Lymphoma Network of New Zealand

Guidelines for the follow -up of patients in complete remission following curative treatment for Non- Hodgkin Lymphomas.

Introduction:

Evidence to guide development of lymphoma follow-up protocols is suboptimal, with very few randomised studies available for analysis. Retrospective studies, non randomised prospective series, and review of various international consensus panel protocols were studied in the development of these guidelines, which have been ratified by the New Zealand Lymphoma Network. The majority of material sourced related to Diffuse Large B-Cell Lymphoma (DLBCL)or early stage follicular lymphoma treated with curative intent; however these recommendations may be used to guide follow up after treatment of potentially curative mature T-cell lymphomas (i.e. not lymphoblastic lymphoma/leukaemia), acknowledging the lack of data pertaining to this subgroup in particular.

These guidelines provide a template for assessment and monitoring patients who have achieved a complete response at completion of initial therapy for a potentially curative Non-Hodgkin Lymphoma. They recommend minimum requirements for follow-up and in certain situations clinicians may opt for a more aggressive follow up strategy. These recommendations are not intended for patients who have received treatment for non-curative lymphoma- it is assumed these patients will not be discharged from specialist clinic.

In the initial years following treatment completion, the focus of follow-up is detection of disease relapse. Relapse risk will vary considerably and is typically estimated based on lymphoma subtype, histology, cytogenetic studies, prognostic scores (such as IPI) and treatment received. The majority of DLBCL relapses occur within 3 years of initial treatment, up to 50% within the first 12 months. {1-5}. “Curative” radiotherapy for early stage follicular lymphoma is associated with disease free survival at 5 years of 55%, and at 20 years 37%. Relapse after 10 years is uncommon occurring in approximately 11% of patients. {6-7}. Relapse in patients treated with aggressive T-cell lymphomas is more common, for example 70-80% of peripheral T-cell lymphoma NOS patients will relapse, the majority of occurring within 24 months of initial therapy{7,9,16}. Younger patients may receive high dose chemotherapy with stem cell transplant as first line therapy, increasing the risk of late toxic effects{9}.

From 5 years post treatment monitoring for late therapy associated toxicities must be considered. The risks of various late effects depend on the age of the patient during treatment, gender, intensity and duration of therapy, the site and field of radiation, and patient co-morbidity and lifestyle factors. These guidelines include recommendations for long-term monitoring and a template letter to General Practitioners. Ideally individualised survivorship plans and clear advice for long term monitoring should be available for patients and General Practitioners when patients are discharged from specialist care.

1. **Specialist Clinic Review:**

   A suggested schedule of patient contacts following completion of therapy for high grade lymphoma:

- 2-3 monthly for 6 months
- 3-6 monthly from 6-24 months
- 6 -12 monthly years 3-5
- Consider discharge at 5 years in remission
- Alternate appointments with trained specialist nurses are acceptable. From 24 months post treatment until discharge a minimum annual clinic appointment is recommended with additional patient contact by phone or video conference etc.

A suggested schedule of patient contacts following completion of therapy for early stage follicular lymphoma following curative radiotherapy:

- 3-6 monthly for 2 years
- 6-12 monthly years beyond 2 years
- Consider discharge at 5-6 years post rx if no evidence of recurrent disease.

Comment:

Between 68-85% of patients with relapsed DLCBL present with symptoms (especially B symptoms) prompting investigation and 40-50% of patients will have abnormal examination findings. Most patient have noted an abnormal node themselves prior to physician assessment {4-5}. These findings highlight the need for comprehensive patient education, the importance of early symptom reporting as well as a requirement for a flexible clinic service accommodating an urgent review policy.

In 2010 Dr B. Baker undertook a survey of New Zealand haematologists who were questioned regarding what they felt to be acceptable practice in the follow up of lymphoma- 48% of respondents felt that patient review by a specialist nurse at some follow up appointments was acceptable and 41% of respondents were comfortable with alternating clinic appointments and

telephone interviews. In areas where travel to clinics is more challenging video conferencing or phone interview may be more acceptable to patients.

2. **Laboratory testing.**

Suggested schedule of laboratory testing after completion of therapy:

- FBC each visit or minimum of 6 monthly for 2 years
- LDH at each visit can be considered.

From year 3, continuing indefinitely:

- Minimum annual FBC
- Annual TSH if neck irradiated
- Annual lipid studies if cardiac irradiation, high dose chemotherapy or other CV risk factors.

Consider depending on patient:

- Iron studies pre discharge
- Annual sex hormones
- Annual renal function/electrolytes/LFT.

Comment: There is very little evidence to determine the effectiveness of routine blood tests in the detection of relapse. One study found LDH was elevated in 55% of relapsed DLBCL patients, however almost all these patients had presented with symptoms. {4}.Another study found only 5/30 (17%) relapses of aggressive NHL detected by a combination of laboratory and imaging studies in the absence of symptoms {5}. The utility of LDH alone in detecting relapse in asymptomatic patients appears to be low, but data is limited.

Routine molecular monitoring to detect minimal residual disease in patients treated with curative intent for early stage lymphoma is **not** currently recommended {8}.

Commencing year 3 post monitoring for late effects must be considered. Testing will be patient specific depending on intensity of therapy, radiation fields, transfusion requirements and patient age.

3. **Imaging.**

- There is no requirement for routine surveillance imaging in patients who have documented Complete Response at the end of treatment.

- CT or PET/CT scanning is best reserved for the development of concerning symptoms, signs or laboratory abnormalities.
- Annual CXR in patients who have had thoracic radiation is advised.
- Mammography should be performed annually in women who have received thoracic irradiation starting 8 years following radiotherapy or at age 40 years- whichever is sooner. Breast MRI should be considered as an alternative to mammography in younger women.

Comment:

Regular surveillance CT or PET scanning of asymptomatic patients, known to be in complete remission following treatment is discouraged. Several retrospective and prospective non randomised studies have concluded routine imaging to detect relapsed lymphoma is of limited value and not cost effective {4-5, 10, 17}. In one study routine CT was found to detect only 8/537 (1.5%) of DLBCL relapse prior to development of clinical symptoms {4}. Another study found that where DLBCL was detected on CT prior to symptoms disease bulk and age–adjusted international prognostic index determined at the time of relapse (sAAIPI) was lower; however overall survival at 5 years after salvage treatment was not statistically better than patients who had presented with symptomatic relapse {6}.In north America almost 50% of cost within the first year of follow up is due to routine imaging for relapse detection {4-5}. The toxicity of cumulative radiation exposure during years of surveillance imaging must be considered {11-14}.

4. Survivorship, discharge from specialist clinic, and long term monitoring for late effects

- Discharge from specialist clinic should be considered after 5 years of sustained remission
- At the time of discharge from specialist clinic an individualised survivorship plan or letter summarising the patients' diagnosis, treatment received, significant complications during
- Treatment details, possible future health problems and instructions for ongoing care be given to the patient and the patients General Practitioner
- Patient education reiterating relapse symptoms, possible late effects and importance of life style factors which will ameliorate risk of future cancer, cardiac damage etc should be emphasised- e.g. avoidance of smoking, reduce sun exposure, maintaining healthy weight/diet.
- Patients should be seen and examined at least annually in primary practice with focus on cardiac and respiratory health, cancer risk/surveillance, endocrine/fertility function, osteoporosis prevention/screening, psychosocial and cognitive late effects.

- Skin within radiation fields should be examined at least annually.
- Colon cancer screening should begin 10 years earlier than general population.
- Unless otherwise stated participation in routine population based cancer screening as per NZ guidelines should be strongly encouraged. See imaging section for specific recommendation regarding breast cancer screening in women who have undergone mediastinal radiotherapy.
- Echocardiogram should be considered at end of treatment, then at 10 years post treatment in patients who have received >200mg/m^2 of anthracycline or cardiac irradiation. Early referral to a cardiologist is advised if any abnormality detected.
- The following vaccinations are recommended following therapy: annual influenza vaccination in all patients. If hyposplenic - 5 yearly pneumococcal, meningococcal, and HIB vaccinations also required and medical alert bracelet should be considered.
- Patients are advised to attend annual dental review- especially if the head/neck has been irradiated.
- See earlier section on laboratory testing for recommendations on ongoing blood testing post specialist clinic discharge.

Comment: At the time of clinic discharge patients should be reminded of relapse symptoms and the importance of seeking early medical attention should they occur.

The risk of late effects following lymphoma treatment depend on a number of factors including sex, patients age at the time of therapy, intensity and type of treatment received, radiation fields, co-morbidity, and duration since therapy; therefore an individualised patient education and survivorship plan is ideal for patients being discharged form clinic. Many patients may move from their original treatment centre and it is important patients understand they will need indefinite monitoring- usually in a primary practice setting.

Appendix 1 contains an example of a Survivorship plan currently in use at Middlemore Hospital.

Appendix 2 contains an adaptable template patient discharge letter to GPs.

Resources detailing specific risks of late treatment effects are included in the reference section of these guidelines further information {18-23, 25}.

References/Literature:

1. W. Friedburg. Relapsed/refractory Diffuse Large B-Cell Lymphoma. *ASH Education Book*. 2011;1:498-505.
2. LH Sehn, J. Donaldson, M. Chhanabhai et al. Introduction of combined CHOP plus rituximab therapy dramatically improved outcome of diffuse large B-cell lymphoma in British Columbia. *J Clin Oncol*. 2005;23(22):5027-5033.
3. M. Ziepert, D. Hasenclever, E. Khunt et al. Standard International prognostic index remains a valid predictor of outcome for patients with aggressive CD20+ B-cell lymphoma in the rituximab era. *J Clin Oncol*. 2010; 28(14):2373-2380.
4. A. Carrie et al. Utility of post-therapy surveillance scans in DLBCL. 3013 *J Clin Oncol(suppl;abstr 8504)*
5. A. Elis, D. Blickstein, O. Klein et al. Detection of relapse in non-Hodgkin's lymphoma: role of routine follow-up studies. *Am J Hematol.* 2002;69(1);41-44.
6. MP Mac Manus, RT Hoppe. Is radiotherapy curative for stage I and II low-grade follicular lymphoma? Results of a long term follow-up study of patients treated at Stanford University. *J Clin Oncol*.1996;14(4):1282-1290.
7. International Peripheral T-cell and natural Killer/T-cell lymphoma study: Pathology findings and clinical outcomes. *J Clin Oncol*. 2008;26:4124-4130.
8. M. Dreyling. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Recommendations for diagnosis, treatment and follow-up. *Ann Onc*.2009:20(suppl 4):iv119-iv120.
9. J. Yared, A. Kimball. The role of high dose chemotherapy and autologous stem cell transplantation in peripheral T-cell lymphoma: A review of the literature and new perspectives. *Cancer Treatment Reviews*. 2013;39:51-59.
10. N. Wagner-Johnston, N. Bartlett. Role of routine imaging in lymphoma. *J Natl Compr Canc Netw.* 2011;9:575-584

11. M. Liedtke, P.A. Hamlin et al. Surveillance imaging during remission identifies a group of patients with more favorable aggressive NHL at time of relapse: a retrospective analysis of a uniformly-treated patient population. *Ann Oncol***.** 2006;17(6):909-913.
12. Fazel R, Krumholz HM, Wang Y, et al. Exposure to low-dose ionizing radiation from medical imaging procedures. *N Engl J Med* 2009;361:849–857.
13. Mettler FA Jr, Huda W, Yoshizumi TT, Mahesh M. Effective doses in radiology and diagnostic nuclear medicine: a catalog. *Radiology* 2008;248:254–263.
14. Sodickson A, Baeyens PF, Andriole KP, et al. Recurrent CT, cumulative radiation exposure, and associated radiation-induced cancer risks from CT of adults. *Radiology* 2009;251:175–184.
15. Shenoy P, Sinha R, Tumeh JW, et al. Surveillance computed tomography scans for patients with lymphoma: is the risk worth the benefits? *Clin Lymphoma Myeloma Leuk* 2010;10:270–277.
16. B. Coiffier et al. Peripheral T-cell lymphomas have a worse prognosis than B-cell lymphomas: a prospective study of 361immunophenotyped patients treated with the LNH-84 regimen. *Ann Oncol.* 1990;1(1):45-50.
17. Zinzani PL, Stefoni V, Tani M, et al. Role of [18F]fluorodeoxyglucose positron emission tomography scan in the follow-up of lymphoma. J Clin Oncol 2009;27:1781–1787.
18. N.Y. Mudie, A.J. Swerdlow, C.D. Higgins et al. Risk of second malignancy after non-Hodgkin's lymphoma: a British Cohort Study. *J Clin Oncol*. 2006;24(10):1568-1574
19. L.B. Travis et al. Second cancers among long-term surviours of non-Hodgkin's lymphoma. J Natl Cancer Inst. 1993;85(23):1932-1937
20. K. Hemminki et al. Risk of subsequent solid tumors after non-Hodgkin's lymphoma: effect of diagnostic age and time since diagnosis. *J Clin Oncol*.2008;26(11):1850-1857.
21. E.C. Moser et al. Long-term risk of cardiovascular disease after treatment for aggressive non-Hodgkin lymphoma. Blood. 2006;107(7):2912-2919.
22. J.O. Armitage, P.P. Carbone, J.M. Connors et al. Treatment-related myelodysplasia and acute leukemia in non-Hodgkin's lymphoma patients. *J Clin Oncol*.2003:21(5):897-906.
23. M. Davies, D. Fisher. Overview of care for adult survivors of non-Hodgkin lymphoma. 2013. Available at www.uptodate.com.
24. H. Tilly, M. Dreyling. Diffuse large B-cell non-Hodgkin's lymphoma: ESMO Clinical Recommendations for diagnosis, treatment and follow-up. Ann Oncol. 2009;20(suppl 4):iv110-iv112.
25. http://www.nccn.org/professionals/physician_gls/pdf/survivorship.pdf
26. http://www.nccn.org/professionals/physician_gls/pdf/nhl.pdf

Appendix 1: MMH Surviourship guide.

COUNTIES MANUKAU HEALTH

Lymphoma Survivorship Care Plan

Patient details	
Patient name	
Patient NHI	
Date of Birth	
Date of diagnoses	

Professional Care Team	
Haematologist	
Clinical Nurse Specialist	
Cancer coordinator	
Social Worker	
General Practitioner	

Summary of disease at Diagnosis		
Diagnoses •		
Study	**Date**	**Findings/Details**
BMB		
CT scan		
Other:		

LDH		ECHO	
Heb B		HIV	
Extra Nodal sites:			
Stage :			

Prognostic score :	☐ 0 or 1	☐ 2	☐ 3	☐ 4or 5

Summary of Treatment			
Height:		Pre-treatment weight:	
Post treatment weight:		Pre-treatment BSA:	
Treated on clinical trial : -			
ECOG performance status prior to treatment: ☐ 0 ☐1 ☐ 2 ☐ 3 ☐ 4		ECOG performance status after treatment: ☐ 0 ☐1 ☐ 2 ☐ 3 ☐ 4	
Chemotherapy protocol: • Nil required.			
Radiotherapy Site: Dose:		Radiotherapy start date: Radiotherapy end date:	
Toxicities:			

Summary of Response	
CT Scan	
Bone marrow	
Other:	

Follow-up
We continued to see patient in clinic for 5 (five) years after diagnosis, initially every three months for two years and then 6 monthly for three years. We have now discharged you to your GPs care.

Long Term Care Planning	
Potential late effects of disease, chemotherapy regimes and/or radiotherapy. Tick box if applicable to patient ☐ Cataracts ☐ Hypothyroidism ☐ Heart failure ☐ Lung problems ☐ Liver disease ☐ Kidney impairment ☐ Increased risk of other cancers ☐ Early menopause ☐ Osteoporosis ☐ Fatigue Comments: •	
Call your GP if you have any of these symptoms: • Palpable lymph nodes (lumps) • Night sweats/fever • Unexplained weight loss • Unexplained general un wellness	
Completed by:	Date:
Contact Details:	

Appendix 2: Template letter for discharge of patient form specialist care to GP.

Dear Doctor.

Your patient was diagnosed with stage (***insert stage and subtype)*** non-Hodgkin's lymphoma in (***insert date***) and treated with (**insert**). The patient has now been in remission for 5 years since completion on therapy and is well enough to be discharged from specialist clinic.

Although this patient should be urgently re-referred in the event of recurrent B symptoms or adenopathy, the risk of disease relapse is now very modest. Survivors of lymphoma do require lifelong follow up in primary practice is to monitor for the development of late treatment related toxicities including an increased risk of secondary malignancies, cardiac failure, ischemic heart disease, endocrine dysfunction, respiratory illnesses and depression.

It would be appreciated if you would review this patient at least annually for a comprehensive assessment focusing on skin, cardiac, respiratory, endocrine (thyroid, bone, fertility) and basic psychosocial and cognitive function.

Ongoing laboratory testing, imaging and treatment advised for your patient includes: ***(delete as appropriate)***

- Annual full blood count, thyroid function testing, lipid profile, creatinine, liver function and testosterone (***FSH, LH***)
- Annual CXR
- Annual Mammogram starting at age ***(insert date)***
- Echocardiogram at 10 years post treatment ***(insert date)***
- Annual influenza vaccination
- 5 yearly pneumococcal, Hemophilius influenza and meningococcal vaccinations ***(delete unless hypospenic)***
- Participation in all national cancer screening programmes. Screening for colon cancer should begin 10 year earlier than standard recommendations.
- Aggressive management of cardiac risk factors including hypertension, hyperlipideamia, obesity etc. Early referral to a cardiologist is advised in the event of concerning signs or symptoms.
- Annual dental review has been recommended

Thank you for your ongoing care of this patient. Please contact us if you have any questions or concerns.