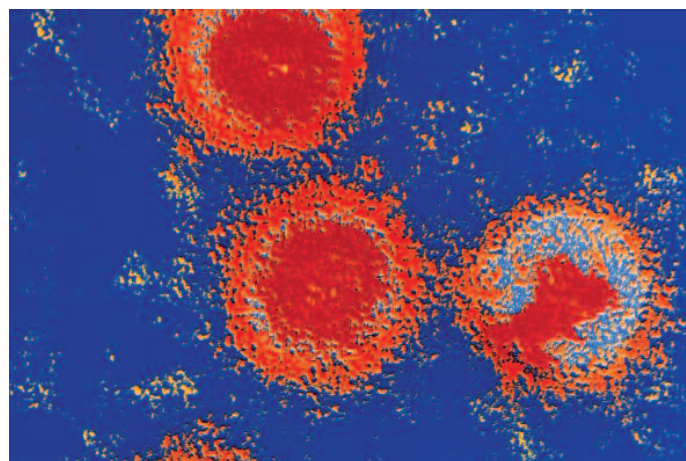


Lymphatic malignancies

— non-Hodgkin's lymphoma

By David Thomson, MRPharmS

All lymphoproliferative system malignancies, other than Hodgkin's lymphoma, are termed non-Hodgkin's. This article outlines the aetiology, pathology, symptoms and treatment of the disease



Coloured transmission electron micrograph of Epstein-Barr viruses, thought to play a part in the development of non-Hodgkin's lymphoma

Non-Hodgkin's lymphoma (NHL) is a term covering all lymphoproliferative system malignancies except Hodgkin's lymphoma. In 2001, 9,281 people in the UK were diagnosed with the disease. The incidence of NHL rises with age (rates increase sharply in people over 50 years and around two-thirds of all cases are diagnosed in people over 60 years). The NHL incidence rate increased by an average of 1.4 per cent per year between 1992 and 2001, but some of this increase in incidence can be explained by changes in the diagnosis, classification and patient registration rates. However, there is evidence to suggest that some of these increases are real, with high-grade lymphoma and follicular lymphoma being among those subtypes to have increased in incidence more than others. In countries with high rates of HIV, increases in immunoblastic and Burkitt's lymphoma have been noted.¹

Survival rates for NHL have improved over the past 30 years. For patients diagnosed with NHL in England and Wales in the early 1970s, the five-year survival rate was around 30 per cent, but for those diagnosed in the late 1990s it was around 50 per cent. These rates vary by age, with the five-year survival rate for those diagnosed aged 15–44 at 65 per cent, for those aged 65–74 at 37 per cent and for those aged 85 or older at 13 per cent.

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In 2004 there were 4,674 deaths from NHL in the UK. Reflecting the increases in incidence, the mortality rates for NHL in the UK increased by an average of around 3 per cent in males and females up to the mid-1990s. Since then, mortality rates have stabilised at around 7.3 per 100,000 in males and 4.9 per 100,000 in females. The increases in mortality have generally been confined to the older age groups, with the rates in the under 40s falling since the 1970s.

Aetiology

Congenital and acquired immunodeficiency is the most clearly defined factor known to increase NHL risk.² Immunosuppressant drugs following transplantation lead to a significantly increased (30–50 times) risk of NHL.³ The risk of NHL in people infected with HIV is more than 100 times that of the general population,⁴ and these lymphomas, if they occur, tend to be of B-cell origin with high-grade histology such as diffuse large B-cell lymphoma (DLBCL) or Burkitt's lymphoma. Infectious organisms such as Epstein-Barr virus, human T-cell lymphotropic virus type I, *Helicobacter pylori* and hepatitis C virus have all been thought to play a part in the development of NHL because infection can result in immune system stimulation or disruption. There are data pointing to a number of occupational, dietary, environmental and other risk factors that may help to explain the rising incidence of NHL, but much of this evidence is con-

tradictory and the increasing incidence of NHL is not fully explained.

Pathology

NHL describes a spectrum of neoplastic conditions, as a result of which many complex and confusing classifications have arisen. The majority of NHL arises from the B lymphocyte but there is a well recognised group which are T-cell derived. Macroscopically, NHL will occur as a mass of neoplastic lymphoid tissue which may reach a considerable size. It may arise in recognised lymph node chains but extra-nodal lymphoma is relatively common, especially involving the gastrointestinal tract, skin and bone.

Microscopically, the appearances are complex and interpretation is difficult. Generally lymphomas may be referred to as low-grade or high-grade. No single marker can be used as the gold standard for diagnosis and a combination of techniques is employed including morphology, genetic features, immunophenotype and clinical features. Confirmation of diagnosis requires a lymph node or other tissue biopsy, ideally with analysis of fresh tissue for patterns of protein expression on the cell surface as well as genetic changes at a molecular level. A classification system is required to incorporate all of this information. The most recent classification of lymphoma is the World Health Organization/revised European-American Lymphoma classification which takes into account some of these newer developments (Panel 1).⁵

The NHLs are a heterogeneous group of diseases linked only by their origin within the lymphatic system. DLBCL, an aggressive lymphoma, represents around 30 per cent and B-cell follicular lymphoma, an indolent (non-aggressive) lymphoma represents around 22 per cent of all cases of lymphoma in the UK. All other types of lymphoma have a frequency of less than 10 per cent, therefore this article will focus on follicular lymphoma and DLBCL.

— Natural history

Low-grade lymphoma may be indolent, remaining asymptomatic for many years and, in the elderly, having little impact upon their life expectancy. A high-grade lymphoma is an aggressive and often rapidly fatal condition. Extra-nodal lymphoma can have both a relatively benign or an aggressive course. In general NHL does not have a clear pattern of spread from one area to the next and dissemination is often wide and unpredictable with frequent lung and hepatic involvement.

— Symptoms

NHL usually presents with a painless lump in a lymph node area (most commonly the neck, but also the axillae or groin). There may be backache due to enlarged para-aortic nodes or upper abdominal pain from hepatosplenomegaly. Weight loss, fever and night sweats (known as B-symptoms and characteristic of lymphomas) are also an important feature. Other features relate to the site of origin of an extra-nodal lymphoma. For example, gastrointestinal lymphoma usually presents with an acute abdominal event due to obstruction, perforation or haemorrhage whereas lymphoma of the central nervous system may cause symptoms of raised intracranial pressure with vomiting, headache and fits. The Department of Health referral guidelines for suspected cancer suggest urgent referral for patients with certain symptoms (Panel 2, p355).⁶

— Staging and treatment

The staging system for non-Hodgkin's lymphoma is the same as that used for Hodgkin's disease and its main use is to distinguish localised stage I and II disease from the disseminated stage III and IV disease (see Hodgkin's lymphoma article, pp345–52).

Treatment is based on the histological grade and stage of the lymphoma. The commonly used chemotherapy regimens are summarised (Panel 3, p355).

Low grade lymphoma is a condition which has a long indolent course but is rarely curable. Regimens used to treat this disease have included oral chlorambucil and fludarabine, as well as CVP and CHOP (see

Panel 1: World Health Organization/revised European-American classification of lymphoid neoplasms

Precursor B-cell neoplasm

- Precursor B-cell acute lymphoblastic leukaemia or lymphoma

Mature (peripheral) B-cell neoplasms

- B-cell chronic lymphocytic leukaemia or small lymphocytic lymphoma
- B-cell prolymphocytic leukaemia
- Lymphoplasmacytoid lymphoma
- Splenic marginal-zone B-cell lymphoma (with or without villous lymphocytes)
- Hairy-cell leukaemia
- Plasma-cell myeloma or plasmacytoma
- Extranodal marginal-zone B-cell lymphoma of mucosa-associated lymphoid tissue
- Nodal marginal-zone B-cell lymphoma (with or without monocytoid B cells)
- Follicular lymphoma
- Mantle-cell lymphoma
- Diffuse large B-cell lymphoma
- Mediastinal large B-cell lymphoma
- Primary effusion lymphoma
- Burkitt's lymphoma or Burkitt's cell leukaemia

Precursor T-cell neoplasm

- Precursor T-cell acute lymphoblastic leukaemia or lymphoma

Mature (peripheral) T-cell and natural-killer neoplasms

- T-cell prolymphocytic leukaemia
- T-cell granular lymphocytic leukaemia
- Aggressive natural-killer cell leukaemia
- Adult T-cell lymphoma or leukaemia
- Extranodal natural-killer/T-cell lymphoma (nasal type)
- Enteropathy-type T-cell lymphoma
- Hepatosplenic gamma-delta T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides or Sezary syndrome
- Anaplastic large-cell lymphoma, T-cell/null cell, primary cutaneous type
- Peripheral T-cell lymphoma, not otherwise characterised
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large-cell lymphoma, T-cell/null cell, primary systemic type

Panel 3). Initially more than half of patients respond to treatment, but the response and its duration decrease with subsequent chemotherapy. Follicular lymphoma is the most common indolent lymphoma.

High grade lymphoma is a much more aggressive condition than low-grade lymphoma and in general requires much more intensive chemotherapy. DLBCL is the most common high-grade lymphoma.

— Follicular lymphoma

Patients with follicular lymphoma tend to be elderly and present with advanced stage disease. Median overall survival is 8–10 years, but most patients relapse several times, with cure being unlikely. There are three recognised grades of follicular lymphoma:

- Grade 1 (small-cell follicular lymphoma)
- Grade 2 (mixed small and large-cell follicular lymphoma)

- Grade 3 (large-cell follicular lymphoma)

Grade 3 follicular lymphoma is often treated as a large-cell lymphoma (between 22 and 30 per cent of patients with follicular lymphoma develop DLBCL).⁷

With the introduction of a number of new agents over recent years the treatment of follicular lymphoma is no longer a simple choice between traditional “watch and wait” and alkylator therapies.

Treatment can be delayed until symptoms develop or histological transformation occurs, since no survival advantage has been shown with immediate treatment.

A 2003 trial which randomised asymptomatic patients with advanced stage follicular lymphoma to either observation or chlorambucil found that there was no difference in overall survival with a median follow-up of 16 years.⁸ The median time to the first treatment in the observation group was 2.6 years.

Early stage follicular lymphoma External beam radiotherapy, when given alone, can cure early stage (I or II) follicular lymphoma and this remains the standard of care in this patient group.⁹ Trials however are continuing and will look at a number of areas:

- The comparison of immediate radiotherapy with radiotherapy deferred

Panel 2: Symptoms of non-Hodgkin's lymphoma requiring urgent referral

- Lymphadenopathy (>1cm persisting for six weeks)
- Hepatosplenomegaly
- Three or more of the following symptoms:
 - Fatigue
 - Night sweats
 - Weight loss
 - Itching
 - Breathlessness
 - Bruising
 - Recurrent infection
 - Bone pain

- until the patient is symptomatic
- Adding multi-agent chemotherapy to the treatment regimen
- The outcomes of using radioimmunotherapy

Advanced stage follicular lymphoma

Therapies for the treatment of advanced (stage III or IV) follicular lymphoma are usually administered intermittently over a period of several years as the disease pursues a remitting and recurring course. As initial therapy, combination chemotherapy gives a higher response and longer time to first relapse than the use of single agent alkylators alone, but does not improve overall survival.¹⁰ Therefore patients with advanced follicular lymphoma usually receive a conservative initial therapy such as chlorambucil or the CVP regimen. Patients are treated until remission and then regularly monitored until progression. This approach leads to a median survival of about 10 years, with patients receiving about three therapies at approximately three-yearly intervals.

High response rates have been seen with combination regimens incorporating fludarabine, ie, the FC regimen. However, there remains concern over the toxicity profile of this agent in this patient group,¹¹ and it con-

tinues to be studied in trials. Interferon (IFN)-alpha has also been studied in follicular lymphoma both in combination with chemotherapy and as maintenance therapy, however neither progression-free survival nor overall survival were improved and IFN-alpha was associated with increased toxicity.¹²

Relapsed follicular lymphoma Previous response to therapy is the most important factor in determining the next treatment. Generally, patients who relapse two years or more after treatment with alkylating agents (chlorambucil or CVP) will respond to further treatment with the same agents. Patients who relapse earlier may respond to single-agent or combination chemotherapy, biological agents or radiotherapy.

Cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP), or CHOP-like regimens have been shown to induce remissions of around 12 months in patients with relapsed follicular lymphoma. Fludarabine, as a single agent or in combination chemotherapy, may give response rates of around 32–62 per cent and 90 per cent respectively.

Clinical trials investigating treatment with rituximab in relapsed or refractory indolent

Panel 3: Commonly used chemotherapy regimens in non-Hodgkin's lymphoma

Chemotherapy regimen name	Drug and dose	Route	Cycle schedule	Cycle length
■ Chlorambucil	Chlorambucil 10mg/m ²	po	Days 1–14	28 days
■ CVP	Cyclophosphamide 600mg/m ² Vincristine 1.4mg/m ² Prednisolone 40mg/m ²	iv iv po	Day 1 Day 1 Days 1–5	28 days
■ CMD	Chlorambucil 10mg Mitozantrone 12mg/m ² Dexamethasone 20mg	po iv po	Days 1–3 Day 1 Days 1–5	28 days
■ FMD	Fludarabine 40mg/m ² Mitozantrone 12mg/m ² Dexamethasone 20mg	po iv po	Days 1–3 Day 1 Days 1–5	28 days
■ CHOP	Cyclophosphamide 750mg/m ² Doxorubicin 50mg/m ² Vincristine 1.4mg/m ² Prednisolone 50mg/m ²	iv iv iv po	Day 1 Day 1 Day 1 Days 1–5	21 days
■ FC	Cyclophosphamide 250mg/m ² Fludarabine 25mg/m ²	iv iv	Days 1–3 Days 1–3	28 days
■ FCM	Fludarabine 24mg/m ² Cyclophosphamide 150mg/m ² Mitozantrone 6mg/m ²	po po iv	Days 1–5 Days 1–5 Day 1	28 days
■ DHAP	Dexamethasone 40mg Cisplatin 100mg/m ² Cytarabine 2G/m ²	po iv iv	Days 1–4 Day 1 2 doses on day 2	21–28 days

Most of these regimens have been combined with rituximab 375mg/m², which is usually administered on day 1 of the regimen

lymphomas have shown overall response rates (ORR) of nearly 50 per cent.¹³ Rituximab has since become part of standard treatment of follicular lymphoma and in the UK is approved by the National Institute for Health and Clinical Excellence (NICE) for the third-line or subsequent (except last-line recurrent or refractory stage III or IV) treatment of follicular lymphoma.

The high response rates seen with rituximab in the relapsed setting have also led to the incorporation of rituximab into front-line chemotherapy regimens in an approach known as chemoimmunotherapy. When rituximab was combined with CHOP, response rates were high (ORR 100 per cent, complete response [CR] 58 per cent), and the median time to progression was 83 months.¹⁴ A number of phase III trials have investigated the addition of rituximab to CHOP, CVP, and FCM and all have reported that this addition to chemotherapy increases the time to progression.¹⁵⁻¹⁷ It is likely therefore that chemoimmunotherapy is superior to chemotherapy alone and will be introduced as first-line therapy in the future.

These results also led to trials studying the use of rituximab as single-agent therapy in untreated individuals, one of which reported a 73 per cent response rate and a median time to progression of 552 days in asymptomatic patients with follicular lymphoma.¹⁸ There is now mounting evidence in support of maintenance therapy in follicular NHL. Two phase III trials have studied this approach. One of these trials showed that repeated doses given at specified intervals after completion of the initial four weekly treatment extended time to progression.¹⁹

Panel 4: International prognostic index predictive model for diffuse large B-cell lymphoma

- Age (more than 60 years)
- Ann Arbor Stage (III/IV)
- Serum lactate dehydrogenase (elevated levels)
- Extra-nodal involvement (>1 site)
- Performance status (2-4)

Panel 5: Prognostic categories for diffuse large B-cell lymphoma

International prognostic index risk group	Number of risk factors
Low risk	0 or 1
Low/intermediate risk	2
High/intermediate risk	3
High risk	4 or 5

Radioimmunotherapy Ibritumomab tiuxetan (Zevalin) is a murine monoclonal antibody directed against CD20 and bound to yttrium-90, a beta emitter. It is licensed for the treatment of CD20-positive follicular B-cell non-Hodgkin's lymphoma, unresponsive to rituximab or which is relapsed. This agent uses the targeting features of a monoclonal antibody to deliver radiation from the attached radionucleotide and limit the effects on normal tissues. Both overall response and complete response are significantly higher in refractory or relapsed follicular lymphoma compared with rituximab.²⁰ Ibritumomab tiuxetan is effective in patients who have received multiple prior therapies and has an acceptable toxicity profile. Trials are assessing this agent in first-line therapy or to consolidate the responses achieved with first-line chemotherapy, rituximab or both.

Novel therapies Monoclonal antibodies such as epratuzumab, apolizumab and alemtuzumab are in various stages of clinical development in order to assess whether they will complement the existing treatments available.

Bortezomib (Velcade) was approved recently for the treatment of relapsed and refractory multiple myeloma. Bortezomib is a proteasome inhibitor which inhibits the ubiquitin-proteasome pathway which is a complex system that degrades regulatory proteins involved in control of the cell cycle. Inhibition of this pathway results in apoptosis, therefore proteasome inhibitors may stop tumour growth. The use of bortezomib in lymphoma is supported by early trial work and is being further investigated.²¹

Administration of dendritic cells loaded with tumour-associated proteins or peptides results in the induction of immune response against different types of malignant cells. Vaccines based on dendritic cells have already shown promise in the treatment of follicular lymphoma.²²

DLBCL

DLBCL is characterised by an aggressive clinical behaviour and patients typically present with rapidly enlarging lymphadenopathy. DLBCL is treated with curative intent as cure can be expected in 40-50 per cent of all patients.

International prognostic index (IPI)

The IPI is a predictive model for patients with DLBCL based on five clinical features at presentation (Panel 4). Based on this patients can be divided into four prognostic categories (Panel 5).

Treatment of localised (stage I or II) disease Treatment approaches for localised disease differ depending on a number of factors: disease bulk (<10cm versus >10cm),

IPI risk group, the presence of primary extra-nodal disease. For patients with localised disease, radiotherapy was the treatment of choice, but this strategy has now proved to be insufficient. Therefore, over the past two decades, two approaches have been developed for these patients: chemotherapy alone with the CHOP regimen or a shortened course of chemotherapy followed by radiotherapy. These approaches have been compared and it was found that patients who received both chemotherapy and radiotherapy had better progression-free and overall survival.²³ This is the standard approach now used in the UK.

Treatment of advanced (stage III or IV) disease IPI risk group will determine the treatment of patients with advanced DLBCL.

The most effective treatment for low- or low-intermediate-risk advanced stage DLBCL is chemotherapy, and many combination regimens have been developed, with six to eight cycles of CHOP being the standard therapy in the UK.

Patients with high/intermediate- and high-risk disease have a less than 50 per cent chance of cure with this conventional chemotherapy approach and therefore trials in this patient group are assessing alternative approaches. Trials in patients under 60 years are assessing the role of high-dose therapy and autologous stem-cell transplantation (where stem cells are taken from the patient and returned after the chemotherapy has been administered) as part of first-line therapy.

The Groupe d'Etude des Lymphomes de l'Adulte (GELA) trial showed that in patients over 60 years the addition of rituximab to CHOP chemotherapy improved overall survival in patients with high/intermediate or high-risk disease.²⁴ In the UK the National Institute for Health and Clinical Excellence has recommended the use of rituximab with CHOP for the first-line treatment of people with CD20-positive DLBCL at clinical stage II, III or IV.

A number of clinical trials are ongoing in this patient group. The MabThera International Trial (MiNT) is comparing CHOP with CHOP plus rituximab in patients younger than 60 years with early and advanced stage disease.²⁵ Preliminary results suggest that this is the first trial supporting the use of rituximab in younger patients. Dose intensity is another strategy that is being explored with trials suggesting possible benefit from dose-intensified CHOP given every 14 days rather than the standard 21 days.^{26,27} This approach is still experimental and associated with increased toxicity, with further trials examining incorporation of rituximab into intensified therapy.

Treatment of relapse or progression and refractory disease Cure is still a possibility for a limited number of patients who

have relapsed or refractory disease, but this is less likely in elderly patients, those with extensive disease and those with a poor performance status. In these patients, less intensive chemotherapy with single agent vincristine, alkylating agents or anthracyclines is often used. Most younger patients, however, do tend to receive second-line combination chemotherapy regimens. These regimens usually incorporate drugs such as cisplatin, ifosfamide, etoposide and cytarabine, often in combination with rituximab.

Patients under 70 years who do respond to second-line therapy should proceed to high-dose therapy and autologous stem cell transplantation. A trial in patients who had relapsed from a complete remission and responded to two cycles of DHAP were randomly allocated to high-dose chemotherapy or continued treatment with DHAP.²⁸ Autologous transplantation was associated with better overall survival rates of around 50 per cent (compared with around 30 per cent with continued DHAP). This is now the treatment of choice for the limited number of patients who fit the strict selection criteria for transplantation.

Novel therapies for DLBCL Depsipeptide is a bicyclic peptide that has been shown to arrest the cell cycle at stages G0/G1. Phase I trials in peripheral T-cell lymphoma

and cutaneous T-cell lymphoma have reported responses with a number of associated toxicities.²⁹ A phase II trial is ongoing and the agent is being investigated in a number of malignancies.

The macrolide rapamycin (Sirolimus) and its derivatives suppress growth and proliferation of lymphocytes and tumour cell lines. Rapamycin is used as an immunosuppressive agent for renal transplant recipients and a related compound, CCI-779, is being developed as a lymphoma treatment. On the basis of phase I studies, CCI-779 appears to be well tolerated and exhibits antitumour activity.³⁰ Phase II studies are now under way investigating CCI-779 in NHL.

Antisense oligonucleotides are chemically modified single-strand DNA molecules that have a nucleotide sequence which is complementary to the target mRNA and capable of inhibiting expression of that target gene. The Bcl-2 gene is a potentially important target because it is overexpressed in most follicular B-cell NHLs and in about a quarter of large B-cell lymphomas. Bcl-2 is thought to be responsible for maintaining the viability of tumour cells as well as being involved in multidrug resistance, resulting in poor response to therapy in NHL and other haematological malignancies.

G3139 (oblimersen sodium) is the first antisense molecule to be widely tested. A

phase I study of G3139 in patients with NHL was reported, which, despite the low doses used, resulted in some major responses.³¹ A large number of clinical trials are subsequently investigating this agent in NHL both as a single agent and in combination with standard chemotherapy.

— Conclusion

Until the late 1990s, conventional chemotherapy was the only option available for the treatment of NHL. Monoclonal antibodies and radioimmunotherapies have recently been introduced for these patients. In the short term it is unlikely that improvements in therapy will be achieved without combining these agents with standard chemotherapy. It is likely that newer regimens will be developed to substitute non-specific cytotoxics with targeted therapies such as monoclonal antibodies.

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