6mgs/m² iv every 14 days), etoposide 100 - 150mgs daily po for 7-14 days every 28 days according to degree of myelo-suppression encountered)

TREATMENT FLOW CHART (see appendix D)

NON-HODGKIN LYMPHOMA

Consider clinical studies

Survival according to Revised IPI score (%) (Sehn et al., *Blood*, 2007)

	4 yrs
Very good (0)	94
Good (1,2)	79
Poor (3,4,5)	55

1. AGGRESSIVE SUBTYPES

a. Stage I, diffuse large B-cell lymphoma (inc. variants) and follicular lymphoma, grade 3B

3 cycles of CHOP (doses determined by age) followed by involved field RT is recommended by NICE but R-CHOP is usually preferred.

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

b. Stages II-IV, diffuse large B-cell lymphoma (including variants) and follicular lymphoma, grade 3B

6 cycles of R-CHOP (doses of CHOP determined by age) followed by consideration of radiotherapy to sites of bulk disease/residual abnormality in patients with IPI score 0, 1 or 2

8 cycles of R-CHOP (doses of CHOP determined by age) followed by consideration of radiotherapy to sites of bulk disease/residual abnormality in patients with IPI score 3, 4 or 5

Central nervous system prophylaxis is an area of uncertainty. Apart from Burkitts and testicular lymphoma, CNS prophylaxis should be employed in patients with para-spinal or base of skull disease or those with an IPI score that places them into a poor risk group. Such patients should have a lumbar puncture with a sample of csf submitted for cytopsin/microscopy and installation of 12.5mg methotrexate. If there is no evidence of CNS involvement one dose of methotrexate should be given at cycle 1 R-CHOP. If the CNS is involved, twice weekly doses of methotrexate until

lymphoma cells have been eliminated from the csf and then one dose with each remaining cycle of R-CHOP should be given. Local practice may vary.

For further information on administration of intra-thecal drugs see R-CODOX-M/R-IVAC section (page 40).

c. Large cell transformation of follicular lymphoma

6 cycles of R-CHOP followed by high dose BEAM with autologous haemopoetic stem cell rescue if patient age/condition appropriate for this intensity of treatment. On recovery from this consider RT to previous sites of bulk disease or residual abnormalities on the re-staging CT scan.

d. Burkitt and Burkitt-like lymphoma

For low risk patients give 3 cycles R-CODOX-M with doses dependent on patient age

For high risk patients give alternating cycles R-CODOX-M and R-IVAC to a maximum of 4 cycles with doses dependent on patient age

e. Lymphoblastic lymphoma (B and T cell types)

Refer to a haematology team for ALL like treatment

f. T-cell lymphoma (including peripheral T-cell and anaplastic large cell lymphomas)

6 cycles of CHOP (in potentially transplantable patients) (8 cycles GCVP for patients with impaired LVEF or significant cardiac disease) followed by consideration of radiotherapy to sites of bulk disease and/or high dose chemotherapy with autologous haemopoetic stem cell rescue is commonly employed. Overall the prognosis is poor for this group of tumours and ***patients should be offered clinical trials wherever possible.***

g. Primary refractory B/T cell lymphomas of aggressive type or relapse after CHOP or R-CHOP

If potentially suitable for high dose chemotherapy, give salvage chemotherapy e.g. DHAP (or R-DHAP if more than 12 months since last exposure to rituximab) ESHAP or ICE, with stem cell harvest after cycle 2 or 3 followed, in patients with responsive disease, high dose BEAM with autologous haemopoetic stem cell rescue.

If disease is unresponsive to DHAP/R-DHAP, do not give high dose BEAM but consider gemcitabine based combinations, ifosfamide/cytosine arabinoside given by ambulatory infusion pump, high dose methotrexate (3g/m²), palliative measures (including radiotherapy) or experimental protocols. If any of these treatments induce remission, consolidation using BEAM/autograft is then appropriate

h) Primary cerebral lymphoma

This is a rare condition often associated with HIV positivity. Treatment and the possibility of entry into an IELSG trial should be discussed with Dr Kim Linton (0161 446 3753)

i) Cutaneous lymphoma

Refer to supra-regional cutaneous lymphoma service for initial assessment and management plan - contact Dr. Richard Cowan/ Dr. Eileen Parry, The Christie - 0161 446 3332

j) PTLD – withdraw immunosuppressants, consider single agent rituximab or combination chemotherapy.

For access to specific protocol for renal PTLD contact Dr. Kate Ryan, Manchester royal infirmary 0161 276 6448

For other immune related lymphomas liaise with appropriate physicians

k) Testicular lymphoma is an aggressive entity with a propensity for CNS involvement. Treatment should be with 6-8 cycles R-CHOP and prophylactic intra-theical methotrexate given with cycles 1-4 and 3 cycles of IV methotrexate (3gms/m²) at the completion of R-CHOP. Radiotherapy to the contralateral testis should also be undertaken in addition to consideration of RT to sites of initial bulky disease or residual abnormality

l) HIV related lymphoma

Consider referral to Dr. Martin Rowlands, Pennine Acute Trust (**contact No**) or other specialist unit with HIV expertise

TREATMENT FLOW CHART (see appendix D)

2. INDOLENT SUB-TYPES

Consider clinical studies

In general, indolent lymphomas are characterised by a long natural history with a chronic remitting/relapsing course. Over time response rates fall and duration of remission shorten and in the follicular sub-type there is an increasing risk of transformation to large cell lymphoma. Repeat biopsy at each relapse is therefore recommended.

The FORT study (comparison between 2 and 12 fractions) should be considered for patients requiring radiotherapy)

Adverse features for follicular lymphoma (FLIPI)

Solal-Celigny et al., Blood 2004:1258-1265

Male Sex
Age \geq 60 years
Clinical stage III/IV
Nodal sites $>$ 4
Bone marrow infiltration
Hb $<$ 12/dl
Lymphocytes $<1 \times 10^9/l$
LDH \geq 550

Score	5 year OS %	10 year OS %
0-1	90.6	70.7
2	77.6	50.9
\geq 3	52.5	35.5

a. Stage I/II follicular WHO grades 1, 2 and 3A, small lymphocytic, lymphoplasmacytic but excluding marginal zone lymphoma

These tumours typically present in stages III or IV often with bone marrow involvement. In the unusual event of stage I however, local RT is appropriate and approximately 50% of these patients will not experience any further problems.

Stages III/IV follicular WHO grades 1, 2 and 3A

Indications for treatment are bulky disease, symptoms undermining quality of life and bone marrow involvement causing peripheral blood cytopenias). In the absence of these indications a careful watch and wait policy is appropriate.

First line treatment is with R-CVP or for frail, elderly patients, single agent chlorambucil may still be an appropriate choice

Following attainment of first remission consider rituximab maintenance for 2 years (results of PRIMA study show benefit)

Treatment for first relapse after chlorambucil is R-chemo (or chlorambucil again if the patient is frail/elderly and the duration of first remission was at least one year)

Treatment for first relapse after R-CVP is R-CHOP unless there has been a prolonged first remission (>4 years) in which case further R-CVP can be considered. At remission consider high dose BEAM with autologous haemopoetic stem cell rescue or reduced intensity/full allogeneic transplantation in suitable patients. Discuss such patients with Dr Adrian Bloor The Christie 0161 446 3869.

Following attainment of second remission Rituximab maintenance (375mg/m² 3 monthly for 2 years or until the onset of progressive disease, whichever is sooner) is indicated (Van-Oers et al; NICE approved).

Treatment options for subsequent relapses are radioimmunotherapy, (see below), bendamustine or fludarabine (as a single agent or in combination), single agent rituximab, external beam radiotherapy or experimental approaches.

Radioimmunotherapy

For treatment indications see flow chart

Patients being considered for this treatment who have no more than 25% of the inter-trabecular bone marrow space occupied by lymphoma should be discussed with Professor Tim Illidge at the Christie 0161 446 8574

b. Transformed follicular lymphoma

6 cycles R-CHOP (with stem cell collection after clearing of any bone marrow disease) followed by high dose BEAM with autologous haemopoetic stem cell rescue. On recovery from this consider radiotherapy to previous sites of bulk disease or residual abnormalities on the re-staging CT scan.

c. Stage I/II marginal zone lymphoma

Stage I extra-nodal presentations are typical (gastric, salivary, lacrimal, conjunctival, pulmonary, thyroid, cutaneous, bladder) and with the exception of the gastric type where eradication of *H. pylori* should first be attempted, local radiotherapy should be considered. Where this is unsuitable, or in younger patients either a watch and wait strategy or oral chlorambucil should be used

d. Mantle cell lymphoma

There is uncertainty about the best treatment for this type of lymphoma but a watch and wait policy in asymptomatic, slowly progressive disease, radiotherapy for localised disease, CVP, fludarabine (alone or in combination) and CHOP can be employed. There is little evidence for the use of rituximab in this setting. In the younger patient however, intensive treatment such as the NORDIC protocol would be the treatment of choice

For older patients FC/FCR or chlorambucil

Mantle cell lymphoma (Hoster E, Dreyling M, Klapper W et al. A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. *Blood* 2008 111: 558-565.)

e. Small lymphocytic lymphoma/chronic lymphocytic lymphoma

The indications for treatment are as outlined in the BCSH guidelines (weblink)

For further information/referral contact Dr. Adrian Bloor, The Christie 0161 446 3869

f. Waldenstrom's macroglobulinaemia /lymphoplasmacytoid lymphoma

A watch and wait approach can be adopted for asymptomatic patients. Indications for treatment are outlined as per the BCSH guidelines (weblink); treatment should not be based solely on IgM levels.

Urgent treatment for hyperviscosity symptoms is plasmapheresis with 1 plasma volume exchange procedure, repeated as necessary.

First line treatment

Current evidence suggests a role for rituximab for first line therapy in combination with chemotherapy. This has yet to be approved by the network and cases should be considered on an individual basis.

Rituximab should not be used in patients with IgM levels >40g/l due to the risk of IgM flare.

- Suitable for ASCT (<70y and good PS): R-CHOP . Consider stem cell collection in 1st CR
- >70y or not suitable for ASCT but able to tolerate chemotherapy : R – FC
- Elderly or frail patients: oral chlorambucil or rituximab monotherapy if severe cytopenias

Second line treatment:

This will depend on prior response, physical status and suitability for ASCT. If previous good remission > 12 months consider same regime as used for induction. Otherwise consider fludarabine if fit +/- rituximab.

Preliminary evidence suggests a role for high dose treatment. High-risk young patients may therefore be considered for ASCT in 2nd remission; cases should be discussed individually with a transplant centre.

There is emerging data for bortezomib in refractory disease or difficult cases.

ICDF has now approved bortezomib/ rituximab / dexamethasone for refractory lymphoplasmacytoid lymphoma (after alkylator and rituximab containing regimens)

TREATMENT FLOW CHART (see appendix D)

FOLLOW-UP FOR PATIENTS WITH LYMPHOMA.

Purpose:

- Detection of recurrent disease.
- Monitoring late effects of treatment on heart, lung and endocrine function, fertility and incidence of second cancers.
- Psychological support / reassurance

The published data suggests that the routine investigation of well patients is not an efficient way of detecting recurrent disease. Instead, patients should be encouraged to report new symptoms which should be investigated without delay.

All patients:

- Full re-staging evaluation at completion of therapy to confirm remission status
- Post radiotherapy check up at 6-8 weeks to make sure that all acute toxicity has subsided
- Provide information sheet detailing follow-up policy and stressing the importance of reporting new symptoms

Frequency of follow-up:

- Year 1 : every 3 months
- Year 2 : every 4 months
- Year 3 : every 6 months
- Year 4 + : once a year

At each visit:

- Ask about new symptoms, particularly 'B' symptoms.
- Examine for superficial lymphadenopathy, hepatomegaly, splenomegaly and abdominal masses
- Advise strongly to stop smoking and avoid sunburn

- Record any diagnoses of second malignancy occurring since previous visit
- Encourage patient to make earlier appointment if new problems arise
- Educate patient re risk of late effects of treatment

Investigations:

- Routine bloods or imaging is not required in patients with Hodgkin lymphoma or DLBCL when annual follow up is reached
- Thyroid function tests for patients who have received mediastinal or neck radiotherapy, starting at 3rd anniversary of completion of treatment and at every visit thereafter
- Indolent lymphoma – Routine bloods and it may be necessary to monitor immunoglobulins if a para-protein is identified
- Other investigations should be arranged in response to new symptoms/signs of disease, abnormal routine investigations or in the context of trial protocols

Second cancers:

In general, chemotherapy is associated with an increased risk of MDS/AML and radiotherapy with an increased risk of solid cancers. In lymphoma where radiotherapy to supra-diaphragmatic sites is commonly employed (especially in HL), patients are at particular risk of lung, upper GI (oesophagus and stomach) and in women, breast cancers.

Lung and upper GI cancers:

At present, routine screening for the early detection of these tumours cannot be recommended but patients should be urged to stop smoking and report new symptoms without delay. Clearly these should be investigated as a matter of urgency.

Breast cancer:

The risk is increased in women receiving supra-diaphragmatic radiotherapy under the age of 35 (greatest risk in the youngest women).

Recent Department of Health guidance is for all these women to be offered screening if they are **currently 25 or older and it is at least 8 years since treatment** according to the following protocol:

Age 25-29:	Annual MRI
Age 30-49:	Annual mammography supplemented where necessary by MRI and/or ultrasound
Age 50 plus:	Mammography every 3 years as part of existing breast screening programme for the general population

Any woman developing **breast symptoms** should be advised to see her GP who if necessary will arrange referral to the local breast unit.

With regard to **hormone replacement therapy** there is no indication for this to be stopped or completely avoided but it is prudent for HRT to be used only in women with significant menopausal symptoms or osteoporosis and only for the time that it is really required. If in doubt referral to an endocrinologist is appropriate. Further advice in this area is likely to follow as a result of ongoing research.

Appendix A: Chemotherapy regimens

Chemotherapy regimens for Hodgkin lymphoma

ABVD

3 cycles followed by involved field RT for stages I/II with no mediastinal bulk or B symptoms

6 - 8 cycles for advanced disease (stage III or IV, or stage I or II with 'B' symptoms and/or mediastinal bulk)

Day 1 and Day 15

Doxorubicin 25mg/m² iv bolus

Bleomycin 10,000 IU/m² iv bolus

Vinblastine 6mg/m² iv bolus (12mg max)

Dacarbazine 375mg/m² iv in 500mls normal saline

Cycle: every 28 days

Toxicity: (for grading see toxicity chart)

Myelotoxicity – mild to moderate

Emesis – moderate

Alopecia – usually thins but rarely total

Mucositis – mild to moderate

Amenorrhoea/azoospermia (possible but usually reversible, however all males ≤55yrs must be offered semen cryopreservation)

Cardiomyopathy - none to severe

Lung toxicity – none to life threatening

Notes:

1. Dose reductions and delays:-

There is evidence (Evens et al, BJH 2007; 137: 545-552, Boleti et al, Annals of Oncol, 2007: 18; 376-380, Harris et al, 2008, Manchester Lymphoma Group Audit, Christie Hospital), that ABVD associated neutropenia rarely leads to sepsis in a ≤60 population and therefore treatment need not be delayed on days 1/15 if the patient is well and afebrile. Haemopoietic growth factors are not routinely required.

2. If there is mediastinal involvement, a CXR should be performed after every 2 cycles to monitor response
3. In all cases of early stage disease and in advanced disease with bulk at presentation/residual mass at re-staging, discuss RT with radiation oncologist as soon as possible.
4. If bleomycin reaction (fever/rigors 24-48hrs following chemotherapy), hydrocortisone should be administered pre-treatment with all subsequent cycles. **Strengthen this statement**
5. Persisting respiratory symptoms in the absence of infection must be investigated (CXR, HRCT) to exclude bleomycin toxicity
6. **IRRADIATED** blood products should be employed to prevent transfusion related GVHD

ChIVPP (McElwain et al, BJC, 1977)

6-8 cycles for first line treatment of advanced Hodgkin's lymphoma in a patient not suitable for ABVD or ChIVPP/EVA due to significant cardiac history, general frailty or advanced age. Also an alternative regimen to ChIVPP/EVA for remission induction in patients with recurrent disease after ABVD and where there are concerns about cardiac function

Days 1 - 14:

Chlorambucil 6mg/m² (not exceeding 10mg) daily PO

Procarbazine 100mg/m² (not exceeding 150mg) daily PO

Prednisolone 40mg daily PO

Day 1 & 8:

Vinblastine 6mg/m² (not exceeding 10mg) iv bolus

Cycle: every 28 – 42 days depending on tolerance x 6

Toxicity:

Patchy hair loss

Myelosuppression

Peripheral / autonomic neuropathy - usually mild

Notes:

1. Avoid alcohol during administration of procarbazine (or severe emesis will result)
2. Dose reductions and delays:-

Neutrophils $\geq 1 \times 10^9/l$, 100% dose; neutrophils ≤ 1 , defer treatment 1 week

Platelets $\geq 100 \times 10^9/l$, 100% dose; platelets $< 100 \times 10^9/l$, defer treatment 1 week

3. Following first episode of grade 3 or 4 neutropenic sepsis, or when a nadir blood count shows severe neutropenia ($< 0.5 \times 10^9/l$), **haemopoietic growth factor** support should be given with subsequent cycles (daily from day 15 for 7-10 days or pegylated filgrastim on day 15). Following the second episode of grade 3 or 4 neutropenic sepsis reduce dose of myelosuppressive drugs by 25% and continue with growth factor support as above.

4. After the first treatment delay due to slow neutrophil recovery, a **haemopoietic growth factor** should be prescribed with subsequent cycles to maintain dose intensity.

GDCVP

A regimen for recurrent HL after previous CT where there is resistance to other re-induction therapies such as ChIVPP/EVA , ChIVPP or VAPEC-B.

Day 1:

Gemcitabine 1gm/m² in 250 mls 0.9% saline iv over 30 mins
Dacarbazine 500mg/m² in 250mls 0.9% saline iv over 30 mins
Cyclophosphamide 750mg/m² in 250mls 0.9% saline iv over 30 mins
Vincristine 1.4 mg/m² iv
Prednisolone 40mg/m² po daily for 5 days

Cycle: every 21 days x 6

Toxicity:

Patchy hair loss
Myelosuppression
Peripheral / autonomic neuropathy

Notes:

1. Dose reductions and delays:-

Neutrophils $\geq 1 \times 10^9/l$, 100% dose; neutrophils ≤ 1 , defer treatment 1 week

Platelets $\geq 100 \times 10^9/l$, 100% dose; platelets $< 100 \times 10^9/l$, defer treatment 1 week

2. Following first episode of grade 3 or 4 neutropenic sepsis, or when a nadir blood count shows severe neutropenia ($< 0.5 \times 10^9/l$), **haemopoietic growth factor** support should be given with subsequent cycles (daily from day 2 for 7-10 days or pegylated filgrastim on day 2). Following the second episode of grade 3 or 4 neutropenic sepsis reduce dose of myelosuppressive drugs by 25% and continue with growth factor support as above.

3. After the first treatment delay due to slow neutrophil recovery, a **haemopoietic growth factor** should be prescribed with subsequent cycles to maintain dose intensity.

Chemotherapy regimens for aggressive Non-Hodgkin lymphoma

R-CHOP and CHOP; doses for patients aged under 70

Day 1:

Doxorubicin 50mg/m² iv bolus

Cyclophosphamide 750mg/m² iv bolus

Vincristine 1.4mg/m² iv bolus (capped at 2mg)

Rituximab 375 mg/m² by iv infusion at a rate determined by blood pressure and pulse (**only for R-CHOP**)

Days 1-5:

Prednisolone 40mg/m² po daily

Schedule:

Every 21 days for up to 8 cycles

Toxicity: (for grading see toxicity chart)

Myelotoxicity - moderate

Emesis - moderate

Alopecia - total

Mucositis - mild to moderate

Gastritis/oesophagitis - none to severe but usually responds to omeprazole/lansoprazole. These drugs should be used prophylactically if history of dyspepsia

Peripheral neuropathy - mild to moderate

Jaw pain - mild to severe

Amenorrhoea/Azoospermia - semen cryopreservation **must** be offered to males ≤55yrs

Cardiomyopathy - uncommon

Notes:

1. Dose reductions and delays:-

Neutrophils $\geq 1 \times 10^9/l$, 100% dose; neutrophils ≤ 1), defer treatment 1 week

Platelets $\geq 100 \times 10^9/l$, 100% dose; platelets $< 100 \times 10^9/l$, defer treatment 1 week

2. Following the first episode of grade 3 or 4 neutropenic sepsis, or when a nadir blood count shows severe neutropenia ($< 0.5 \times 10^9/l$), **a haemopoietic growth factor**. If despite use of a haemopoietic growth factor, there is a

second episode of grade 3 or 4 neutropenic sepsis a 25% dose reduction of all myelosuppressive drugs should take place and haemopoetic growth factor support continued.

3. After the first treatment delay due to slow neutrophil recovery, a **haemopoetic growth factor** should be prescribed with subsequent cycles to maintain dose intensity

4. Consider radiotherapy to encompass previous sites of disease.

5. If there is mediastinal involvement, a CXR should be performed after every 2 cycles to monitor response

6. Antibiotic / antifungal prophylaxis is not routinely required, but should be considered if previous significant exposure to steroids

7. If CTC \geq grade 2 neuropathy/constipation, a 50% dose reduction should be employed

R-CHOP and CHOP; doses for patients aged 70yrs or over

Day 1

Doxorubicin 50mg/m² iv bolus

Cyclophosphamide 500mg/m² iv bolus

Vincristine 1mg iv bolus

Rituximab 375 mg/m² by iv infusion at a rate determined by blood pressure and pulse (**only for R-CHOP**)

Days 1-5

Prednisolone 40mg/m² po daily (with appropriate reductions in the presence of co-morbidity)

Schedule:

Every 21 days for up to 8 cycles

Toxicity: (for grading see toxicity chart)

Myelotoxicity – moderate

Emesis – moderate

Alopecia – total

Mucositis – mild to moderate

Gastritis/oesophagitis - none to severe but usually responds to omeprazole/lansoprazole. These drugs should be used prophylactically if history of dyspepsia

Peripheral neuropathy – mild to severe

Jaw pain - mild to severe

Cardiomyopathy – routine monitoring is necessary

Notes:

1. All patients should have cardiac function assessed before starting treatment
2. If patient is frail, >79 years or there is a significant cardiac history, consider commencing at 50% dose (i.e. doxorubicin 25mg/m², cyclophosphamide 250mg/m²) escalating to 75% and 100% dose with each successive cycle if tolerated.

3. Patients with borderline or subnormal LVEF (i.e.<55%) consider replacing doxorubicin with **gemcitabine** as less cardiotoxic alternatives to doxorubicin (consider clinical trial)
4. If patients develop \geq CTC grade 2 neuropathy or constipation, omit vincristine
5. Dose reductions and delays: -

Neutrophils $\geq 1 \times 10^9/l$, 100% dose; neutrophils < 1 defer treatment 1 week
Platelets $\geq 100 \times 10^9/l$, 100% dose; platelets $< 100 \times 10^9/l$; defer treatment 1 week
6. Antibiotic / antifungal prophylaxis is not routinely required, but should be considered if previous significant exposure to steroids
7. If mediastinal involvement, CXR should be performed after every 2 cycles to monitor response
8. Following the first episode of grade 3 or 4 neutropenic sepsis, or when a nadir blood count shows severe neutropenia ($< 0.5 \times 10^9/l$), **haemopoetic growth factor** support should be prescribed with subsequent cycles. If despite use of a haemopoetic growth factor, there is a second episode of grade 3 or 4 neutropenic sepsis a 25% dose reduction of all myelosuppressive drugs should take place and haemopoetic growth factor support continued.
9. After the first treatment delay due to slow neutrophil recovery, a **haemopoetic growth factor** should be prescribed with subsequent cycles to maintain dose intensity.
10. Consider radiotherapy to encompass previous sites of disease.

RGCVP

Indications:

An alternative regimen to RCHOP for DLBCL and other high grade B cell NHL for first-line treatment of patients with impaired left ventricular ejection fraction or significant/uncontrolled cardiac disease (at baseline or after anthracyclines) or for the treatment of relapsed/refractory disease after previous maximal cumulative anthracycline treatment, either as salvage therapy (transplant candidate) or for palliation of symptoms (not fit for transplant).

Patients < 70 years: RGCVP cycle every 21 days x 6-8 cycles

Rituximab	375mg/m ²	IV infusion	Day 1
Gemcitabine	1000mg/m ²	IV infusion	Days 1, 8
Cyclophosphamide	750mg/m ²	IV bolus	Day 1
Vincristine	1.4mg/m ² (max 2mg)	IV bolus	Day 1
Prednisolone	40mg/m ²	oral	Days 1-5

Patients ≥ 70 years: RGCVP cycle every 21 days x 6-8 cycles

Rituximab	375mg/m ²	IV infusion	Day 1
Gemcitabine	1000mg/m ²	IV infusion	Days 1, 8
Cyclophosphamide	500mg/m ²	IV bolus	Day 1
Vincristine	1mg	IV bolus	Day 1
Prednisolone	40mg/m ²	oral	Days 1-5

Toxicity:

Myelotoxicity – moderate
Neutropenic sepsis – very rare
Emesis – common, mild
Alopecia – patchy hair loss
Mucositis - common, mild
Dyspnoea - common, mild
Elevated liver transaminases – transient
Skin rash - common, mild
Haematuria - common, mild
Peripheral neuropathy – mild to severe
Cardiotoxicity - very rare

Notes:

1. Rituximab to be administered and monitored in line with established hospital guidance.
2. Dose reductions and delays (unless low indices due to bone marrow involvement with lymphoma):
 - Neutrophils $\geq 1 \times 10^9/l$, 100% dose; neutrophils < 1 , defer treatment 1 week
 - Platelets $\geq 100 \times 10^9/l$, 100% dose; platelets < 100 , defer treatment by 1 week.
3. Following the first episode of grade 3 or 4 neutropenic sepsis, or when a nadir blood count shows severe neutropenia ($< 0.5 \times 10^9/l$), **haemopoetic growth factor** should be administered on day 2 of subsequent cycles. If despite use of Growth factor there is a second episode of grade 3 or 4 neutropenic sepsis, a 25% dose reduction of all myelosuppressive drugs should take place and growth factor continued.
3. After the first treatment delay due to slow neutrophil recovery, Growth factor should be prescribed with subsequent cycles to maintain dose intensity
4. If patients develop \geq CTC grade 2 neuropathy or constipation, omit vincristine
5. Monitor liver function tests during gemcitabine treatment

GCVP

An alternative regimen to CHOP for peripheral T cell NHL for first-line treatment of patients with impaired left ventricular ejection fraction or significant/uncontrolled cardiac disease (at baseline or after anthracyclines) or for the treatment of relapsed/refractory disease after previous maximal cumulative anthracycline treatment, either as salvage therapy (transplant candidate) or for palliation of symptoms (not fit for transplant).

Patients < 70 years: GCVP cycle every 21 days x 6-8 cycles

Gemcitabine	1000mg/m ²	IV infusion	Days 1, 8
Cyclophosphamide	750mg/m ²	IV bolus	Day 1
Vincristine	1.4mg/m ² (max 2mg)	IV bolus	Day 1
Prednisolone	40mg/m ²	oral	Days 1-5

Patients ≥ 70 years: GCVP cycle every 21 days x 6-8 cycles

Gemcitabine	1000mg/m ²	IV infusion	Days 1, 8
Cyclophosphamide	500mg/m ²	IV bolus	Day 1
Vincristine	1mg	IV bolus	Day 1
Prednisolone	40mg/m ²	oral	Days 1-5

Toxicity:

Myelotoxicity – moderate
Neutropenic sepsis – very rare
Emesis – common, mild
Alopecia – patchy hair loss
Mucositis - common, mild
Dyspnoea - common, mild
Elevated liver transaminases – transient
Skin rash - common, mild
Haematuria - common, mild
Peripheral neuropathy – mild to severe
Cardiotoxicity - very rare

Notes:

4. Dose reductions and delays (unless low indices due to bone marrow involvement with lymphoma):

Neutrophils $\geq 1 \times 10^9/l$, 100% dose; neutrophils < 1 , defer treatment 1 week

Platelets $\geq 100 \times 10^9/l$, 100% dose; platelets < 100 , defer treatment by 1 week.

5. Following the first episode of grade 3 or 4 neutropenic sepsis, or when a nadir blood count shows severe neutropenia ($< 0.5 \times 10^9/l$), **haemopoietic growth factor** should be administered on day 2 of subsequent cycles. If despite use of growth factor there is a second episode of grade 3 or 4 neutropenic sepsis, a 25% dose reduction of all myelosuppressive drugs should take place and growth factor continued.
3. After the first treatment delay due to slow neutrophil recovery, Growth factor should be prescribed with subsequent cycles to maintain dose intensity
4. If patients develop \geq CTC grade 2 neuropathy or constipation, omit vincristine
5. Monitor liver function tests during gemcitabine treatment

VAPEC B x 7 weeks

Induction therapy in patients less than 70yrs with lymphoblastic lymphoma, mantle cell lymphoma or transformed follicular lymphoma proceeding to high dose chemotherapy and auto-transplantation

Weeks:

1. Doxorubicin 35mg/m² iv bolus
Cyclophosphamide 350mg/m² iv bolus
2. Vincristine 1.4mg/m² iv bolus (max 2mg 60 – 69yrs)
Bleomycin 10,000IU/m² iv bolus
3. Doxorubicin 35mg/m² iv bolus
Etoposide 100mg/m² p.o. daily for 5 days
4. Vincristine 1.4mg/m² iv bolus (max 2mg 60 – 69yrs)
Bleomycin 10,000IU/m² iv bolus
5. Doxorubicin 35mg/m² iv bolus
Cyclophosphamide 350mg/m² iv bolus
6. Vincristine 1.4mg/m² iv bolus (max 2mg 60 – 69yrs)
Bleomycin 10,000IU/m² iv bolus
7. Doxorubicin 35mg/m² iv bolus
Etoposide 100mg/m² p.o. daily for 5 days

Prednisolone E.C. 50mg p.o. daily for 6 weeks then tail to zero over 10 days.

Co Medication:

Co-trimoxazole 960mg od 3 x week (Mon, Wed, Fri) for 8 weeks
Fluconazole 50mg od for 8 weeks

Toxicity: (for grading see toxicity chart)

Myelotoxicity – moderate
Emesis – moderate

Alopecia – total

Mucositis – mild to moderate

Gastritis/oesophagitis - none to severe but usually responds to omeprazole/lansoprazole. These drugs should be used prophylactically if history of dyspepsia

Peripheral neuropathy – mild to moderate

Jaw pain - mild to severe

Cardiomyopathy – uncommon

Notes:

1. Dose reductions and delays:-

Neutrophils $\geq 1 \times 10^9/l$, 100% dose; neutrophils ≤ 1 , defer treatment 1 week

Platelets $\geq 100 \times 10^9/l$, 100% dose; platelets $<100 \times 10^9/l$, defer treatment 1 week

2. When treatment delays are initiated, prednisolone should not be continued beyond the standard 6 weeks plus 10 days tail

Ifosfamide and cytosine arabinoside (administered by ambulatory infusion pump)

Consolidation therapy following VAPEC-B for lymphoblastic lymphoma, mantle cell lymphoma and large cell transformation of follicular lymphoma

Day 1 – 4 via LV2 infusor:

Ifosfamide 3g/m²
Mesna 3g/m²
Cytosine arabinoside 800mg/m²

Schedule:

Start 21 days following week 7 of VAPEC B then every 21-28 days

Cycles:

3

Co Medication:

Ondansetron 8mg bd x 4 days

Toxicity: (for grading see toxicity chart)

Myelotoxicity – severe (see patient at day 10)

Emesis – mild to moderate

Alopecia – total

Haemorrhagic cystitis - uncommon

Encephalopathy - rare

Erythematous skin rash and low grade fever during infusion is common (continue if patient well, but remember to exclude possibility of bacteraemia).

Notes:

1. A Hickman line is required prior to therapy
2. Creatinine clearance prior to each cycle should be ≥ 50 ml/min

3. Nadir FBC performed between days 10 and 14

4. Dose reductions and delays:-

Neutrophils $\geq 1 \times 10^9/l$, 100% dose; neutrophils < 1 , defer treatment 1 week

Platelets $\geq 100 \times 10^9/l$, 100% dose; platelets $< 100 \times 10^9/l$, defer treatment 1 week

5. Following first admission with neutropenic sepsis, or when a nadir blood count shows severe neutropenia ($< 0.5 \times 10^9/l$), **haemopoietic growth factor** support should be considered with subsequent cycles. It should be commenced 24 – 72 hours after infusion

6. Following the second episode of grade 3 or 4 infection reduce dose by 25% and continue with growth factor support

High dose methotrexate

CNS prophylaxis for lymphoblastic lymphoma and treatment of refractory lymphomas of aggressive sub-type

N.B. please note the rescue regimen varies between high dose MTX given alone versus high dose MTX given on the CODOX-M regimen, which is detailed on the pre-printed script (Christie) or in the LY10 protocol

Pre-treatment:

Sodium bicarbonate 3gm po every 3 hours for 24 hours prior to administration

Stop co-trimoxazole, sulphonamides and other weak acids e.g. NSAID's (displace MTX from albumin binding sites causing markedly increased toxicity)

Ondansetron 8mg IV prior to chemotherapy and during Day 1 and Day 2

Ensure urine pH >8 (If not give sodium bicarbonate 1.4% (500mls) iv over 2 hours continuously until urine pH >8)

Creatinine clearance prior to each cycle (≥ 50 mls/min)

Avoid blood transfusion and acidic drinks (especially coca-cola)

Dexamethasone 0.1% eye drops 3 hourly starting on Day 2 for 1 week

Day 1:

Pre-hydration:-

Sodium bicarbonate 1.4% (500mls) iv over 1 hour

Sodium bicarbonate 1.4% (500mls) iv over 1 hour

Treatment:-

NaCl 0.9% (1000mls) with Methotrexate $3\text{g}/\text{m}^2$ iv infusion over 6 hours

Post-hydration:-

NaCl 0.9% (1000mls) and Sodium bicarbonate (500mls) 1.4% iv simultaneously over 6 hours x 4

Schedule:

Weekly

Cycles:

3-6

Folinic Acid Rescue:-

Starts 24 hours after start of Methotrexate infusion

First dose should be iv then oral (all doses iv if patient vomiting)

Standard Rescue = 15mg 6 hourly x 6 doses

Check levels at 24hrs and 36hrs after start of Methotrexate infusion. (If slow excretion, measure levels daily until safe to discontinue folinic acid).

Nursing investigations:

24, 36, 48, 72 hour methotrexate levels

Daily urea & electrolytes

Strict fluid balance

Check urine pH until MTX levels are low i.e. <150

Give IV sodium bicarbonate & normal saline if MTX levels are high and urine is acid

Advise patients to avoid acidic drinks especially coca-cola on days 1 – 3.

Guide to level of folinic acid rescue from 24hr methotrexate level:

<u>Plasma Methotrexate level</u>	<u>Folinic acid rescue</u>	<u>Dose (6hrly)</u>
150-650ng/ml	single	15mg
650-2200ng/ml	double	30mg
>2200ng/ml	triple	60-100mg (give iv)

NB: MTX has a molecular weight of 454 g/mole if MTX levels are reported in nmol

Duration of rescue:

Single – 24 hours, then stop if 36hr level <100ng/ml

Double – 24 hours then single rescue for at least 48 hours

Triple – 48 hours then single rescue and check Methotrexate level daily until advised safe level

* If very high levels, continue alkaline diuresis and iv folinic acid as gut toxicity will prevent absorption

* Contact laboratory to warn of folinic acid rescue

Toxicity: (for grading see toxicity chart)

Myelotoxicity – moderate

Emesis – mild

Alopecia – total

Mucositis-profound

Conjunctivitis

Notes:

1. Dose reductions and delays: -

Neutrophils $\geq 3 \times 10^9/l$, 100% dose; neutrophils ≤ 1 , defer treatment 1 week

Platelets $\geq 100 \times 10^9/l$, 100% dose; platelets $< 100 \times 10^9/l$, defer treatment 1 week.

Following first admission with neutropenic sepsis, or when a nadir blood count shows severe neutropenia ($< 0.5 \times 10^9/l$), **haemopoietic growth factor** support should be considered with subsequent cycles).

R-CODOX-M AND R-IVAC

R-CODOX-M alone (for low risk disease, protocol A) or alternating R-CODOX-M/R-IVAC (for high risk disease, protocol B) for patients with Burkitt or Burkitt-like lymphoma. In both groups, doses are reduced for patients >65 years.

Low Risk

Patients must have **at least 3** of the following features:-

- Normal LDH level
- WHO performance status 0-1
- Ann Arbor stage I-II
- Number of extra-nodal sites ≤ 1

High Risk

All remaining patients are high risk. They should have **2 or more** of the following features:

- Raised LDH level
- WHO performance status 1-2
- Ann Arbor stage III-IV
- Number of extra nodal sites ≥ 2

NB: Prescribing and administration of intrathecal drugs

*Please note that in accordance with Revised Health Service Circular HSC, 2008/001 dated 11 August 2008, national guidelines on the safe administration of intrathecal (IT) chemotherapy must be followed. In particular please note that these guidelines require there to be written proof that any intravenous cytotoxic drugs for the named patient for that day have been administered **before** intrathecal drugs can be issued (this is relevant to Day 1 of R-CODOX-M).*

Full guidelines:-

<http://www.dh.gov.uk/en/Publicationsandstatistics/Lettersandcirculars/Healthservicecirculars>

*In addition, intrathecal chemotherapy must only be administered **within normal working hours** under normal circumstances. This has implications on the timings of the administration of IT chemotherapy specified in this section of the protocol. Listed below are recommendations on how to change the timing of the administration of IT chemotherapy in order to*

keep with the above guidelines. Also for guidance on using minibags to administer vinka alkaloids go to:-

<http://www.npsa.nhs.uk/patientsafetyalerts-and-directives/rapidrr>

Where a R-CODOX-M cycle starts on either a Thursday or a Friday, the day 3 IT Cytarabine is due during the weekend centres should:

- Start on a Thursday, but give the day 3 IT Cytarabine 2 days late
- Start on a Friday, but give the day 3 IT Cytarabine a day late

Where R-IVAC starts on a Tuesday or a Wednesday, the day 5 IT Methotrexate is due during the weekend centres should:

- Start on a Tuesday but give day 5 IT Methotrexate 2 days late
- Start on a Wednesday but give day 5 IT Methotrexate a day late

Protocol A: Low Risk

Patients will receive a total of 3 cycles of R-CODOX-M with dose dependent on patient age.

R-CODOX-M for low risk patients aged ≤65 years

Day	Drug	Dose	Method	Time
1	Cyclophosphamide Vincristine Doxorubicin Rituximab Cytarabine	800mg/m ² 1.5mg/m ² (max 2mg) 40mg/m ² 375mg/m ² 70mg	IV IV IV IV IT	
2-5	Cyclophosphamide	200mg/m ²	IV	Daily
3	Cytarabine	70mg	IT	
8	Vincristine Rituximab	1.5mg/m ² 375mg/m ²	IV IV	
10	Methotrexate ^Φ	300mg/m ² 2700mg/m ²	IV IV	1 hour Given over next 23 hours
11	Leucovorin ^{Ψ†}	15mg/m ² 15mg/m ² 15mg/m ²	IV IV IV	At hour 36 Every 3 hrs between 36-48 Then every 6 hrs until methotrexate level is <5 x 10 ⁻⁸ M
13	pegylated filgrastim	6mg	SC	one dose
15	Methotrexate	12.5mg	IT	
16	Leucovorin	15mg	PO	24 hrs after IT methotrexate
Commence next cycle on the day that the unsupported absolute granulocyte count is >1.0x10 ⁹ /l, with an unsupported platelet count of >75x10 ⁹ /l.				

^Φ **Methotrexate:** Methotrexate should only be given in the presence of a normal serum creatinine for the patient's age and a measured creatinine clearance of >50 ml/min/meter². Commence methotrexate regardless of blood counts. Stop infusion at hour 24 regardless of dose given.

^{Ψ†} **Leucovorin:** Commence Leucovorin at hour 36 from start of methotrexate infusion. Continue Leucovorin until serum methotrexate

level $<5 \times 10^{-8} M$. Leucovorin may be given orally after the first 24 hours if patients are compliant, not vomiting, and otherwise without complication.

R-CODOX-M for low risk patients aged > 65 years

Note the reduced day 10 intravenous methotrexate dose for this group of patients

Day	Drug	Dose	Method	Time
1	Cyclophosphamide Vincristine Doxorubicin Rituximab Cytarabine	800mg/m ² 1.5mg/m ² (max 2mg) 40mg/m ² 375mg/m ² 70mg	IV IV IV IV IT	
2-5	Cyclophosphamide	200mg/m ²	IV	Daily
3	Cytarabine	70mg	IT	
8	Vincristine Rituximab	1.5mg/m ² 375mg/m ²	IV IV	
10	Methotrexate ^Φ	100mg/m ² 900mg/m ²	IV IV	1 hour Given over next 23 hours
11	Leucovorin ^{Ψ †}	15mg/m ² 15mg/m ² 15mg/m ²	IV IV IV	At hour 36 Every 3 hrs between 36-48 Then every 6 hrs until methotrexate level is $<5 \times 10^{-8} M$
13	Pegylated filgrastim	6 mg	SC	one dose
15	Methotrexate	12.5mg	IT	
16	Leucovorin	15mg	PO	24 hrs after IT methotrexate
Commence next cycle on the day that the unsupported absolute granulocyte count is $>1.0 \times 10^9/l$, with an unsupported platelet count of $>75 \times 10^9/l$.				

^{ΦΦ} **Methotrexate:** Methotrexate should only be given in the presence of a normal serum creatinine for the patient's age and a measured creatinine clearance of $>50 \text{ ml/min/meter}^2$. Commence methotrexate regardless of blood counts. Stop infusion at hour 24 regardless of dose given.

[†] **Leucovorin:** Commence Leucovorin at hour 36 from start of methotrexate infusion. Continue Leucovorin until serum methotrexate level $<5 \times 10^{-8} M$. Leucovorin may be given orally after the first 24 hours if patients are compliant, not vomiting, and otherwise without complication.

DOSE MODIFICATIONS

There will be no dosage modifications based on the degree or duration of myelosuppression. In the presence of motor weakness or severe sensory symptoms, consider reducing or withholding vincristine.

Protocol B: High Risk

Treatment will consist of alternating cycles of regimens R-CODOX-M and R-IVAC for a total of 4 cycles given in the following sequence: R-CODOX-M, R-IVAC, R-CODOX-M, R-IVAC.

R-IVAC for high risk patients aged ≤65 years

Day	Drug	Dose	Method	Time
Start day 1 of R-IVAC on the first day after R-CODOX-M that the unsupported absolute granulocyte count is $>1.0 \times 10^9/l$, with an unsupported platelet count of $>75 \times 10^9/l$.				
1-5	Etoposide	60mg/m ² (in 500ml of N.saline or 5% dextrose)	IV	Daily over 1 hour
	Ifosfamide	1.5g/m ²	IV	Daily over 1 hour
	Mesna	300mg/m ² (mixed with ifosfamide)	IV	Over 1 hour
Day 1 only	Rituximab	Then 300mg/m ² 375mg/m ²	IV IV	4 hourly x 2
1 & 2	Cytarabine	2g/m ²	IV	Over 3 hours, 12 hourly total of 4 doses
5	Methotrexate	12.5mg	IT	
6	Leucovorin	15mg	PO	24 hours after IT methotrexate
7	Pegylated filgrastim	6mg	SC	one dose
8	Rituximab	375mg/m ²	IV	Variable rate (see separate Rituximab script)

Commence next cycle (R-CODOX-M) on the day that the unsupported absolute granulocyte count is $>1.0 \times 10^9/l$, with an unsupported platelet count of $>75 \times 10^9/l$.

R-IVAC for high risk patients aged > 65 years

Note: a reduced dose of ifosfamide and cytarabine is used for this group of patients.

Day	Drug	Dose	Method	Time
Start day 1 of R-IVAC on the first day after R-CODOX-M that the unsupported absolute granulocyte count is $>1.0 \times 10^9/l$, with an unsupported platelet count of $>75 \times 10^9/l$.				
1-5	Etoposide	60mg/m ² (in 500ml of N.saline or 5% dextrose)	IV	Daily over 1 hour
	Ifosfamide	1g/m ²	IV	Daily over 1 hour
	Mesna	200mg/m ² (mixed with ifosfamide)	IV	Over 1 hour
Day 1 only	Rituximab	Then 200mg/m ² 375mg/m ²	IV IV	4 hourly x 2 Variable rate (see separate Rituximab script)
1 & 2	Cytarabine	1g/m ²	IV	Over 3 hours, 12 hourly total of 4 doses
5	Methotrexate	12.5mg	IT	
6	Leucovorin	15mg	PO	24 hours after IT methotrexate
7	G-CSF	5µg/kg	SC	Daily until granulocyte count $> 1.0 \times 10^9/L$
8	Rituximab	375mg/m ²	IV	Variable rate (see separate Rituximab
Commence next cycle (R-CODOX-M) on the day that the unsupported absolute granulocyte count is $>1.0 \times 10^9/l$, with an unsupported platelet count of $>75 \times 10^9/l$.				

DOSE MODIFICATIONS

There will be no dosage modifications based on the degree or duration of myelosuppression.

DHAP/R-DHAP (rituximab to be included for patients who last received this antibody more than 12 months previously)

Indications:

Patients ≤ 70 years with relapsed, progressive or refractory B/T cell lymphomas of aggressive sub-type usually prior to high dose chemotherapy

Creatinine clearance prior to each cycle should be ≥ 50 ml/min

A Hickman line is not mandatory, but is helpful

Day 1:

Pre chemotherapy hydration 2 hours 30 mins consisting of:-
Normal Saline (1000mls) + KCl 20mmol + MgSO₄ 10mmol iv over 1 hour
Normal Saline (500mls) iv over 1 hour
Mannitol 20% (200mls) iv over 20 mins

Cisplatin 100mg/m² iv 24 hour infusion
Hydration:- Normal Saline (1000mls) + KCl 20mmol + MgSO₄ 10mmol 8 hourly running concurrently x 3

Days 1 – 4:

Dexamethasone 40mg daily oral or iv stat over 15 mins
Ondansetron 8mg IV pre chemotherapy then 12 hourly throughout regimen and 2 days supply on discharge

Day 2:

Cytarabine 2g/m² x 2 doses over 3 hours 12 hours apart
Hydration:- Normal Saline (1000mls) + KCl 20mmol + MgSO₄ 10mmol iv over 9 hours in between cytarabine bags

Schedule:

3 – 4 weeks

Cycles:

3 - 4

Co-medication:

Dexamethasone 0.1% eye drops 3 hourly starting on Day 2 for 1 week
Haemopoietic growth factor support (pegylated filgrastim) should be administered on day 13 (R-CODOX-M or day 7 (R-IVAC)

Co-trimoxazole 960mg od 3 x week (Mon, Wed, Fri) for 8 weeks

Fluconazole 50mg od for 8 weeks

Nursing investigations:

Strict fluid balance

Daily weights – report 1kg or higher weight gain to medical staff- provided this is post voiding

Urea and electrolytes prior to discharge – unless there are concerns that these will be abnormal, the patient may leave before results are available

Toxicity: (for grading see toxicity chart)

Tumour lysis syndrome -precautions as above

Conjunctivitis -(cytarabine)

Myelotoxicity - (profound 10 –14 days)

Emesis - (moderate to severe)

Gastritis/oesophagitis – may be severe and omeprazole/lansoprazole should be used on a prophylactic basis

Altered taste (cisplatin) -common

Ototoxicity - tinnitus/high pitched hearing loss -(mild to moderate)

Neuropathy (cisplatin) -mild

Infertility - irreversible

Mucositis - (moderate to severe)

Alopecia - total

Notes:

1. All patients require admission (remember to book bed in advance)
2. Treatment takes approximately 42 hours per cycle
3. Nadir FBC performed between days 10 and 14. Send patient home with 24hr urine bottle
4. An extra cycle may be required whilst awaiting admission for high dose therapy

ESHAP

Indications:

Day 1

Cytarabine 2g/m²

Days 1 – 4

Etoposide 40 mg/m²

Cisplatin 25 mg/m²

Ensure >2.5L /day N/Saline IVI d 1-4 + magnesium and potassium supplements

Days 1 – 5

Methylprednisolone 500mg IV

Schedule: 3 weekly

Cycles: 2 – 3 pre transplant

Co-medication:

Ondansetron 8mg IV prior to chemotherapy, then 12 hourly throughout regimen.

2 day supply following discharge.

Dexamethasone 0.1% eye drops qds.

Growth factor support:

- Commence on day 6
- Neulasta 6 mg s.c on non-harvested cycles
- Daily G-CSF for PBSCH attempts as per protocol (BSA <1.8, 300 mcg, >1.8, 480 mcg)

Nursing Investigations:

Strict fluid balance

Daily weights - report 1kg or higher weight gain to medical staff -

Provided this is post voiding!

Daily Urea & Electrolytes, but full FBC/biochemistry on admission & discharge. On discharge, unless there are concerns that they will be abnormal, the patient could leave before results are available

Gemcitabine single agent treatment

A palliative treatment for patients with relapsed/refractory lymphoma of any subtype who are unfit for combination chemotherapy, have received multiple previous lines of treatment and are unsuitable for salvage chemotherapy/transplant or a clinical trial

Gemcitabine on days 1, 8 and 15 every 28 days x 6-8 cycles

Gemcitabine 1200mg/m² IV infusion Day 1, 8 and 15

Toxicity:

Myelotoxicity – moderate

Neutropenic sepsis – very rare

Emesis – common, mild

Alopecia – none

Mucositis - common, mild

Dyspnoea - common, mild

Elevated liver transaminases – transient

Skin rash - common, mild

Haematuria - common, mild

Cardiotoxicity - very rare

Notes:

1. Dose reductions and delays (unless low indices due to bone marrow involvement with lymphoma):

Neutrophils $\geq 1 \times 10^9/l$, 100% dose; neutrophils < 1 , defer treatment 1 week

Platelets $\geq 100 \times 10^9/l$, 100% dose; platelets < 100 , defer treatment by 1 week.

2. Following the first episode of grade 3 or 4 neutropenic sepsis, or when a nadir blood count shows severe neutropenia ($< 0.5 \times 10^9/l$), **haemopoietic growth factor** should be administered on day 2 of subsequent cycles. If despite use of growth factor there is a second episode of grade 3 or 4 neutropenic sepsis, a 25% dose reduction of all myelosuppressive drugs should take place and growth factor continued.

3. After the first treatment delay due to slow neutrophil recovery, growth factor should be prescribed with subsequent cycles to maintain dose intensity
4. Monitor liver function tests during gemcitabine treatment

Chemotherapy regimens for indolent lymphoma

Consider clinical studies

R-CVP and CVP

Indications:

First line systemic treatment of patients with follicular lymphoma (grades 1, 2 and 3A) or second line treatment of patients previously treated with chlorambucil or radiotherapy

CVP can also be used for the first line treatment of mantle cell lymphoma or the second line treatment of lymphoplasmacytoid or marginal zone lymphoma.

Day 1:

Vincristine 2mg iv bolus (1 mg if patient \geq 70yrs)

Cyclophosphamide 750mg/m² iv (500mg if patient \geq 70yrs)

Rituximab 375mg/m² by iv infusion at a rate determined by blood pressure and pulse (**only for R-CVP**)

Days 1 – 5:

Prednisolone 40mg/m² po daily

Schedule:

Every 3 weeks x 6 - 8 cycles

Toxicity: (for grading see toxicity chart)

Myelosuppression – mild to moderate

Emesis – none to mild, oral metoclopramide is usually sufficient

Alopecia – usually thins but rarely total

Gastritis/oesophagitis - none to severe but usually responds to omeprazole/lansoprazole. These drugs should be used prophylactically if history of dyspepsia

Peripheral neuropathy – CTC grade 0 – 2

Amenorrhoea/Azoospermia – semen cryopreservation **must** be offered to males ≤ 55 yrs

Notes:

1. Consider nadir FBC at 14 days following cycle 1.

If CTC grade 2 neuropathy – give 50% dose vincristine. If >grade 2 neuropathy omit vincristine

2. Dose reductions and delays:-

Neutrophils $\geq 1 \times 10^9/l$, 100% dose; neutrophils < 3 , defer treatment 1 week

Platelets $\geq 100 \times 10^9/l$, 100% dose; platelets $< 100 \times 10^9/l$, defer treatment 1 week

3. Haemopoietic growth factor may be required in heavily pre-treated patients.

Chlorambucil (oral agent)

Indications:

First line systemic treatment of patients with lymphoplasmacytoid or marginal zone lymphoma or frail elderly patients with follicular lymphoma (grades 1, 2 and 3A) and small lymphocytic lymphoma (where R-chemo and FC chemotherapies respectively are considered inappropriate). Re-treatment with chlorambucil can be considered at first or subsequent relapse for frail/elderly patients unlikely to tolerate more intensive approaches especially if the first remission lasted for 12 months or more

Dosage:

Chlorambucil 6mgs/m² (usually 10 mgs) daily. For patients over the age of 80, the dose should be reduced to 6 or 8mgs daily, for 10 – 14 days

Schedule:

2 weeks on treatment (days 1-14) followed by 2 weeks rest (days 15-28) x 6 cycles. Check blood count every 4 weeks

Toxicity:

Myelosuppression – mild

Emesis – none to mild, oral metoclopramide is usually sufficient

Alopecia – none

Amenorrhoea/azoospermia -semen cryopreservation **must** be offered to males ≤55yrs

Notes:

1. Review patient every 2 weeks for check blood count during initial 6 weeks if giving chlorambucil according to schedule a).
2. Dose reductions and delays: -

Neutrophils $\geq 1 \times 10^9/l$, 100% dose; neutrophils ≤ 1 , defer treatment 1 week

Platelets $\geq 100 \times 10^9/l$, 100% dose; platelets $<100 \times 10^9/l$, defer treatment 1 week

In the presence of bone marrow infiltration it may be appropriate to continue treatment despite low neutrophils/platelets. In these circumstances discuss with a consultant

FC (oral regimen)

First line treatment for patients with SLL/CLL requiring treatment or for those patients previously treated with chlorambucil who have progressive disease

Days 1-5:

Fludarabine 24mg/m² po
Cyclophosphamide 150mg/m² po

Co-medication:

Cotrimoxazole 960mg once daily for 3 days per week throughout treatment and for 6 months after final dose
Fluconazole 50mg once daily throughout treatment and for 1 month after treatment
Aciclovir 400mg twice daily throughout treatment and for 6 months after final dose

Schedule:

Every 28 days x 6

Toxicity:

Nausea and vomiting – moderate
Alopecia – none to mild
Myelosuppression
Immunosuppression – may be severe and antimicrobial prophylaxis required

Note:

1. **IRRADIATED** blood products should be employed to prevent transfusion related GVHD

2. Fludarabine is contraindicated in patients with creatinine clearance < 30ml/min. A 50% dose reduction should be given for those with creatinine clearance 30-60 ml/min.

Fludarabine (single agent by mouth)

Indications:

Follicular and lymphoplasmacytic lymphoma usually after treatment with chlorambucil or CVP

Dose:

40mg/m² po daily for 5 days

Schedule:

Every 28 days x 6 cycles

Co Medication:

Cotrimoxazole 960mg once daily for 3 days per week throughout treatment and for 6 months after final dose

Fluconazole 50mg once daily throughout treatment and for 1 month after treatment

Aciclovir 400mg twice daily throughout treatment and for 6 months after final dose

Toxicity:

Immunosuppression – severe and antimicrobial prophylaxis required

Myelosuppression - moderate

Emesis - none to mild

Alopecia - none

Haemolysis

Notes:

1. Review every patient at 2 weeks post first cycle for nadir FBC

2. Consider 25% dose reduction with cycle 1 in heavily pre-treated patients but escalate to 100% protocol dose if <grade 3/4 toxicity
3. Dose reductions and delays: -
 - Neutrophils $\geq 1 \times 10^9/l$, 100% dose; neutrophils < 3 , defer treatment 1 week
 - Platelets $\geq 100 \times 10^9/l$, 100% dose; platelets $< 100 \times 10^9/l$, defer treatment 1 week
4. Following first admission with neutropenic sepsis, or when a nadir blood count shows severe neutropenia ($< 0.5 \times 10^9/l$), **haemopoietic growth factor** support should be considered with subsequent cycles.
5. Following the second episode of grade 3 or 4 infection reduce dose of myelosuppressive drugs by 25% and continue with growth factor support.
6. **IRRADIATED** blood products should be employed to prevent transfusion related GVHD.
7. Fludarabine is contraindicated in patients with creatinine clearance < 30 ml/min. A 50% dose reduction should be given for those with creatinine clearance 30-60 ml/min.

FMD

Indications:

Follicular, small lymphocytic and lymphoplasmacytic lymphoma usually after treatment with chlorambucil or CVP

Day 1:

Fludarabine 25mg/m² iv bolus
Mitoxantrone 10mg/m² iv bolus

Days 2 and 3:

Fludarabine 40mg/m² po

Days 1 – 5:

Dexamethasone 20mg po

Schedule:

Every 28 days x 6 cycles

Co Medication:

Cotrimoxazole 960mg once daily for 3 days per week throughout treatment and for 6 months after final dose

Fluconazole 50mg once daily throughout treatment and for 1 month after treatment

Aciclovir 400mg twice daily throughout treatment and for 6 months after final dose

Toxicity:

Immunosuppression – severe and antimicrobial prophylaxis required

Myelosuppression - moderate

Emesis – none to mild
Alopecia – none
Haemolysis

Notes:

1. Review every patient at 2 weeks post cycle for nadir FBC
2. Consider 25% dose reduction with cycle 1 in heavily pre-treated patients but escalate to 100% protocol dose if <grade 3/4 toxicity
3. Reduce dexamethasone to 10mg/day in patients ≥ 70 yrs
4. Dose reductions and delays: -

 Neutrophils $\geq 1 \times 10^9/l$, 100% dose; neutrophils < 3 , defer treatment 1 week
 Platelets $\geq 100 \times 10^9/l$, 100% dose; platelets $< 100 \times 10^9/l$, defer treatment 1 week
4. Following first admission with neutropenic sepsis, or when a nadir blood count shows severe neutropenia ($< 0.5 \times 10^9/l$), **haemopoietic growth factor** support should be considered with subsequent cycles.
5. Following the second episode of grade 3 or 4 infection reduce dose of myelosuppressive drugs by 25% and continue with growth factor support.
6. **IRRADIATED** blood products should be employed.
8. Fludarabine is contraindicated in patients with creatinine clearance < 30 ml/min. A 50% dose reduction should be given for those with creatinine clearance 30-60 ml/min.

R-CHOP and CHOP

Indications

Follicular and lymphoplasmacytic lymphoma usually after treatment with chlorambucil or CVP/R-CVP or fludarabine (as a single agent or in combination). Mantle cell lymphoma.

Rituximab as a single agent

Indications:

B-cell (CD20+ve) lymphomas of indolent type recurrent after previous chemotherapy (usually 3rd or 4th line), especially in situations where minimal bone marrow toxicity would be advantageous.

Day 1:

Pre-medication:-

Paracetamol 1gm po 30 mins prior to treatment

Chlorpheniramine 10mg iv 30 mins prior to treatment

Give iv hydrocortisone 100mg if allergic reaction i.e. fevers, chills, rigors

Rituximab 375mg/m² iv infusion in 500mls normal saline as per infusion chart which can take up to 6 hours (dependent on vital signs during infusion).

Monitor temp, pulse, blood pressure every 15 mins for first hour and then hourly if satisfactory (monitor vital signs every 15 mins for first 2 hours with first infusion)

Schedule:

Weekly x 4

Toxicity:

Allergic reactions e.g. chills, rigors, fevers - common (usually mild to moderate)

Bronchospasm (approx 10%) - consider bronchodilator

Nausea (approx 18%) - mild during infusion

Tachycardia

Hypotension (approx 10%)

Notes:

1. If patient taking anti-hypertensive medication it is recommended that that days dose is omitted before commencing rituximab
3. If there is an objective response to treatment, rituximab may be considered for subsequent relapse.

Appendix B: Karnofsky performance (KP) score

Able to carry on normal activity; no special care is needed	100	Normal; no complaints; no evidence of disease
	90	Able to carry on normal activity; minor signs or symptoms of disease
	80	Normal activity with effort; some signs or symptoms of disease
Unable to work; able to live at home and care for most personal needs; a varying amount of assistance is needed	70	Cares for self; unable to carry on normal activity or to do active work
	60	Requires occasional assistance but is able to care for most of his needs
	50	Requires considerable assistance and frequent medical care
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly	40	Disabled; requires special care and assistance
	30	Severely disabled; hospitalisation is indicated although death not imminent
	20	Very sick; hospitalisation necessary; active supportive treatment is necessary
	10	Moribund; fatal processes progressing rapidly
	0	Dead

ECOG WHO performance score

0	Able to carry out all normal activity without restriction	KP = 100
1	Restricted in physically strenuous activity but ambulatory and able to carry out light work	KP = 80, 90
2	Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours	KP = 60, 70
3	Capable only of limited self-care; confined to bed or chair more than 50% of waking hours	KP = 40, 50
4	Completely disabled; cannot carry out any self-care; totally confined to bed or chair	KP = 20, 30

Appendix C: Management of Tumour Lysis syndrome

Please consult full document (**available through guidelines group**) for further details.

Definition

Tumour lysis syndrome (TLS) is characterized by several metabolic derangements that may be life-threatening. It is most commonly seen after therapy for aggressive haematologic malignancies, such as high-grade lymphomas and acute leukemias. In addition, TLS may be seen after the treatment of solid tumours and may occur spontaneously.

High Risk Malignancies

TLS is most often associated with the treatment of Burkitt's lymphoma, acute lymphoblastic leukaemia and other high-grade lymphomas, but can also be associated with chronic leukaemias and low-grade lymphomas.

TLS has also been reported in patients with metastatic breast carcinoma, small-cell lung carcinoma, non-small-cell lung carcinoma, seminoma, thymoma, medulloblastoma, ovarian carcinoma, rhabdomyosarcoma, melanoma, vulval carcinoma and Merkel-cell carcinoma.

Clinical Presentation and Diagnosis

CAIRO-BISHOP DEFINITION OF TUMOUR LYSIS SYNDROME AND CLINICAL TUMOUR LYSIS SYNDROME

Uric acid ≥ 0.48 $\mu\text{mol/L}$ or 25% increase from baseline

Potassium ≥ 6 mmol/L or 25% increase from baseline

Phosphate ≥ 2.1 mmol/L or 25% increase from baseline

Calcium ≤ 1.75 mmol/L or 25% decrease from baseline

Creatinine ≥ 1.5 times upper limit of normal
Cardiac arrhythmia
Seizure
Adapted from Cairo and Bishop, <i>Br J Haematol</i> 2004

Treatment

Every attempt should be made to anticipate and prevent TLS in patients at risk.

Risk Factors

Major risk factors

- Elevated LDH
- Leukocytosis ($>50 \times 10^9 /L$)
- Elevated uric acid and/or hypercalcaemia on admission
- Elevated creatinine levels ($>140 \mu\text{mol/l}$)
- Decreased glomerular filtrate rate

Predisposing factors

Tumour characteristics

- High tumour growth fraction
- Advanced stage of malignancy
- Rapid tumour growth rate
- Abdominal organ involvement
- High sensitivity to chemotherapy

Patient characteristics

- Compromised baseline renal function
- Evidence of urinary tract obstruction via imaging
- Polypharmacology
- Drug–drug interactions

Prophylaxis

Low to intermediate risk – presence of predisposing factors, but **NOT** risk factors

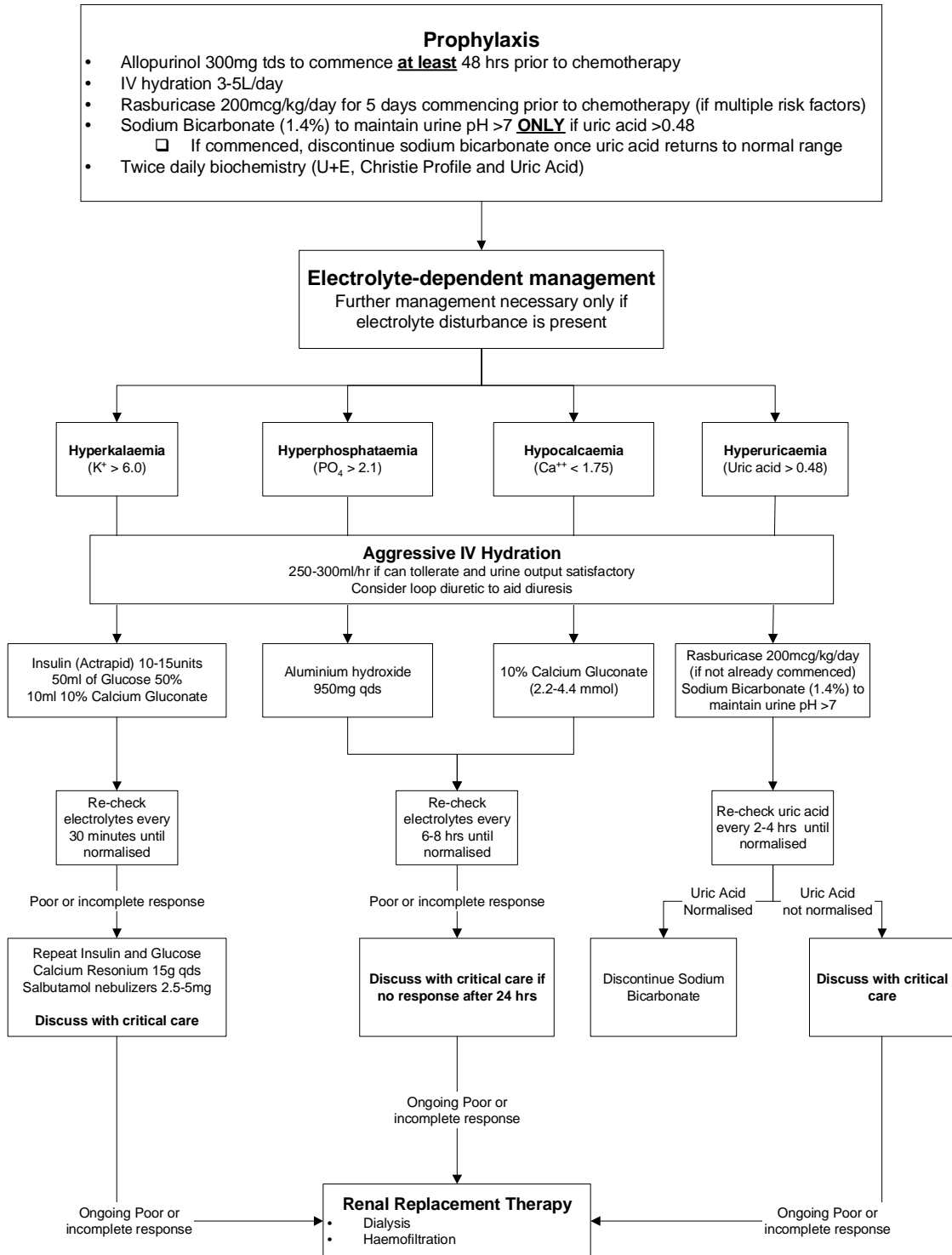
- Allopurinol 300 mg bd to tds. Reduce to 300 mg od after 3 days of chemotherapy
- Hydration 3-5 L/day, 1-2L N saline, 2-3L 5% Glucose
- Monitor urine output, blood pressure at least 4-hourly
- Consider prophylactic bicarbonate, which can be discontinued if the serum urate does not rise

- Monitor electrolytes, urea, creatinine, uric acid, Ca⁺⁺ and PO₄ every 12–24 hours initially

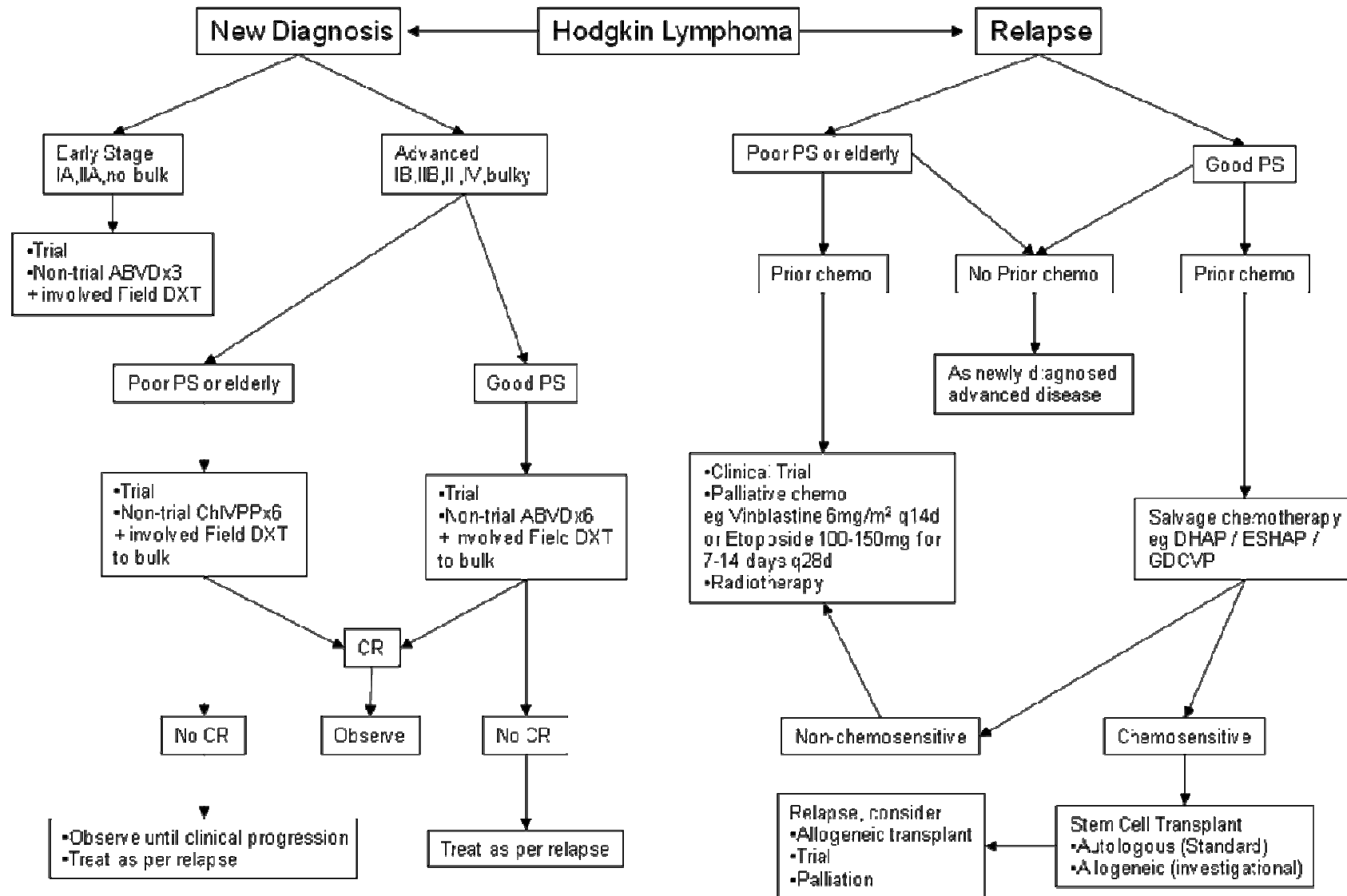
Presence of major risk factors or 3 or more predisposing factors

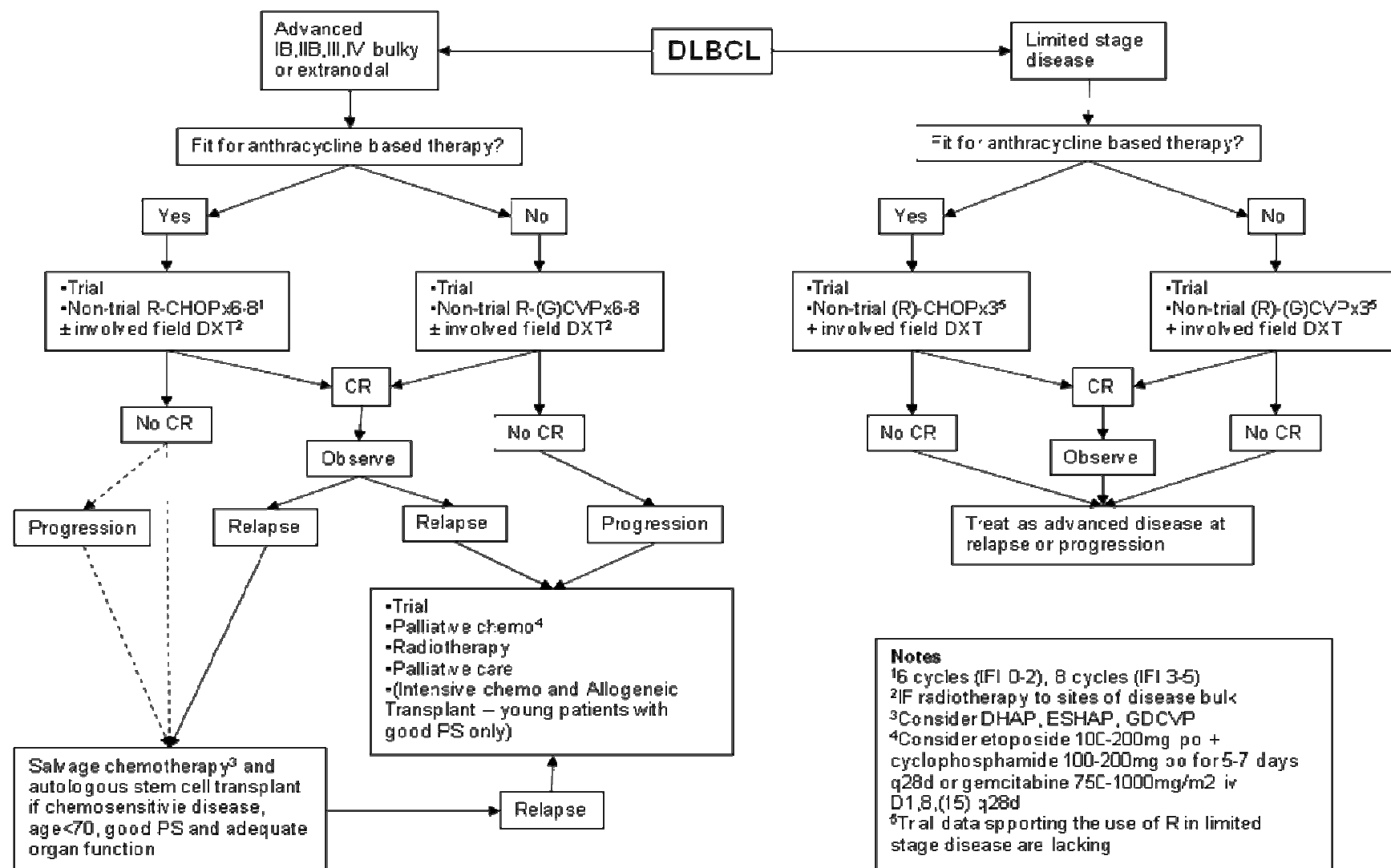
- As above, but consider use of Rasburicase 200mcg/kg od for 5 days.

Established Tumour Lysis



**APPENDIX D
TREATMENT FLOW CHARTS**





Notes
¹6 cycles (IFI 0-2), 8 cycles (IFI 3-5)
²If radiotherapy to sites of disease bulk
³Consider DHAP, ESHAP, GDCVP
⁴Consider etoposide 100-200mg po + cyclophosphamide 100-200mg po for 5-7 days q28d or gemcitabine 750-1000mg/m² iv D1,8,(15) q28d
⁵Trial data supporting the use of R in limited stage disease are lacking

