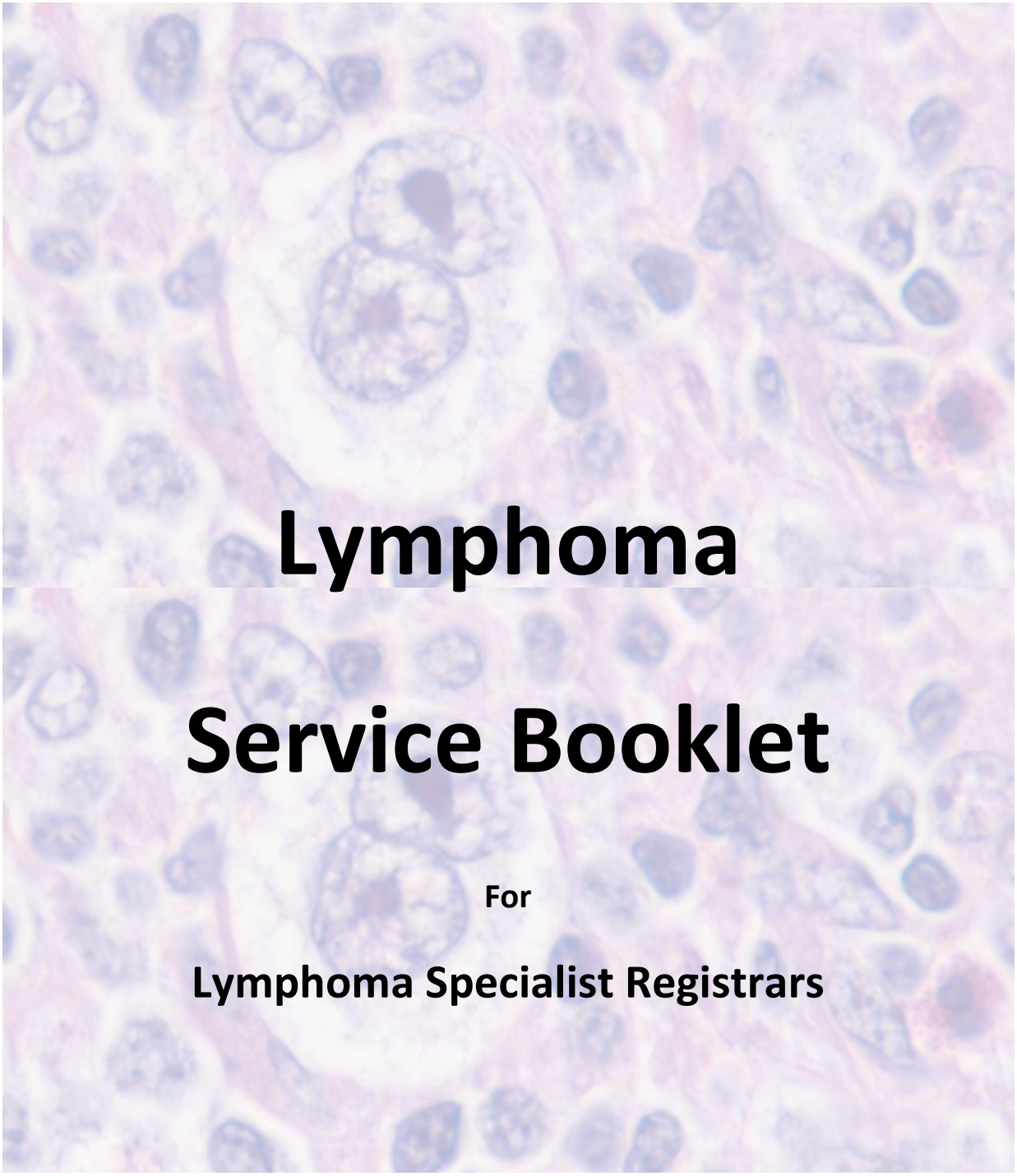

Lymphoma

Service Booklet

For

Lymphoma Specialist Registrars

Contents

Acknowledgements: Sue Moore, Caroline Pledger, Tracy Mitchell-Floyd and Anya Aspinall for their assistance with the ASCT and CNS section and Niamh Appleby for her assistance with the lymphoma work up section.

1. New Patient Work Up

This section is intended as a guide for registrars to help with the diagnosis, staging and preparing for treatment of patients with lymphoid malignancy treated outside of clinical trials. Enrolment in a clinical trial may modify pre-treatment requirements. Specific information has been provided for the most common lymphoma subtypes only. For indolent lymphoid malignancies that may undergo a period of active surveillance, the investigations described may be deferred until treatment is required.

1.1 Establishing the diagnosis of lymphoid malignancy

- Samples suspected of a lymphoid malignancy should be reviewed by a dedicated haematopathologist at the Specialist Integrated Haematological Malignancy Diagnostic Service (SIHMDS).
- Fine needle aspirate is generally not adequate to establish the diagnosis of lymphoma but may place a role in confirmation of relapse for very selected patients.
- The relative advantages and disadvantages of lymph node core biopsy and lymph node excision biopsy should be evaluated for each patient. While a core biopsy may be better tolerated by the patient, the lymphatic architecture may be more difficult to appreciate and there may not be sufficient material for all diagnostic and prognostic testing.
- Repeat tissue biopsy is generally recommended in suspected relapsed Hodgkin lymphoma, persistent FGD-PET avid lesions post-therapy and in suspected high-grade transformation.
- Immunohistochemical staining panels are performed in accordance with the Reporting Guidelines for OUH Haematopathology Service MO40 v3.0
    i. Selection of the immunohistochemical panel (and supplementary tests) are guided by the clinical details provided. It is really useful to include as much clinical information as possible on the request form, as this will

ensure the appropriate immunohistochemical panel and supplementary tests are requested. This is particularly important with core biopsies as the material is limited.

- Fluorescent *in-situ* hybridisation (FISH) in lymphoid haematopathology
    i. *MYC* (and, if present, *BCL2* and *BCL6*) gene rearrangements are performed on all new cases of DLBCL
    ii. FISH for del(17p) *TP53* and del(11q) *ATM* are generally performed on CLL patients before every line of treatment using peripheral blood EDTA samples, not marrow or lymph node tissue.
    iii. FISH for rearrangements in *CCND1*, *MYC*, *BCL2* and *ALK-1* are performed where relevant to the diagnosis
- Karyotyping is not routinely indicated for B-cell and T-cell lymphoma.
- PCR based B-cell and T-cell clonality testing is not routinely indicated. Any tests of this nature should be discussed with one of the lymphoma consultants.
- *TP53* gene mutation testing by sequencing is indicated in CLL prior to each line of therapy. *TP53* sequencing analysis is not routinely recommended for patients with other lymphomas.
- Referral forms can be found at http://www.oxford-translational-molecular-diagnostics.org.uk/

Summary of additional haematopathology testing for lymphoid malignancy						
	Flow cytometry	Karyotyping	Fluorescent in-situ Hybridisation	*TP53* mutation	B-cell clonality	Other molecular test
Classical Hodgkin lymphoma	✗	✗	✗	✗	✗	✗
Diffuse large B-cell lymphoma	≈	✗	✓	✗	✗	✗

			MYC *BCL2* *BCL6*			
Follicular lymphoma	✓	×	*BCL2-IGH*	×	×	×
Mantle cell lymphoma	✓	×	*CCDN1-IGH*	×	×	×
Lymphoplasmacytic lymphoma / Waldenstroms	✓	×	×	×	×	≈ *MYD88*
Marginal zone lymphoma	✓	×	≈ *MALT1-IGH*	×	×	×
Chronic lymphocytic leukaemia	✓ ♦	×	✓ ♦ 17p*TP53* 11q(ATM)	✓ ♦	×	≈ *IGHV* *NOTCH1*
Hairy cell leukaemia	✓	×	×	×	×	*BRAFV600F*

✓ Recommended

× Not routinely recommended for outside of clinical trials

≈ Can be performed on selected patient samples

♦ Usually performed on peripheral blood EDTA samples

1.2 Staging of lymphoma

The Ann Arbor staging system is used for Hodgkin and non-Hodgkin lymphoma

Ann Arbor Staging System	
Stage I	Single lymphoma node region (I) or single extralymphatic site (I_E)
Stage II	Two or more lymph node regions on the same side of the diaphragm (II) or localised extralymphatic site and lymph node region on the same side of the diaphragm (II_E)
Stage III	Involvement of lymph node region on both sides of the diaphragm (III). May be accompanied by localised involvement of extralymphatic site (III_E) or spleen (III_S)
Stage IV	Diffuse involvement of one or more extralymphatic organs +/- associated lymph node enlargement
A- No symptoms B- Fever, drenching night sweats, > 10% weight loss over 6 months X- Bulky disease (> 1/3 mediastinum; > 10 cm nodal mass diameter)	

The Rai and Binet staging systems are used for Chronic Lymphocytic Leukaemia

Rai	Binet
0 Lymphocytosis only	
1 Lymphadenopathy	A < 3 lymphoid areas
2 Hepatosplenomegaly	B ≥ 3 lymphoid areas
3 Haemoglobin < 110 g/L or platelets < 100 x 10^9/L	C Haemoglobin < 100 g/L or platelets < 100 x 10^9/L

Radiological staging using PET-CT or CT-Neck-Chest-Abdomen-Pelvis (NCAP)

For patients with Hodgkin lymphoma, PET-CT upstages 13-24% of patients when compared with CT NCAP alone. PET-CT is recommended at diagnosis, interim after 2 cycles of ABVD for Hodgkin lymphoma, at end of treatment and in the event of relapse. PET-CT should be reported on the 5 point Deauville scale. NB: in patients with Hodgkin lymphoma who have a negative interim PET scan, a further PET is NOT required at end of treatment (CT only)

- PET-CT with iv contrast is desirable.
- For patients with low-grade lymphoma and CLL, CT NCAP is recommended for staging prior to therapy. The role of PET-CT in low grade lymphoma is: 1) to aid in the identification of high-grade transformation 2) to confirm early stage disease in those with suspected stage I/IIA amenable to radical radiotherapy.
- All imaging should be reported as per the International Conference Malignant Lymphoma (ICML) Imaging Working Group and discussed Lymphoid MDT.

1.3 Prognostic assessment

Do you have all the information needed to calculate a prognostic score?

- Early stage classical Hodgkin lymphoma is classified into favourable and unfavourable risk

Criteria for early stage, unfavourable Hodgkin lymphoma	
EORTC	**German Hodgkin Study Group**
Large mediastinal adenopathy	Large mediastinal adenopathy
ESR ≥ 50 without B-symptoms	ESR ≥ 50 without B-symptoms

ESR ≥ 30 with B-symptoms	ESR ≥ 30 with B-symptoms
Age > 50 years	Extranodal disease
≥ 4 lymph node sites	≥ 3 lymph node sites

- Advanced stage classical Hodgkin lymphoma

  The International Hodgkin's Lymphoma Prognostic Score (Hasenclever score) assigns 1 point for each of age <45 years, male gender, serum albumin < 40 g/L, haemoglobin < 105 g/L Ann Arbor Stage IV disease, leucocytosis > 15 x 10^9/l and lymphopenia <0.6 x 10^9/L.

- Diffuse Large B-cell lymphoma International Prognostic Indices

Clinical Factors	**R-IPI**	**Age-adjusted IPI**	**NCCN-IPI**
Age (years)	1 > 60	2 > 60 years	>75 years 3 60-75 years 2 < 60 years 1
Stage III/IV	1	1	1
Performance status ≥ 2	1	1	1
Serum LDH ≥ upper limit normal	1	1	1 LDH 1-3 x ULN 2 LDH >3 x ULN
Extranodal disease	--	--	1

NB- the NCCN-IPI is becoming the preferred method of prognostication

- Follicular lymphoma International Prognostic Index (FLIPI)
    i. Score 1 point for Age > 60 years, Ann Arbor Stage III/IV, haemoglobin <120 g/L, >4 nodal areas and LDH > upper limit of normal.

- Mantle cell lymphoma International Prognostic Index (MIPI)

Points	Age (years)	ECOG	LDH	WBCx10^9/L
0	< 50	0-1		< 6.7
1	50-59	--		6.7-9.9
2	60-69	2-4	1-1.5 x ULN	10-14.9
3	≥ 70	--	≥ 1.5 x ULN	➢ 15

0-3 points low risk, 4-5 points intermediate risk, 6-11 points high risk

The combined biologic score is calculated as 0.03535 times age (years) plus 0.6978 (if ECOG > 1) plus 1.367 times $\log_{10}$(LDH/ULN) plus 0.9393 times $\log_{10}$(WBC count) plus 0.02142 times Ki-67 (%). Online calculators can be found at http://www.european-mcl.net/en/clinical_mipi.php

- International Prognostic Scoring System for Waldenstrom's Macroglobulinaemia
    i. Score 1 point for each of haemoglobin < 115 g/L, platelet count < 100 x 10^9/L, β2 microglobulin > 3 mg/L, monoclonal IgM band > 7 g/dL
    ii. Low risk 0-1 point, intermediate risk 2 points, high risk ≥ 3 points

- CLL-IPI incorporates clinical and biological factors

Points	Adverse factor
4	*TP53* deletion or mutation
2	*IGHV* unmutated
2	B2M > 3.5mg/L
1	Binet B/C or Rai III-IV
1	Age > 65 years
0-1 points, low risk; 2-3 points intermediate, 4-5 high risk and > 6 very high risk	

Summary of pre-treatment testing for newly diagnosed patients with lymphoid malignancies

	FBC & blood film	Renal & CrCl	LDH & Urate	SPEP & B2M	ESR	Albumin	Pregnancy test	Blood group & DAT	HIV test	Hepatitis serology	, P53 analysis	EBV, CMV and VZV serology	Bone marrow	ECHO	PFT	Radiology	Other
Classical Hodgkin lymphoma	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗	✓	✗	Selected	✓	PET-CT	
Follicular lymphoma	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗	✓	Selected	Selected	✗	CT Neck/TAP	

Mantle cell lymphoma	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	✓	Selected	Selected	×	CT Neck/TAP	GI Endoscopy for colonic disease
Diffuse Large B-cell lymphoma (DLCBL)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	Selected	Selected	Selected	PET-CT	Lumbar puncture with CSF sample for flow cytometry
Lympho-plasmacytic lymphoma and Waldenstroms	✓	✓	✓	✓	✓	✓	✓	✓ ☢	✓	✓	×	✓	✓	Selected	Selected	CT Neck/TAP	Plasma viscosity Serum free light chain Cryoglobulins
Marginal zone lymphoma	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	✓	Selected	Selected	Selected	CT Neck/TAP	*H.pylori* testing for gastric MRI if orbital Cryoglobulins
Chronic lymphocytic leukaemia	✓	✓	✓	✓	✓	✓	✓	✓ ☢	✓	✓	✓	✓	Selected	Selected	Selected	CT Neck/TAP	CMV PCR for alemtuzumab / idelalisib
Hairy cell leukaemia	✓	✓	✓	✓	✓	✓	✓	✓ ☢	✓	✓	×	✓	✓	×	×	Abdominal CT	

☢ Patients with Hodgkin lymphoma and patients treated with purine analogues (fludarabine, cladribine) required irradiated blood products for life. Irradiated blood products are recommended for patients treated with bendamustine and alemutuzumab until further data available on risk of TA-GVHD.

✓ Recommended

× Not routinely recommended for patients outside of clinical trials

N.B. All patients for echo are selected. Indication is: patients due to receive anthracycline AND:

1. Over 70 years or over

2. Under 70 with cardiac risk factors or abnormal ECG

1.4 Consenting patients

It is always important that you as a registrar feel trained and competent at consenting patients, so if you are unsure of side effect profiles, mortality risk or the intent of therapy (curative verses palliative) it is important that you ask a senior physician; either a consultant or fellow senior registrar. Mortality percentage risk are typically listed on the NSSG website under each individual chemotherapy regimen. Chemotherapy for new referrals and relapsed patients should be completed by the senior doctor who has seen the patient in the outpatient clinic. Patient consent, a chemotherapy prescription on ARIA, supportive care medication on ARIA, and a pharmacy e-referral on ARIA should all be completed by the doctor seeing the patient in clinic prior to the patient being transferred for outpatient chemotherapy to the day treatment unit.

1.5 Chemotherapy Prescribing

It is important to always remember that clinicians are legally responsible for any prescriptions they make. They should therefore ensure that they have enough information on the patient for whom they are prescribing in order to prescribe safely, otherwise they should pass the prescription onto someone else (e.g. the patient's consultant). If the situation occurs when you are asked to prescribe chemotherapy on the day unit for a patient that you don’t know, please inform one of the lymphoma consultants.

The department is fined for late orders of chemotherapy, and as such it is important to prescribe treatment in a timely way. As a rule of thumb, please aim to prescribe 2-3 courses in advance (for maintenance rituximab then prescribing 6 courses in advance is absolutely fine and encouraged). Consenting for chemotherapy should NOT be left to the DTU registrar; if the patient is an outpatient, every effort should be made to consent the patient in clinic by the clinician that reviews the patient at that time point.

The initial chemotherapy prescription should be made by an experienced registrar or consultant and it should be prescribed in a timely fashion, preferably on the same day as referral to the day treatment unit.

If bendamustine, a purine nucleoside analogue (e.g. fludarabine, cladribine) or alemtuzumab are prescribed; or if the patient has Hodgkin lymphoma, the blood bank must be informed of the life-long need of irradiated blood products for the patient; the patient must also be informed (by the clinician or CNS) of this and should be given an information booklet, and card for their wallet / purse with that in mind.

Intrathecal prescribing can only be performed by someone who is intrathecal trained and approved for involvement in the intrathecal process

For certain drugs, a Blueteq form is required (e.g. all CDF funded drugs but also some NICE approved drugs e.g. brentuximab, ibrutinib). All SpRs should register on the Blueteq system so they can obtain the necessary approvals.

2. Supportive care medication

When managing patients with lymphoma the supportive medications are a critical aspect of their care. There are some key recurring 'pitfalls' to look out for and these are listed below. This information can all be found on the NSSG website within each regimen, but it is worth highlighting a few of these as they commonly occur and are easy to get wrong!

2.1 High dose cytarabine

This agent is used within regimens to treat CNS lymphoma as the drug demonstrates excellent CNS penetration. It is therefore used in the regimens 'MATRIX', 'MA' and 'IVAC' for this purpose. Cytarabine is a key component of induction therapy for young (typically < 65 years) patients with mantle cell lymphoma as the agent demonstrates particular activity in this disease. As a result, it forms part of the 'NORDIC protocol' Maxi-CHOP-R alternating with high dose cytarabine. Cytarabine can commonly give rise to low grade fevers, rash and

myalgia in patients treated with high doses. The agent can also give rise to a chemical conjunctivitis at high doses, so it is important to not forget to ensure that the patient receives prednisolone (predsol 0.5% or 1%) eye drops during and for 5 days following high dose cytarabine.

2.2 CNS prophylaxis and high dose methotrexate

The international prognostic index (IPI) score is now typically used within the lymphoma MDT to make decisions with regards to which patients may benefit from CNS prophylaxis. Those at 'high risk' are patients with an IPI of 4 or 5 based on the following risk factors:

- Age > 60
- Raised serum LDH
- Stage III or IV
- Performance status > 1
- Multiple extranodal sites (2 or more).

In addition, the following extranodal sites are deemed high risk:

- Testes
- Epidural
- Breast
- Renal or adrenal

It is also important to recognize that there are sites that are not deemed high risk. These include: isolated bone marrow involvement, cranio-facial involvement unless there is direct tumour erosion through base of skull.

As a rule of thumb, patients over 70 years old receive 4 intrathecal (IT) doses of 12.5 mg methotrexate, and those that are younger with adequate renal function should typically receive 2 IT methotrexate doses and 2 cycles of high dose methotrexate. The evidence base

for this management strategy is not strong, but what evidence there is suggests that CNS prophylaxis is more beneficial as early as possible in the treatment course. As such, it is useful to aim at giving the IT doses within the first 1-3 cycles if possible. When the patient is completing their 6th cycle of RCHOP/RCHOP-like immunochemotherapy on the day unit, it is important to prescribe the 2 doses of high dose methotrexate alongside 2 final doses of rituximab at three weekly intervals. Two single doses of rituximab after the 6th RCHOP are now no longer given as stand alone doses. Don't forget to inform the ward, the ward pharmacist and write the patient's details and contact number into the ward diary for those 2 admissions. It is important to liaise with the ward registrar with regards the timing and booking of CT / PET-CT and follow up after the 2nd high dose methotrexate to ensure it is not missed.

The high dose methotrexate regimen involves 12 hours of pre-hydration before a short (3 hours) infusion of high dose of methotrexate (required for CNS penetration). Folinic acid 'rescue' is then required until methotrexate is cleared. It is important to pay careful attention to the fluid prescription on EPR and review the NSSG high dose methotrexate regimen. Methotrexate levels should be checked 24 hours after the end of the methotrexate infusion and every 24 hours after this. It is important to avoid penicillin during this time: several drugs can interfere with tubular secretion of methotrexate. These include penicillins, aspirin and NSAIDs. Tazocin should NOT be used during high dose methotrexate administration or rescue. Consider using meropenem or other alternative if anti-pseudomonal cover is required. Co-trimoxazole should be avoided in the week preceding methotrexate in view of its anti-folate properties.

2.3 Other common interactions

Below are several other important drug side effect profiles to be aware of:

- Avoid concurrent use of allopurinol and bendamustine as there is an increased risk of severe rashes including Steven Johnson's syndrome with the combination. If

prophylaxis is required, use allopurinol before bendamustine administration (stopping prior) or if high risk, consider rasburicase.

- Avoid the use of GCSF in patients with Hodgkin lymphoma undergoing treatment with ABVD. There is a risk of inducing bleomycin lung toxicity when GCSF is given concurrently. Patients with ABVD often run a low neutrophil count throughout their cycles of therapy and are admitted with neutropenic infection in a small number of cases. GCSF is typically unnecessary.
- The dose of prednisolone is relatively high in R-VP. This is a palliative regimen most commonly used in relapsed, refractory high grade B cell lymphoma and as such it is important to monitor for steroid side effects and have a relatively low threshold for dose attenuation.
- Always consider the risk of G6PD deficiency when using rasburicase in patients at high risk of tumour lysis syndrome; the agent has potent anti-oxidant properties and can induce a haemolytic crisis in previously undiagnosed patients.

2.4 Diseases with specific considerations

2.4.1 Post transplantation lympho-proliferative disease (PTLD).

By definition, this disorder occurs in the setting of a patient with a previous solid organ or bone marrow transplantation. This is commonly a renal, bowel or liver solid organ transplant. These patients can be managed with rituximab only or rituximab in combination with chemotherapy depending on the clinical setting, the nature of the histology, and the response to single agent rituximab if given. It is important to remember that these patients are more profoundly immunosuppressed initially than those patients presenting *de novo* with DLBCL, for example. As a result, it is important that patients are given PCP prophylaxis (typically with co-trimoxazole) and GCSF primary prophylaxis. These patients are at higher risk of atypical infection and fungal and as such should be managed with a low index of suspicion in patients undergoing chemo-immunotherapy with an unremitting fever. Some patients with PTLD should be treated as high risk for invasive fungal infection and be given

voriconazole or posaconazole prophylaxis (discuss with consultant). The disease should be managed in close collaboration with the relevant transplant team, with immunosuppressive medication (typically tacrolimus) monitored closely.

2.4.2 HIV associated lymphoma

There are several basic principles that are similar to the setting of PTLD. Namely, that patients are at higher risk of atypical and fungal infection. Patients also require PCP prophylaxis, and often GCSF alongside their specific chemotherapy regimen (although avoid GCSF in HIV associated Hodgkin lymphoma). Patients should be managed collaboratively with their HIV treating physician, and it is generally recommended that HIV medication is continued through immuno-chemotherapy. It is important to liaise with the ward and infectious disease pharmacist to look closely for interactions with HAART medication and chemotherapy. CMV monitoring by PCR is also recommended for these patients and a low threshold for referral to eye casualty in case of raised CMV PCR or altered vision (to exclude CMV retinitis).

3. Ward basics

Running the ward as the lymphoma registrar is a great challenge, hard work but also a lot of fun!

3.1 Discharge planning

It is important to communicate well with your juniors regarding the timing of discharge of patients post chemotherapy-induced neutropenic infection and for patients post ASCT. Generally, the period of neutropenia following the typical chemotherapy regimens used for lymphoma and CLL patients is limited to a few days. As a result, there is a relatively quick turnover of patients. Preparation for discharging these patients and ensuring adequate follow up is important; in particular anticipating and booking DTU appointments, scans, MDT discussions and clinic visits.

3.2 Ward MDT

The ward registrar should attend the weekly ward MDT on a Monday afternoon at 2pm. This is a forum to present and discuss all the inpatients on the haematology ward. It is also an opportunity to discuss some of the more complex discharges for patients on outlying wards with the discharge liaison coordinator. The meeting is attended typically by the physiotherapists covering the ward, the occupational therapist, the dietician, the ward sister, and on occasions the chaplain and palliative care team. It is an excellent opportunity to discuss patients with complex care needs with the MDT members on a weekly basis.

3.3 Microbiology MDT

The ward MDT is preceded by the microbiology liaison meeting from 1.30pm to 2pm on a Monday afternoon in the doctor's office on the ward. The microbiology consultant and registrar covering the haematology ward typically attend. Any patients with positive blood cultures should always be discussed in addition to any other patients with specific microbiological issues. The meeting is a useful educational opportunity.

3.4 Chemotherapy planning:

It is the responsibility of the ward registrar to oversee the logistics of delivery of inpatient regimens, for example ICE, ESHAP, DA-EPOCH, CODOX-M / IVAC, high dose methotrexate. We have introduced a new system in the August of 2017 to make this more reliable and efficient, particularly in the context of current bed closures limiting admissions:

- Patients are booked in the ward diary by emailing HaematologyTCI@oxnet.nhs.uk with the desired dates.
- Each Monday at 14:45 the ward SpRs, pharmacist and ambulatory chemotherapy nurse meet in the nurses office on the ward to review the patients for the next 7-10 days using a spreadsheet drawn up by the nurse to check: prescription, IV access / PICC line, consent, screening and administration have all been thought about and identify any outstanding issues that need resolving. The Trust is fined for items of

chemotherapy ordered with less than 48 hours notice so it is important to plan ahead.

- Preventing chemotherapy expiring or not being available requires close liaison with the pharmacist. Review the chemotherapy for the weekend on the Thursday or Friday ward round and check it is on the ward with the pharmacist as orders must be placed before 16:00 Friday and Baxter's close at 12:00 Saturday. It is also sensible to order "on hold" for drugs with short expiry, especially etoposide, until the patient definitely has a bed.

3.5 Weekend Handover

Weekend handover takes place in the haematology doctor's office on the ward. It typically runs from approximately 4.30pm until 5.30pm. The ward registrars should attend and handover each patient for the weekend to the first-on call and second-on call registrar. The meeting is also typically attended by the lymphoma and leukaemia consultant covering the ward during the week, the consultant covering the weekend, and the weekend SHO. The dial in details for the 'conference call' phone in the handover office is 08444 737373 and the PIN is 427480.

3.6 Clinical Governance

There is a monthly clinical governance meeting which is held on the first Tuesday of the month. The ward registrar has the responsibility to attend and present all the cases of significant morbidity and mortality from the preceding month. This involves completing a table template with some key medical data regarding the patients that passed away in the preceding month. It is useful keeping the details of the patients that die on the medical ward list as an aide memoire so that patients are not missed from the monthly discussion. Registrars often rotate just before the monthly clinical governance meeting, so it is important that the outgoing registrar completes the preceding month's mortality list as they know the patients from that month.

3.7 Triage

As the ward registrar, you are likely to receive regular bleeps from the triage unit which is located just off the oncology ward. Patients will typically call in with a fever having received recent chemotherapy. It is critical that patients who have the possibility of neutropenic sepsis are brought to triage promptly for assessment. Triage nurses will often also run queries passed you about patients who are unlikely to be neutropenic who call triage with a range of complaints. It is important to use your clinical judgement and support the nurses in decision making about the nature of the complaint and the appropriate medical input for this. It is sometime reasonable for the patient to attend A+E or their GP if you feel their problem is unrelated to their underlying lymphoma or doesn't require an urgent triage assessment. It is also sometimes appropriate for patients with possible neutropenic fever to attend a local hospital if this is deemed to be to be considerably quicker and safer. A courtesy phone call to the relevant department to whom the patient is then planned to attend is generally well received!

4. Educational activities

The lymphoma firm has an excellent reputation for educational activities. These include organizing a series of evening educational events throughout the calendar year, regular involvement at bi-monthly registrar teaching and an outstanding annual national lymphoma course held in Oxford. On a weekly basis, Tuesday morning journal club (8.15 am - 9.00 am in the Haem-Onc meeting room, level 2 of the Cancer Centre Haem-Oncology administration block) provides an excellent forum for reviewing the up-to-date literature on lymphoma, CLL, and myeloma clinical trials and basic science. Registrars on the lymphoma firm are very much encouraged to present new papers as they are published. Journal reviews and consultant led teaching sessions are typically run on alternate weeks.

5. Key tips, hints and pitfalls for trials

Broadly speaking, the haematology department has an excellent wider reputation for the innovation and delivery of both early and late phase clinical trials. This is particularly true for myeloma, CLL and lymphoma where there is a very active programme. As such, on the day treatment unit, early phase trial unit, outpatient clinic and the ward, you are likely to be involved in managing patients on clinical trials. Below are some key tips for documentation when managing patients on trials. These are particularly helpful for data managers of trials if you do this well and will avoid extra queries coming your way!

Documentation:

- When filling in a trial proforma, make sure you have the previous completed trial proforma open in front of you so you can know what new drugs were started last time (and may need a stop date) and what new AEs were reported (and therefore may need updating)
- Please ensure that the start and end date for a new medication are included on any trial proformas when you complete them
- Record clear, specific symptoms if a patient describes them. It is helpful to avoid multiple, non-specific symptoms on the proformas if possible and rather to focus on clear, specific symptoms, aetiology and causality wherever possible. Sometimes in these instances more is less! Specific and precise adverse event recording is more useful.
- Ensure that you are on the relevant delegation logs for the trial that you are involved in. You should also be formally trained by the principle investigator of the site, have signed the relevant delegation log, understand the nature of the clinical trial and your role within it, have had your questions answered, know who to go to with queries, and have full access to the patient information sheets, consent forms and full up-to-date protocol.

- When a patient information sheet (PIS) is given out, please ensure that it is the correct, most recently approved version. For good clinical practice (GCP) compliance purposes, it is critically important that you document the date and time of when the PIS is given to the patient as well as the trial name and version number of the PIS. This is the ensure that there is an audit trail so that regulators can see that patients are given a minimum of 24 hours to consider the trial as a therapeutic or experimental option for their ongoing care.
- When consenting, ensure that you sign and date in the notes that consent is completed and include the version of the consent form and the trial name within the notes.
- Trial patients should be admitted onto the haematology or oncology ward. This is imperative for early phase trial patients on novel agents. The ward nurses should be aware of this policy.

6. Electronic Patient Record (EPR)

A relative recent change on the ward has been the introduction of the electronic patient record (EPR). This has been integrated into requesting of blood tests, scans, x-rays and CSF samples, for example. Alongside this, all oral medications and all supportive care medications for chemotherapy regimens must be prescribed on EPR as well as the chemotherapy prescribing system, ARIA. These can easily be missed and so particular attention must be given to antiemetics, GCSF, allopurinol, aciclovir, fluconazole and co-trimoxazole as these are commonly used. Oral chemotherapy prescribed on ARIA must also be transcribed onto EPR. Some common examples include 5 days of 40mg/m^2 prednisolone in the CHOP regimen, dexamethasone, thalidomide, lenalidomide and pomalidomide in numerous multiple myeloma regimens.

7. The Lymphoma Multidisciplinary team meeting (MDT)

The lymphoma firm runs a weekly multi-disciplinary team meeting (MDT) on a Wednesday afternoon from 1pm to approximately 3.30pm. Local oxford cases are discussed and as are the challenging regional cases. Attendance is mandatory and the MDT is an excellent learning forum where key management decisions are made. Referral proformas for the MDT are found on the NSSG website (http://nssg.oxford-haematology.org.uk/lymphoma/lymphoma-mdt-proforma.pdf). Completed proformas need to be filled out and submitted by 4.30pm on the Monday before the Wednesday if a patient needs discussing that specific week. The email address for submission is lymphomamdt@nhs.net

7.1 What needs to be discussed at the MDT:

- all new lymphoma diagnoses
- all new lymphoma relapses
- all patient at major treatment landmarks e.g. stem cell transplant consideration or initiation of palliative treatment
- interim PET (iPET) scan results in patients with classical Hodgkin lymphoma
- End of treatment CT or PET-CT scan in non-Hodgkin lymphoma patients (this is most commonly DLBCL) – this is to make sure the team reviews the remission status and recommend radiotherapy to patients with initial bulk disease at presentation in appropriate cases.
- Refractory disease at interim CT NCAP scan.

7.2 What doesn't need discussing:

- Interim standard CT NCAP results in patients with chemo-sensitive disease.

- Patients without a diagnosis of lymphoma unless there is a specific need for MDT input

7.3 Radiotherapy

The clinical oncology team (Dr. David Cutter and / or Dr. Katherine Hyde) regularly attend the MDT and discuss cases when radiotherapy is a possible treatment modality option. Prompt referrals to the radiotherapy team should be made after decisions for radiotherapy are made. This is ideally made at the START of the chemotherapy regimen – when referring to radiotherapy, it is helpful to indicate when the chemotherapy is likely to finish so that an appropriate out patient appointment can be scheduled. This is particularly the case when a decision regarding radiotherapy to a site of bulk is agreed early in the patient treatment pathway. It is also important to note that if radiotherapy is performed at the end of treatment, there should be a 3-month delay after the end of radiotherapy and the end of treatment PET-CT assessment to reduce to risk of false positive uptake at the site of radiation.

7.4 PET-CT

PET-CT scans are a useful modality to stage patients with DLBCL at the start of therapy, particularly if there is a suspicion of occult extra-nodal disease. Interim scans in DLBCL should be a standard CT NCAP as there is no good evidence that any additional information provided by a iPET in this setting is helpful for subsequent management decisions, such as therapy escalation. It is reasonable to perform end of treatment PET-CT after the high dose methotrexate if given.

There is good evidence that interim PET (iPET) scans can be used in Hodgkin lymphoma to de-escalate therapy by dropping bleomycin from ABVD cycle 3-6 in late stage HL in patients with negative iPET (The RATHL Trial), and evidence for escalation of therapy to escBEACOPP in early stage HL in patients with a positive iPET (The H10 Trial). As such, iPET is a useful prognostic modality which can be used to tailor therapy. iPET should be performed at least 11 days after course 2B. Course 3A ABVD should not be delayed whilst waiting for the result. If iPET-CT scan was Deauville 1 or 2 then a contrast-enhanced CT NCAP should be performed at the end of treatment; a PET is not required.

8. ASCT patients

The Oxford Cancer centre performs approximately 60-70 autologous stem cell transplants (ASCT) each year and these are managed exclusively by the lymphoma / myeloma firm. The majority of patients that undergo high dose therapy are relapsed or refractory DLBCL or Hodgkin lymphoma, myeloma (in first remission), high grade transformation of previously treated follicular lymphoma, and patients with an aggressive clinical course of follicular lymphoma (typically in second remission after a short first remission), mantle cell lymphoma (in first remission) and rarely germ cell tumour patients / sarcoma patients referred from the oncology department.

8.1 Brown envelope work up forms

Patients that are considered for ASCT are referred from regional hospitals or are seen from our OUH patient pathway. When patients are considered for ASCT, a stem cell harvest pack (in a brown envelope located in the lymphoma clinic cupboard) needs to be completed by the consultant or registrar seeing the patient. The pack contains:

- A 2B mandatory virology form - to be signed by patient and doctor seeing the patient. This should be photocopied and original copy should be given back to the patient
- An irradiated blood product information for patients
- A dental letter referring the patient for dental assessment prior to ASCT
- Patient information regarding the stem cell collection procedure.
- An MRSA screening swab also needs to be taken

The patient should be told to expect a phone call from NHSBT to arrange a vein assessment and blood tests. They must take the 2B consent form with them. The ASCT clinical nurse specialists should be contacted with details about the patient. Blood bank should also be notified about their irradiated blood requirements.

8.2 ASCT clinical nurse specialists

The clinical nurse specialists for ASCT are Caroline Pledger (extension 72395, Bleep 5536) and Sue Moore (extension 35285, Bleep 5103). Both work full time and are based on level 2 in the BMT CNS office. They have a joint NHS email account that can be used to discuss ASCT patient details orh-tr.autograft@nhs.net. Although patients are not specifically assigned to each individual CNS, one will be covering the inpatient clinical work load, clinic and the day treatment unit whilst the other will be coordinating and scheduling new patients referred for ASCT. The roles swap every 3 months.

The CNS ASCT coordinator role involves booking PBSCH slots with NHSBT, booking patients into clinic after PBSCH, organising the ASCT work up, organising (alongside the medical team) the requesting of post PBSCH or pre-ASCT CT / PET-CT scans, and to refer and book patients for priming salvage chemotherapy only, and organize blood tests pre-PBSCH. It is important for the day unit registrar to closely liaise with the ASCT coordinating CNS with regards to the timeline for PBSCH and the non-priming salvage cycles. Sometimes the timing of the pre-ASCT scans can be crucial within the transplant schedule, so putting a date on the request does really help.

The clinical CNS ASCT role is to see patients on the day treatment unit having priming chemotherapy and a pre-PBSCH blood count check, to attend clinic appointments post-PBSCH to meet the patient, to support the ward patients undergoing the ASCT, to co-ordinate the first appointment with the referring DGH or DTU at discharge and to send the discharge information via email to the relevant referring teams. For the OUH patients, the clinical CNS will see the patient on the day treatment unit post-ASCT, book their first outpatient appointment, and refer the patient back to their disease-specific CNS when their line is out and they are discharged from early day unit follow up post-ASCT.

8.3 ASCT discharge planning

The ward registrar should be able to approximately predict when a patient is due to be discharged post-ASCT (i.e. after engraftment, off intravenous antibiotics, adequately mobile, eating and drinking and generally well). Prior to that time point, TTOs / discharge summaries should be prepared and patients should be adequately transfused RBCs and platelets to avoid an additional unnecessary burden on the day treatment unit. Patients should be discharged with PCP prophylaxis (typically co-trimoxazole), although this should only be started from D+28 after formal medical review of blood count recovery as premature, high doses of co-trimoxazole can be detrimental for safe and adequate count recovery. Patients often need pre-emptive platelet transfusions requesting at first day unit follow up and this should be coordinated with the ASCT clinical CNS.

There is a flowchart pathway on the NSSG detailing harvest, work-up and discharge which is a useful aid memoire and can be found in the BMT section under the headings Harvest/Pre-transplant/Discharge. There is also another pathway for lymphoma ASCT patients specifically in the pathway, referral and MDT section on the NSSG.

8.4 Front sheets, ASCT sign off and EPR prescriptions

For each patient being planned for ASCT, a front sheet, a sign off sheet and an EPR prescription needs completing. These are completed by the DTU lymphoma SpR. The front sheet is a basic summary of the patient's prior therapies, details of their harvest CD34 collection, any co-morbidities the patient may have, and the high dose regimen to be used. The pdf document is found on the NSSG website and should be completed and emailed to Shirley Hudson. A copy is placed at the front of the patients notes as an aide memoire for during their inpatient stay.

The patients undergo a work up day for which they undergo a series of baseline investigations to ensure they are fit for ASCT. These include virology, baseline basic renal and hepatic function, pulmonary function tests, an echo, and an ECG. All these results need

assessing and signing off on a tick sheet which needs completing prior to ASCT. Please ask any of the consultants if there are any issues with regards to any of these investigations.

An inpatient encounter is added in advance on EPR which enables the anti-emetic, anti-microbial and other supportive medication to be added to EPR ahead of time. Please ensure that the dates for the start and end of supportive medication are added according to the ASCT protocols on the NSSG website. Please remember the dexamethasone on D-6 and D-1 (BEAM protocol), and the GCSF from D+5 (all protocols) as these are easy to forget! Pentamidine on D+1 does not need placing on EPR as it is already on ARIA.

9. Lymphoma clinical nurse specialists

The department has two lymphoma specific specialist nurses:

Anya Aspinall

Tuesday, Wednesday, Thursday 8am-4pm

Email anya.aspinall@ouh.nhs.uk

anya.aspinall@nhs.net

Tracy Mitchell-Floyd

4 days - Monday, Thursday, Friday and either Tuesday or Wednesday 9-5pm

Email tracy.mitchell-floyd@ouh.nhs.uk

t.mitchell-floyd@nhs.net

They are based in the nurse specialist office on admin floor level 2 at the Churchill Cancer Centre.

Tel: 01865 235283

Bleep 4122

They provide specialist nurse cover for adult patients with a lymphoma diagnosis in the OUH trust and they also provide specialist support and advice to specialist nurse colleagues within the NSSG Network.

Within the OUH trust, they cover the wards, out-patient clinics and the day treatment unit and will also visit out-lying patients at the JR if necessary. They don't provide face to face cover to patients at the Horton but will do provide telephone support and patients can make an appointment to see them at the Churchill if they wish.

They play an active role in the lymphoma MDT and try to ensure that there is cover for this at most meetings.

Ward rounds

They don't routinely see every patient on the ward round as this is not best use of their time but they do endeavour to be present for complex patients, newly diagnosed patients, and where important changes to therapy are made. The team usually do their own 'ward round' simultaneously (or at other times during the week) seeing those that they feel need their specific input. They will usually catch up with SpRs and consultants either at the beginning or the end of the medical round. They are also very happy to be called to come and see patients as and when the medical team feel it is appropriate.

It is important to let the CNS team know if you are going to be discussing new diagnoses, a new course of treatment, end of life, DNAR as they will always prioritise these patients.

They support ward nursing staff with complex social/palliative discharges but always stress that they don't take a lead on this. They can liaise with hospital and community palliative care teams, GPs, OT, physio, social work team to help facilitate discharge.

The CNS team encourage the ward medical team to ensure that patients have the necessary arrangement made for discharge (DTU follow-up, out-patient follow-up, booked onto ward for next chemotherapy cycle, scans, MDT referral etc). They can advise on the timing and

finer details of this but ask the ward team to make the arrangements. Having said this, they will always help out in a crisis!

DTU

They try and catch up with patients on chemotherapy regularly in the day unit but this can be quite *ad hoc*. Do contact the CNS's if you would like their input or support with patients, particularly regarding breaking bad news, change of treatment etc.

Out-patient clinics

There is specialist nurse cover for the tuesday and thursday lymphoma clinics. They provide verbal and written information on lymphoma and treatments to patients at any point of the pathway however the bulk of this happens at diagnosis and relapse. They also sign-post or refer patients to other services (Maggie's Centre, community palliative care team, TYA team (Teenage and Young Adult Service), Talking Space (mental health charity), dietician, social services, Benefits Advice team, Here for Health). They will refer male patients pre-chemotherapy for sperm storage, and female patients for fertility advice to the Oxford Fertility Unit. If they are not around in clinic, then email them the details. If they are on leave then the referral forms are on the NSSG website on the lymphoma homepage. Please ensure that all virology bloods (these are listed on the referral forms) are done as they won't accept the referral until this is done and not doing them can cause delays.

Please let the CNS team know if you are going to see a new patient (or a relapse) in clinic. As much notice as possible is ideal. If you can't see them in clinic please bleep 4122 as they will prioritise this over anything else. It is really important that they hear what you say to the patient, for their own information but also so that they can help that patient understand what was said after the consultation. It is usually after the consultation that the patient comes up with all the questions and it makes their life easier if they hear it directly.

General information

The majority of CNS workload with patients happens on the phone. They encourage patients to call with any non-urgent queries or concerns. Most calls are regarding chemo side effects (physical and psychological) and how to manage them at home, lifestyle issues (diet, exercise, work, family relationships), information regarding disease or treatment, scans and out-patient appointments.