

EARLY DIAGNOSIS AND REFERRAL OF LYMPHOMA IS CRITICAL

LYMPHOMA IS A SIGNIFICANT HEALTH ISSUE IN NEW ZEALAND WHERE IT IS ONE OF THE MOST RAPIDLY INCREASING CANCERS, WITH ONE OF THE HIGHEST INCIDENCE RATES IN THE WORLD.

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The number of cases of lymphoma has doubled in the last 20 years¹ and there is no satisfactory explanation as to why.

Ranked the sixth most common cancer in New Zealand, lymphoma is the most commonly occurring blood cancer and over 800 cases of the disease will be diagnosed this year.

While lymphoma is potentially fatal, some forms are curable and a patient's survival may be enhanced by early diagnosis. Comprehensive and accurate diagnosis is essential for optimal management of the diverse forms of lymphoma.

Diagnosing lymphoma is often difficult due to a range of non-specific symptoms, many of which also occur after a variety of infections and other illnesses.

The aim of this article is to firmly position lymphoma on the radar of every general practitioner in New Zealand by:

- providing an update on the signs and symptoms of lymphoma and advice on investigations to assist in the early diagnosis of these diseases
- advising early referral to a haematologist or medical oncologist with expertise in lymphoma, or to a general physician for rural patients, and
- helping GPs to support their patients through complex, intensive courses of treatment and their progress over the long term.

This more detailed article expands on the early diagnostic process for lymphoma that is outlined in the accompanying diagnostic support tool *Is Lymphoma On Your Radar?*

ABOUT LYMPHOMA

Lymphoma is a generic term that refers to a complex group of many related but biologically discrete diseases, each with its own separate molecular pathogenetic features, anatomical sites, and differing response to treatment.

This heterogeneous group of haematological

neoplasms is characterised by proliferation of malignantly transformed T- or B-lymphocytes.

Lymphoma is one of the more common malignancies in New Zealand and is among the most diverse, due to its origin from varying cell types at different stages of maturation and the molecular process of malignant transformation. The manner of their presentation, the clinical course of the diseases and their response to therapy varies widely and presents GPs with difficulties in establishing the diagnosis from symptoms that may mimic many benign disorders.

TYPES OF LYMPHOMA

There are two major categories of lymphoma: non-Hodgkin lymphoma (NHL) is the most common form and accounts for 89% of lymphoid tumours and Hodgkin lymphoma (HL) accounts for 11% of cases².

Based on biological, pathological and clinical criteria, there are more than 30 specific subtypes (different syndromes) of NHL. These classifications have evolved over the last 2–3 decades and reflect an increasing understanding of the molecular basis of lymphomagenesis and clinically important distinctions between the subtypes.

The subtypes are derived from B- or T-cells. Most cases of NHL are derived from malignant transformation of B-lymphocytes in lymph nodes. B-cell lymphomas represent more than 90% of NHL, with follicular and diffuse large B-cell lymphomas the most frequent forms, compromising around 20% and 50% (respectively) of total cases of NHL. T-cell lymphomas account for less than 10% of NHL².

The clinical behaviour of NHL is diverse and ranges from highly malignant and rapidly growing tumours in people of all ages, to relatively benign and even non-progressive lymph node enlargement in elderly people. Therefore simpler groupings are based on

clinical behaviour and tend to be considered in two groups: indolent or low grade, and aggressive or high grade.

Indolent lymphomas, including follicular lymphoma and marginal-zone lymphoma, are characteristically diseases of older people (mainly men over the age of 50 years), with a median untreated survival time measured in years. The usual presenting feature is lymphadenopathy, most commonly in the neck. Most patients are otherwise asymptomatic, but a few report weight loss, sweats and fevers. Enlarged lymph nodes are usually firm, mobile and non-tender, and may fluctuate in size, with spontaneous regression well documented. Rapid growth of nodes is unusual. The response to therapy is generally good, but relapse is common. This group of diseases is considered incurable with conventional therapy.

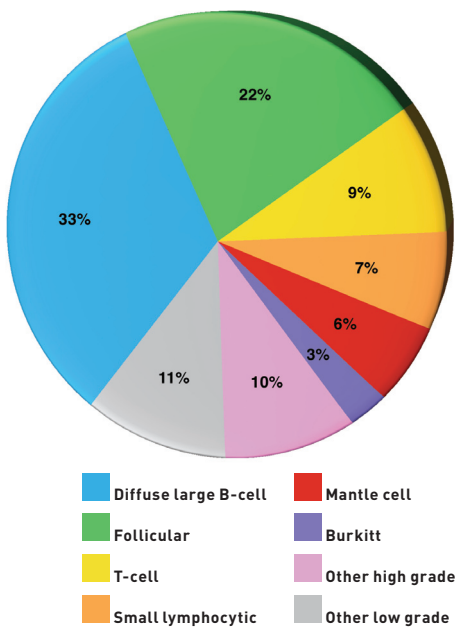


Figure 1: Common types of non-Hodgkin lymphoma and their relative frequency. (Source: World Health Organisation.)

The aggressive lymphomas include diffuse large B-cell lymphoma and Burkitt's lymphoma/leukaemia. These may present at any age but occur more frequently in the elderly. Staging investigations show that only a small minority of cases are truly localised, with spread of disease to adjacent or distant sites evident in 90% of cases.

There is an untreated survival time of months, or weeks in the case of highly aggressive forms (a small minority of cases). Although these forms are highly progressive, in contrast to indolent diseases, these lymphomas, in many cases, are curable with conventional drug therapy.

While patients with indolent lymphomas may live for years even with only a partial response to therapy, in the aggressive lymphomas, only patients with a complete response to therapy are likely to have a favourable outlook.

Hodgkin lymphoma is a biologically and histologically distinct disease, distinguished by the presence of Hodgkin or Reed Sternberg cells. These tumour cells are present in the abnormal lymph nodes in only small numbers, against a background of reactive cells. There are four subtypes based on the lymph node pathology, including the common subtypes of nodular sclerosing and mixed-cellularity HL, and a rarer variety, lymphocyte predominant HL.

The clinical presentations of these types vary. Nodular sclerosing disease classically presents as early-stage disease in younger people, with a preponderance in females, and generally has an excellent response to therapy. Mixed cellularity and lymphocyte-predominant forms may present later in life, with a tendency to present with advanced or extranodal disease.

The distinctions between the lymphoma subtypes help determine the most appropriate therapy and can predict the clinical behaviour of a given tumour and the response to therapy.

HL is the most curable of all the lymphomas with the overall chance of cure being 60% to 80%.

EPIDEMIOLOGY

In 2007, lymphoma was the fifth most common cancer in males, the fifth most common cancer in females, and the third most common cancer in

children under the age of 14 years².

Lymphoma accounts for 4% of newly diagnosed cancers.

Lymphoma is the fifth most common cause of cancer death² with both the incidence and mortality rates increasing with age, peaking in the seventh decade. The lifetime risk of NHL is 1 in 64 for men and 1 in 88 for women.

Over the last several decades the incidence of NHL has been increasing in New Zealand, in both men and women. The reasons for this increase are not known.

Hodgkin lymphoma is uncommon and can occur in patients of any age but generally affects younger people compared to NHL. The incidence of HL peaks between the ages of 15 – 34 years, and again after the seventh decade. The lifetime risk of HL is 1 in 559 for men and 1 in 766 for women and the incidence has remained relatively stable over time.

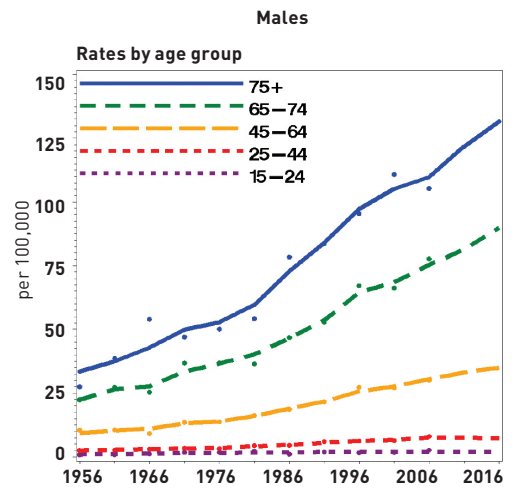
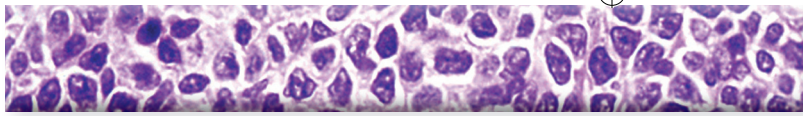


Figure 2: Incidence and projected incidence of non-Hodgkin lymphoma, by age group, in the New Zealand male population, 1956-2016³

RISK FACTORS

The causes of most cases of lymphoma are unknown and no predisposing risk exposure can be identified.

Efforts to identify constitutional or environmental risk factors have been limited by the diversity of types of lymphoma.



Certain subtypes of lymphoma have been associated with infection. NHL of mucosal-associated lymphoid tissues (MALTomas) is strongly associated with *Helicobacter pylori* infection and some rare T-cell lymphomas are caused by human T-cell lymphotropic virus.

20 times higher than the general population, and similar increases are evident in patients on chronic immunosuppressive regimens following solid organ transplantation.

Autoimmune diseases, including coeliac disease, SLE, rheumatoid arthritis and Sjögren syndrome, have also been associated with the development of lymphoma.

There is also an increased risk of lymphoma in families with a history of lymphoma or leukaemia among first-degree relatives.

Lymphomas have been reported in most sites of the body (including the central nervous system, gonads, skin, breast and bone), as well as primary intravascular and effusion lymphomas, but most lymphomas arise within the lymphatic glands.

Patients may have palpable lymphadenopathy plus or minus splenomegaly, or a constitutional illness characterised by weight loss, fever and malaise. Extranodal lymphoma, which may involve a specific organ or organs, is less common.

For people at risk of immunodeficiency-associated lymphoma, surveillance is recommended.

Predominant presentations can include:

- Enlarged, usually painless lymph nodes anywhere in the body (commonly in the neck, axilla or groin)
- Unexplained fever
- Night sweats
- Unintentional weight loss/anorexia.

Less common but possible presentations may include:

Persistent fatigue/lack of energy; flu-like illness; generalised itching; abdominal pain; recurrent infections; anaemia and other low blood counts; bone pain; shortness of breath/protracted cough; and neurologic symptoms.

Most often, these symptoms will be due to other conditions, not lymphoma.

INITIAL INVESTIGATIONS

Full medical history (include fever, sweats, weight loss, malaise)

Physical examination (particularly of lymph nodes and spleen)

Full blood count, creatinine, electrolytes, LFTs, viral serological studies (if clinically indicated)

Chest x-ray (to image the mediastinum)

CT scan (of chest, abdomen, pelvis, as clinically indicated)

The aim of the initial investigations is for GPs to eliminate the most

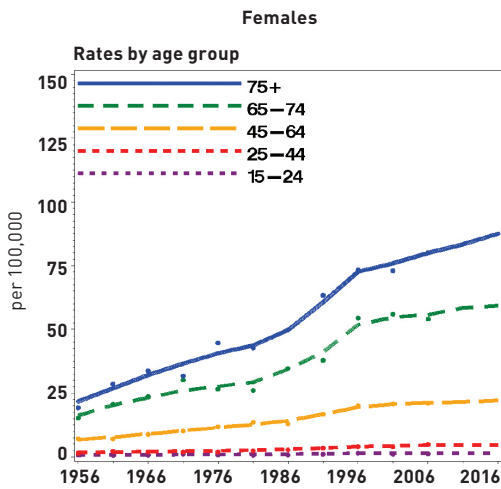


Figure 3: Incidence and projected incidence of non-Hodgkin lymphoma, by age group, in the New Zealand female population, 1956-2016³

Epstein Barr virus infection, in conjunction with immune deficiency, is associated with increased risk of lymphoma, and infectious mononucleosis is a moderate risk factor for HL, increasing risk two- to three-fold.

Other infectious organisms, occupational exposure to pesticides and herbicides, and certain other chemicals, medical procedures, medical history, and lifestyle factors including smoking represent a moderate to weak risk in the development of certain types of lymphoma.

An abnormal immune system increases the chances of developing lymphoma. People with acquired or congenital immunodeficiencies and immune dysregulation states have an increased risk of developing lymphoproliferative disorders, including lymphoma.

Having HIV/AIDS incurs a lifetime risk of lymphoma that is 10-

DIAGNOSING LYMPHOMA

On average, a GP may encounter seven to eight lymphoma patients during their career*.

Diagnosing lymphoma can be difficult. The symptoms of lymphoma are often very non-specific and can be similar to the common symptoms of less serious or minor conditions, such as having the flu or being rundown or stressed.

An aim of the Leukaemia & Blood Foundation (LBF), as a primary provider of information and support to lymphoma patients and their families, is to raise the profile of lymphoma and clearly position this increasing health problem on the radar for GPs and health agencies. The result being that when a patient describes or presents a range of potential lymphoma signs and symptoms, GPs 'think lymphoma' and conduct the correct initial investigations to either eliminate lymphoma or provide early detection.

Educating GPs to assist in the early diagnosis of lymphoma is the aim of **World Lymphoma Awareness Day** (15 September).

*Based on current diagnostic rates, the number of GPs in New Zealand and an average career length of 30 years.

SIGNS AND SYMPTOMS OF LYMPHOMA

There are no screening tests for the early diagnosis of lymphoma and the spectrum of presentation for lymphoma is diverse.

common differential diagnoses for lymphoma which include:

- Infectious mononucleosis
- Toxoplasmosis
- Cytomegalovirus
- HIV
- Rubella
- Viral hepatitis and other viral infections
- Cat-scratch disease.

GPs who think a patient may have lymphoma are urged to refer to a haematologist, medical oncologist or general physician with expertise in lymphoma without delay.

PERSISTENT LYMPHADENOPATHY

Persistent lymphadenopathy is the most common presentation for lymphoma and is most often suspected after the discovery of a progressively enlarging or persistent non-tender lymph node, most commonly in the neck, axilla or groin.

Not all lymphadenopathy is due to lymphoma or is malignant.

Infectious and immunological diseases may cause benign lymphadenopathy and the vast majority of patients who present to their GP with lymphadenopathy will have non-specific or reactive aetiology that require few diagnostic tests.

Less than 1% of patients who present with peripheral lymphadenopathy actually have malignant disease.

When delineating the various causes of lymphadenopathy, emphasis should be placed on possible exposure to an infectious cause, or the presence

of any constitutional symptoms (fevers, sweats and weight loss) and the time, course and progression of the abnormality.

Physical examination can indicate the likely cause of lymphadenopathy.

In addition to the sites of lymphadenopathy, include fields draining to enlarged nodes, looking for evidence of infection, inflammation, or malignant disease. Splenomegaly in the absence of features of mononucleosis-like illness raises the possibility of a lymphoproliferative disease.

The size and texture of lymphadenopathy also provides diagnostic information, with lymph nodes <1cm in diameter often being non-malignant and those >2cm in diameter being more frequently associated with neoplastic disease.

Tender lymph nodes are usually benign. Nodes involved with lymphoma are most often firm or rubbery, with a rock-hard node more commonly associated with non-haemopoietic cancer.

Lymphadenopathy can be slow and insidious and occur in an otherwise asymptomatic person, or develop rapidly and be associated with local or constitutional symptoms such as fevers, sweats, weight loss or pruritus.

Rapid and progressive enlargement of lymph nodes often heralds the diagnosis of an aggressive lymphoma, whereas waxing and waning lymph node size – including their complete disappearance and reappearance – is more frequently seen in the indolent lymphomas.

The site of lymphadenopathy may also provide a strong clue to its aetiology.

Lymph node swelling in the stomach or intestinal tract may result in abdominal pain and/or bloating, or in the chest it may cause coughing, shortness of breath or chest pain.

Headache, swelling (affecting the head, neck or arms), difficulty

breathing, or vision problems can result from superior vena cava syndrome caused by lymph nodes in the centre of the chest enlarging quickly.

The compression of vital internal structures such as the ureter, trachea or major blood vessels may occur with rapidly progressive lymphomas, and occasionally may result in acute medical emergencies.

Enlarged intra-abdominal or retroperitoneal nodes are usually malignant.

Indications for biopsy:

Careful clinical assessment is required to establish the need to perform a biopsy on an enlarged lymph node, bearing in mind that in general practice, only a small minority of enlarged nodes are due to malignancy.

Factors that may predict malignancy are:

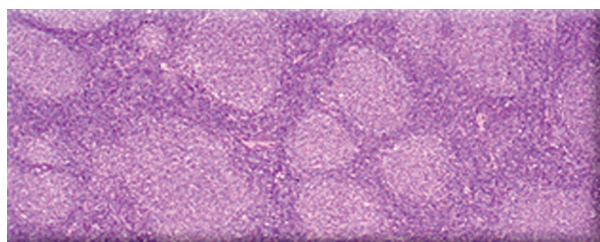
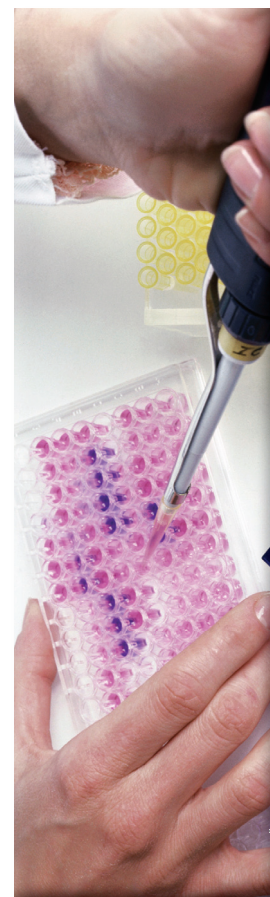
- patients are aged 40 years and over
- supraclavicular location of enlarged lymph nodes
- an affected lymph node with a diameter >2cm
- firm to hard in texture
- lack of tenderness to palpation
- present for several weeks
- abnormal CXR
- significant constitutional symptoms.

The chance of malignant disease as a cause of lymphadenopathy increases over the age of 50 years.

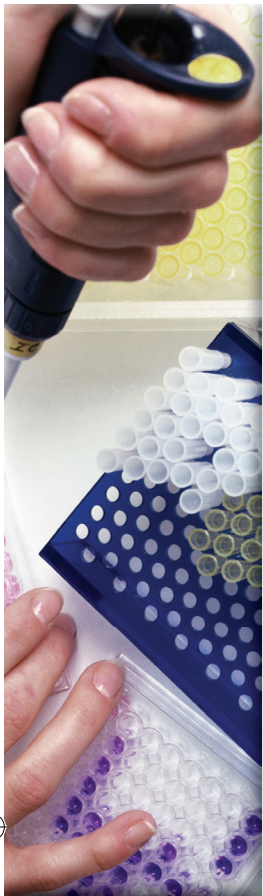
Further investigations to be carried out by a GP before referral to a specialist for a surgical biopsy:

- coagulation screen
- flow cytometry (if a peripheral blood lymphocytosis is present)
- ultrasound of lymph node(s)
- consider fine needle aspirate (FNA) of enlarged lymph node.

Referral to a specialist or hospital for biopsy is urgent if there is evidence



Follicular lymphoma histology



of any emergent complications of lymphoma including:

- spinal cord compression
- pericardial tamponade
- superior or inferior vena cava obstruction
- airway obstruction
- possible CNS mass lesions
- intestinal obstruction
- ureteric obstruction
- severe hepatic dysfunction
- patient is unwell.

SYSTEMIC AND CONSTITUTIONAL SYMPTOMS

Thoracic and abdominal presentations include specific organ involvement such as mediastinal enlargement on a chest x-ray and a protracted cough. Differential diagnoses to consider are sarcoidosis; tuberculosis; metastatic carcinoma and thymoma. Refer to a specialist for further investigations including:

- mediastinoscopy with biopsy; open thoracotomy and lung biopsy for mediastinal mass
- CT-guided core biopsies or laparoscopic lymph node biopsy for abdominal and retroperitoneal lymphadenopathy, and
- bone marrow aspirate and biopsy.

For splenomegaly the differential diagnoses include portal hypertension; infiltrative disease of spleen; extramedullary haematopoiesis and myeloproliferative disease. Refer to a specialist for further investigations:

- ultrasonography
- CT (to show intra-abdominal lymph nodes).

The presence of an enlarged spleen is easily determined by ultrasonography and is less costly than CT. However, CT offers the advantage of visualising intra-abdominal lymph nodes which is important when lymphoma is suspected.

Where there is constitutional illness, objective confirmation that weight loss has occurred is important, with a focus on signs or symptoms that are associated with systemic disease that may cause weight loss. In the elderly, differential diagnoses include depression; malignant disease; and benign gastrointestinal disease, and in younger patients differential diagnoses include diabetes; hypothyroidism; psychiatric disturbance; and infection. Refer to a specialist for further investigations.

Patients with unexplained fever and night sweats may have either malignancy or chronic infection. Further investigation includes a careful history assessing the potential for systemic disease (infection; inflammatory disease; malignancy; drug reactions) and referral to a specialist.

HODGKIN LYMPHOMA PRESENTATION

The mode of presentation of HL is variable. Patients are generally younger than those with NHL but the disease can occur at any age. Some HL patients present with clinically localised lymphadenopathy, often in the neck or mediastinum, without other symptoms. Others have more extensive disease that is often associated with systematic symptoms such as weight loss, sweats and fever. Patients less commonly present with symptoms or signs of involvement of a specific extranodal site such as the GI or CNS.

REFERRAL

All patients with suspected lymphoma are to be referred to a clinical haematologist or medical oncologist, who has appropriate expertise in the management of lymphoma, and who works in association with a multi-disciplinary team which includes pathologists and radiation oncologists. In rural areas, refer to a general physician or surgeon, as appropriate.

The combined expertise of diagnostic and clinical experts in multidisciplinary teams also enhances access to clinical trials which is critical due to this rapidly evolving area of medicine.

Contact the Leukaemia & Blood Foundation for further advice or information about your local multidisciplinary treatment centre. 0800 15 10 15.

BIOPSY

Diagnosis depends on obtaining adequate tissue to evaluate the histology of the tumour and subtype, as well as immunohistochemical and molecular diagnostic information.

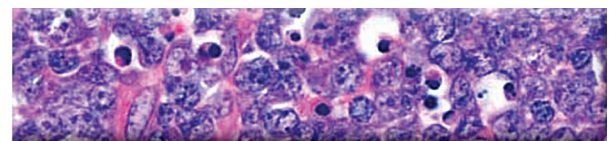
An open biopsy of an affected lymph node or tissue is usually necessary to make a definitive diagnosis of lymphoma.

The use of fine needle aspirate (FNA), core or excision biopsy will depend on the nature and location of the target lesion.

It is critical that the appropriate biopsy is performed by an experienced operator to ensure a satisfactory sample is obtained for histopathology, flow cytometry, chromosomal analysis and molecular studies. It should be interpreted or reviewed by a pathologist expert in haematopathology who can integrate the histological findings with the results of other investigations to arrive at a precise final diagnosis.

When a pathological node is not readily available, such as with intra-abdominal disease, a needle core biopsy is a reasonable initial procedure if open biopsy is not feasible.

Fine needle aspiration cytology is generally considered inadequate for diagnosing lymphoma, but can provide ancillary information or be useful in confirming a reactive lymph node.



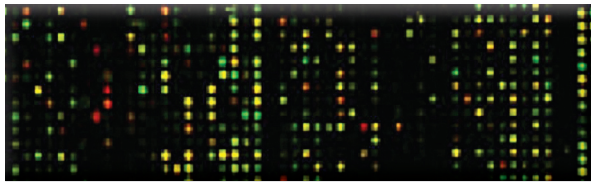
Burkitt's lymphoma histology



FNA may also be used to exclude solid malignancies of the head or neck as a cause of lymphadenopathy, as an open biopsy may prejudice later definitive surgical management. FNA may also have a role in diagnosing recurrence of lymphoma.

Peripheral lymph node excision biopsy is preferable and where there is intra-thoracic/abdominal or solid organ involvement, a radiologically-guided core biopsy is frequently adopted.

Before biopsy, patients should have a full blood count and coagulation screen to identify unexpected cases of leukaemia or bleeding tendency, and a chest x-ray to exclude unexpected intrathoracic disease. An ultrasound



Microarray analysis of diffuse large B-cell lymphoma

to further image the lymph node(s) may be undertaken in some cases.

CLASSIFICATION

Classification of the subtype of lymphoma is extremely complex and is used to decide what treatment is necessary for each type of lymphoma depending on whether the lymphoma is slow growing and can be managed for many years, or requires intense chemotherapy in an attempt to cure the lymphoma.

In New Zealand, most haematopathologists and clinicians use the WHO classification which was first published in 2001, and subsequently updated in 2008. It subdivides lymphomas and other blood cancers based on cell type, immunotype, molecular, cytogenetic and clinical characteristics.

STAGING

Lymphoma is staged as I, II, III or IV and divided into A or B, depending on the absence or presence of systemic

symptoms. The staging system for both Hodgkin and non-Hodgkin lymphoma is the Ann Arbour Staging System which is vital for deciding the correct treatment and helps estimate the prognosis.

Stage 1: One lymph node area involved

Stage 2: Two or more lymph node areas on the same side of the diaphragm

Stage 3: Lymph nodes involved on both sides of the diaphragm

Stage 4: Any of the above with involvement of sites other than lymph nodes (most commonly the bone marrow, liver or lungs)

B symptoms: Fever, night sweats or significant weight loss

Staging relies on physical examination, x-rays, CT scans (commonly of the abdomen and pelvis and sometimes of the neck and chest), and bone marrow examination. Nuclear medicine imaging, particularly PET and gallium scanning is assuming an increasingly important role.

TREATMENT

The major difficulty in treating lymphoma is deciding the most appropriate management plan for each patient, given the wide spectrum of clinical behaviour, the curability of some lymphomas with optimal treatment and the range of treatments that are now available.

Unlike most other cancers, the treatment for most lymphomas is based on the precise pathological subtype more so than the clinical and radiological stage of the disease at the time of diagnosis. The pathological subtype of a lymphoma predicts strongly for both biological behaviour and treatment response. Therefore accurate histological diagnosis is paramount and a close working relationship between the clinician and the pathologist is the key to the management of lymphomas.

Table 1: CLASSIFICATIONS OF LYMPHOMAS

Based on presenting features

- Indolent lymphomas
- Aggressive lymphomas
- Highly aggressive lymphomas

Based on WHO Lymphoma Classification⁴

Non-Hodgkin lymphoma

B-cell lymphomas

- Small lymphocytic
- Lymphoplasmacytic
- Splenic marginal zone
- Nodal marginal zone
- Extranodal marginal zone, of mucosa-associated lymphoid tissue (MALT lymphoma)
- Follicular⁺
- Mantle cell
- Diffuse large cell⁺
- Mediastinal large cell
- Intravascular large cell
- Primary effusion
- Burkitt's
- Post-transplant lymphoproliferative
- ⁺ most common forms

Non-Hodgkin lymphoma

T-cell lymphomas

- T-lymphoblastic
- Extranodal NK/T lymphoma, nasal
- Enteropathy-type T-cell
- Subcutaneous panniculitis-like T-cell
- Mycosis fungoides
- Sézary syndrome
- Primary cutaneous anaplastic large cell
- Angioimmunoblastic
- Peripheral T-cell

Hodgkin lymphoma

- Classical Hodgkin lymphoma
- Nodular lymphocyte predominant Hodgkin lymphoma



Following a definitive histologic diagnosis, patients begin a pathway typical of the management of all patients with malignant disease that involves staging, prognostic assessment, and a treatment plan that reflects either a curative or palliative approach.

Often a combination of treatment modalities is used, including surgery, radiotherapy, chemotherapy, biological therapy (interferon), monoclonal antibody therapy (rituximab) and bone marrow transplantation.

Some types of lymphomas grow slowly and need no treatment initially. These patients may have extended periods of non-progressive disease and regular check-ups are all that is required during this time. Others require treatment and will respond, at least initially, to a variety of chemotherapeutic drugs and radiation therapy.

Current practice is to manage lymphoma using a multidisciplinary team of experienced diagnostic and clinical experts (pathologists, radiologists, radiation therapists, physicians trained in medical oncology or clinical haematology and palliative care physicians). They formulate a comprehensive management plan that can include access to clinical trials, to enable optimal treatment and coordinated care for each patient.

The highest priority of treatment is to maximise patients' overall survival, maintain quality of life and avoid treatment-related morbidity.

Treatment for NHL is largely dictated by histology and anticipated clinical course rather than disease stage, with predominantly palliative intent for indolent NHL and curative intent for aggressive disease.

Follicular lymphoma: The treatment for follicular lymphoma has not been standardised and is subject to individual physician preference, the individual characteristics of each

patient and their disease. The initial treatment choice is influenced by the age and general health of the patient, disease 'bulk' (large tumour masses or small lymph nodes) and extent (localised or widespread), the speed of disease progression, and the presence of symptoms due to lymphoma. For example, elderly asymptomatic patients with slowly progressive localised non-bulky disease may need no treatment initially and may be managed by observation alone. Progressive localised disease may be treated with local radiotherapy alone. Younger patients with progressive symptomatic disease will require chemotherapy.

First line chemotherapy is most commonly combination chemotherapy such as CVP or CHOP in conjunction

on those developed for the treatment of childhood acute lymphoblastic leukaemia, including prophylactic treatment to the central nervous system.

Hodgkin lymphoma: The management of HL is dictated by accurate staging of the disease. Truly localised disease can be cured by radiation therapy, but more recently, in a combined modality treatment approach, radiation therapy has been given in reduced doses and more limited fields in conjunction with abbreviated courses of combination chemotherapy (ABVD protocol).

TREATMENT FOR RELAPSED DISEASE

Relapsed follicular lymphoma: Relapse is usual for follicular lymphoma even when intensive combination chemotherapy is used for initial treatment. Responses to subsequent therapy, including the same modality used previously, are usually seen and multiple re-treatments are possible. Agents that have value in the treatment of relapsed follicular lymphoma, including rituximab and the purine analogue, fludarabine (Fludara), are most useful in combination with other chemotherapy agents.

In younger patients, high dose chemotherapy with haemopoietic stem cell rescue using the patient's stored cells (autologous stem cell transplantation) produces prolonged complete responses in more than 50% of cases after first relapse. Allogeneic stem cell transplantation also has a high response rate in younger patients with relapsed disease.

Relapsed aggressive lymphomas and Hodgkin lymphoma: The treatment of relapsed aggressive lymphomas and HL is a greater therapeutic challenge. Without stem cell transplantation the outlook is usually grim, with less than 10% of patients surviving in the long term.



with rituximab (MabThera), a chimeric monoclonal antibody against the CD20 protein expressed on human B-cells, including follicular lymphoma.

Aggressive lymphomas: Virtually all patients with aggressive lymphomas have progressive and disseminated disease and require combination chemotherapy. The gold standard is R-CHOP given in courses every 14 to 21 days for a total of six to eight courses. The addition of rituximab to CHOP improves response rates without additional toxicity.

Highly aggressive lymphomas: Lymphoblastic and Burkitt's lymphomas require prompt and highly specialised care using protocols based



Re-treatment with intensive salvage protocols is required to obtain a second response prior to stem cell transplantation, and patients whose lymphoma is refractory to chemotherapy are usually considered ineligible for transplantation. Patients who show a response to salvage treatment are usually offered autologous stem cell transplantation, a procedure feasible up to the age of 70 years. There is a high response rate to this procedure with approximately 40% of patients with relapsed chemotherapy-sensitive aggressive lymphoma remaining free of lymphoma after an autograft.

PROGNOSIS

The overall prognosis in lymphoma varies widely and depends mainly on the type of disease and the response to initial treatment.

Follicular lymphoma: In follicular lymphoma, the average survival from diagnosis is seven years. Around 20% of patients survive more than 10 years without therapy, emphasising the highly heterogeneous behaviour of the disease.

Aggressive lymphomas: Prognosis in aggressive lymphomas is heavily influenced by factors relating to both the patient (age and general health) and the disease (tumour stage and bulk), but the most important determinant is response to chemotherapy. About 60% of cases of diffuse large cell lymphoma have a complete response to R-CHOP. Those failing have a very poor outlook. About one third of complete responders relapse, often within 12 months of treatment; some of these may be rescued by stem cell transplantation.

Hodgkin lymphoma: In HL, the prognosis is dependent on disease stage. Where the disease is localised, patients have an excellent outcome, with more than 90% having prolonged disease-free survival. The outlook for patients with more advanced disease treated by chemotherapy is worse but more than 50% have prolonged complete responses.

Follow-up: A GP plays a crucial role in detecting relapsed or recurrent

disease and monitoring for late effects of therapy as the long-term follow-up of patients who have been successfully treated for lymphoma. Attention to other aspects of their health includes their psychosocial wellbeing, encouraging the maintenance of a healthy lifestyle and preventive health measures including screening for other malignancies, as appropriate.

DIAGNOSING LYMPHOMA DECISION SUPPORT TOOL



The Leukaemia & Blood Foundation has developed a diagnosing lymphoma decision support tool, *Is Lymphoma on your Radar?* which accompanies this article. Further copies of this, and other materials, can be downloaded from the LBF's website: www.leukaemia.org.nz

GLOSSARY

ABVD: protocol acronym for combination chemotherapy of doxorubicin, bleomycin, vinblastine, dacarbazine (all intravenous).

R-CVP: protocol acronym for combination chemotherapy of rituximab cyclophosphamide, vincristine, prednisone.

R-CHOP: protocol acronym for combination chemotherapy of rituximab (intravenous), cyclophosphamide (intravenous), doxorubicin (intravenous), vincristine (intravenous), prednisone (oral).

The Leukaemia & Blood Foundation is the only organisation in New Zealand dedicated to supporting patients and their families living with leukaemia, lymphoma, myeloma and related blood conditions.

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FOR MORE INFORMATION ON DIAGNOSING LYMPHOMA

www.leukaemia.org.nz

Leukaemia & Blood Foundation

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