BMJ 2018;362:k3204 doi: 10.1136/bmj.k3204 (Published 22 August 2018)

PRACTICE

CLINICAL UPDATES

Non-Hodgkin lymphoma

Anna Bowzyk Al-Naeeb *consultant clinical oncologist*[1], Thankamma Ajithkumar *consultant clinical oncologist*[2], Sarah Behan *haematology clinical nurse specialist*[3], Daniel James Hodson *consultant haematologist and MRC clinician scientist*[3 4]

[1]Department of Oncology, Bedford Hospital, Bedford, UK; [2]Department of Oncology, Cambridge University Hospitals NHS Trust, Cambridge, UK; [3]Department of Haematology, Cambridge University Hospitals NHS Trust, Cambridge, UK; [4]Wellcome Trust-Medical Research Council Stem Cell Institute, University of Cambridge, Cambridge, UK

What you need to know

- A clinical or radiological finding of enlarged lymph nodes may raise suspicion of lymphoma, but a diagnosis cannot be made without tissue biopsy
- Refer patients with unexplained persistent (>6 weeks), progressive, or generalised lymphadenopathy to the team most appropriate to arrange biopsy as directed by local referral pathways.
- The commonest high grade lymphoma is diffuse large B cell lymphoma—an aggressive malignancy that is curable in 60-70% of patients with combined immunochemotherapy
- The commonest low grade (indolent) lymphoma is follicular lymphoma—generally considered incurable, it follows a relapsing-remitting course with treatment required intermittently
- The relapsing and remitting nature of indolent lymphomas can present unique mental health challenges for patients and requires patient education and emotional support

Non-Hodgkin lymphoma are malignant disorders arising from cells of the immune system, and manifest predominantly as lymphadenopathy or solid tumours. The classification of non-Hodgkin lymphoma is complex and ever-evolving, with more than 50 different subtypes listed in the latest World Health Organization classification.[1] For non-specialists, however, they can most usefully be categorised as low grade (indolent) or high grade (aggressive) lymphoma since this broad distinction determines the likely natural course and management of the disease. In this clinical update we discuss the principles of diagnosis and management that are of particular relevance to non-specialist physicians, who may encounter patients with non-Hodgkin lymphoma during their initial presentation, therapy, and follow-up.

Sources and selection criteria

We searched PubMed using the key words "non-Hodgkin lymphoma," "diffuse large B cell lymphoma," and "follicular lymphoma" to identify reviews and major studies published since 2000. This was supplemented by a review of management guidelines (listed in the "Further educational resources" box), by personal experience of the authors, and by feedback from patients.

How common is non-Hodgkin lymphoma?

Non-Hodgkin lymphoma is the sixth commonest malignancy in the UK with 13 000 new cases diagnosed annually (fig 1).[3 4] The International Agency for Research on Cancer reported 0.39 million diagnoses of non-Hodgkin lymphoma worldwide in 2012, but there are almost certainly large variations in the quality of data reporting worldwide that make this figure hard to interpret.[5] The commonest indolent lymphoma is follicular lymphoma, while the commonest aggressive lymphoma is diffuse large B cell lymphoma (DLBCL) (fig 2). There are geographical variations in incidence of individual subtypes, with follicular lymphoma being more common in Western countries, T cell lymphoma more common in Asia, and Epstein-Barr virus related (endemic) Burkitt lymphoma more common in Africa.[6]

What causes non-Hodgkin lymphoma?

Most non-Hodgkin lymphomas arise from mature B lymphocytes, with a minority derived from T lymphocytes or natural killer (NK) cells.

Lymphoma develops due to the progressive acquisition of DNA alterations that include gene mutation, amplification or deletion and chromosomal translocation. Particular subtypes of lymphoma are associated with specific acquired genetic abnormalities—for example, the translocation of the *BCL2* oncogene in follicular lymphoma or translocation of the *MYC* oncogene in Burkitt lymphoma.[7]

Correspondence to: D J Hodson djh1002@cam.ac.uk

Certain subtypes of non-Hodgkin lymphoma are associated with infections, including with Epstein-Barr virus, *Helicobacter pylori*, and hepatitis C virus.[8] Non-Hodgkin lymphoma is more common in patients who are immunosuppressed, such as patients with HIV/AIDS or recipients of an organ transplant. Although smoking may be associated with some lymphoma subtypes,[9] it is not a well established risk factor for non-Hodgkin lymphoma as a whole.[10] There is a slightly elevated risk in family members, but non-Hodgkin lymphoma is not generally considered hereditary. For most patients, there is no clear aetiological factor.

How do patients present?

The presenting features of non-Hodgkin lymphoma are diverse. Patients commonly present with lymphadenopathy or splenomegaly. A single lymph node or several nodes may be enlarged. The swelling develops over months or years in the case of low grade lymphoma but is much faster with high grade lymphoma. In up to a third of patients non-Hodgkin lymphoma may be extranodal,[11] and almost any organ or tissue can be involved. Non-Hodgkin lymphoma presenting as a solid extranodal tumour may initially mimic other forms of cancer until histology results are known.

An enlarging lymph node or tumour mass can give rise to symptoms from local compression. Systemic symptoms, termed "B symptoms," include fever, sweats, and weight loss. About half of patients with high grade lymphomas describe these symptoms, but they are not specific to the diagnosis. Some patients experience generalised pruritus.

Patients may be entirely asymptomatic, with enlarged lymph nodes detected as an incidental finding on clinical or radiological examination. In other cases, patients may present with symptoms that do not raise initial suspicion of lymphoma but lead to radiological investigations that reveal the presence of intra-abdominal or thoracic lymphadenopathy.

Although there is no characteristic presentation, the crucial feature prompting suspicion is almost always the finding of persistent lymphadenopathy, splenomegaly, or an extranodal mass.

How is it diagnosed?

Blood tests

No blood tests are specific for a diagnosis of non-Hodgkin lymphoma.

In many patients routine blood tests are normal. Renal or liver function tests may be abnormal if the respective organs are affected by lymphoma. Bone marrow involvement may cause anaemia, thrombocytopenia, and neutropenia. Lactate dehydrogenase is often elevated in high grade lymphomas, but the test is not specific.

Biopsy

A biopsy is required to confirm the diagnosis of non-Hodgkin lymphoma. We recommend the full blood count be checked before biopsy to exclude chronic lymphocytic leukaemia, a diagnosis that may spare the patient the need for biopsy. An excision lymph node biopsy is best,[12] but where the anatomical location of the lymph node makes this technically challenging, a radiologically guided core biopsy may suffice. Fine needle aspiration is not usually sufficient for diagnosis. Bone marrow biopsy is sometimes performed for staging but is rarely the diagnostic investigation. A normal bone marrow biopsy does not exclude lymphoma.

Corticosteroids should not be given to patients with suspected lymphoma before biopsy without specialist advice as they can make interpretation of lymphoma histology extremely difficult and delay diagnosis.

Lymphoma pathology is complex and should be overseen by a specialist lymphoreticular histopathologist in a lymphoma referral centre. Diagnosis may require iterations of immunohistochemical staining and molecular analysis of chromosomal aberrations by fluorescent in situ hybridisation. All new cases should be discussed at a specialist lymphoma multidisciplinary meeting.

Staging

Staging refers to the extent of involvement of the tumour according to the Ann Arbor classification (box 1). Contrast enhanced computed tomography (CT) from neck to pelvis or positron emission tomography (PET) CT is used for staging (fig 3). Patients typically receive a pre-treatment prognostic score that predicts disease-free and overall survival. In DLBCL, specialists will calculate the International Prognostic Index (IPI) based on age, lymphoma stage, lactate dehydrogenase level, extranodal disease, and patient's fitness (performance status).[14]

Box 1: Staging of non-Hodgkin lymphoma based on Ann Arbor classification[13]

Early stage

I—Single nodal area

II—More than one nodal area, but does not cross the diaphragm

Advanced stage

III—Both sides of diaphragm involved

IV—Extranodal or bone marrow involvement

Suffix

A—No B symptoms

B—B symptoms (fever, night sweats, and weight loss)

E—Extranodal disease (localised extranodal disease, Stage 1E)

When to refer?

Refer those with unexplained lymph node enlargement that is persistent, bulky, or rapidly enlarging, ideally on a "suspected cancer pathway" (box 2). Local referral pathways vary, but patients should be referred to the team most appropriate to arrange biopsy of the anatomical location of the lymphadenopathy. For example, a patient with head and neck lymphadenopathy might be referred to an ENT surgeon, inguinal lymphadenopathy to a general surgeon, mediastinal lymphadenopathy to a lung clinic, and so on. Referral to a haematology or oncology specialist team is usually done after the diagnosis is confirmed.

Box 2: Typical criteria for urgent referral

- Persistent (>6 weeks) lymphadenopathy
- One or more lymph nodes >2 cm in diameter
- Rapidly increasing lymphadenopathy
- Generalised lymphadenopathy
- Persistent and unexplained splenomegaly

NICE guidance (2015)[15]

"Consider a suspected cancer pathway referral (appointment within 2 weeks) for non-Hodgkin lymphoma in adults presenting with **unexplained** lymphadenopathy or splenomegaly. When considering referral take into account any associated symptoms, particularly fever, night sweats, shortness of breath, pruritus or weight loss."

How is non-Hodgkin lymphoma treated?

Non-Hodgkin lymphoma is best managed by a specialist physician as part of a lymphoma multidisciplinary team in a secondary care setting. The principles of treatment differ for high grade and low grade lymphoma. Management varies from no treatment through to urgent admission for intensive chemotherapy.

Treatment of high grade lymphoma

High grade non-Hodgkin lymphoma may progress rapidly and requires urgent treatment. It is usually treated with curative intent. Typical treatment is combination chemotherapy, which, in B cell tumours, is combined with rituximab, a monoclonal antibody against the B cell-specific surface antigen CD20. After completion of immunochemotherapy, some patients may be offered localised radiotherapy.

The immunochemotherapy regimen most commonly used for DLBCL is R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone). This is given in an outpatient clinic once every three weeks for a total of six treatments. It is generally well tolerated in younger patients (<75 years old) who are otherwise fit. Several large randomised studies have confirmed a survival benefit when rituximab was added to CHOP[16 17] with the proportion of patients alive at two years from diagnosis increasing from 57% to 70% in elderly patients and the proportion alive at three years in younger patients increasing from 84% to 93%. Many trials have examined more intensive regimens and the use of bone marrow or stem cell transplantation as first line treatment of DLBCL.[18 19] However, none of these has yet demonstrated an improvement in patient overall survival when compared with standard R-CHOP.

More intensive regimens, given as inpatient treatment, are required to treat Burkitt lymphoma. Similar regimens have been used for high risk forms of DLBCL, including the so called double hit lymphomas (with translocation of both *MYC* and *BCL2* oncogenes). Evidence to support this approach is of low quality and comes from non-randomised retrospective studies.

Outcomes—In general, patients with high grade lymphoma respond very well to treatment. Typically 60-70% of patients are cured and will never have a relapse of their lymphoma.[18] Patients with DLBCL who reach two years from treatment without relapse have a life expectancy equal to that of the age-matched population.[20] Patients are usually monitored clinically and, in the absence of relapse, will be discharged from follow-up after two to five years. Routine surveillance scanning is not typically required as part of follow up. It is better targeted at those patients who develop features suggestive of disease recurrence. Patients who fail to respond to first line chemotherapy or who relapse after chemoimmunotherapy are harder to treat. Those responding to second line therapy typically go on to have autologous stem cell transplantation to consolidate their treatment.

Treatment of low grade (indolent) lymphomas

Indolent lymphomas are not considered curable with conventional therapy, in contrast with high grade lymphoma. An exception is the small number of patients with indolent lymphoma who present with localised lymphadenopathy. These patients may be cured by surgical excision or by radiotherapy. However, most patients present at an advanced stage, and their lymphoma is best managed as a lifelong, chronic disease.

Early treatment of asymptomatic patients with chemotherapy has not been shown to increase life expectancy.[21-23] Treatment of asymptomatic patients with follicular lymphoma with rituximab may delay the time when chemotherapy is required, but there is no evidence it alters the long term progression of the disease.[24]

Most patients with asymptomatic, indolent disease are managed with a "wait and watch" approach and may never require treatment.[23]

Indications to start treatment include systemic symptoms, bulky lymphadenopathy, progressive nodal enlargement, and threatened compromise of vital organ function.[25] Treatment involves outpatient immunochemotherapy for four to six months. In several randomised trials rituximab improved the overall survival of patients with follicular lymphoma when combined with chemotherapy.[26-28] Typical first line drug regimens include R-CHOP and R-bendamustine.[29]

After chemotherapy is completed, patients typically follow a relapsing-remitting course with remissions lasting several years. Patients may require treatment on multiple occasions during their lifetime. Rituximab given every two months for two years after initial immunochemotherapy increases the length of remission, but there is currently no evidence of prolonged survival.[30] In follicular lymphoma the length of first remission is a major determinant of outcome; patients with a first remission of more than two years have excellent outcomes.[31] A proportion of patients with low grade lymphomas will transform to high grade disease.[32]

What are the complications of chemotherapy?

Early and late toxicity follow chemotherapy depending on the exact treatment used.

Short term side effects include temporary hair loss, changes in taste, and loss of appetite. Nausea is generally well controlled with antiemetic drugs. Many patients undergoing chemotherapy experience fatigue, and some take many months to recover. Most chemotherapy regimens are myelosuppressive, with potential for anaemia, thrombocytopenia, and neutropenia. For example, R-CHOP (moderately myelosuppressive) typically renders patients neutropenic (neutrophil count <1.0) for one or two days, usually starting 7-10 days after each treatment. Neutropenic patients are vulnerable to bacterial septicaemia, which can be serious or even fatal; it is a medical emergency. Patients undergoing chemotherapy should receive clear written instructions about how to seek help in the event of fever. At our institution, patients are given written fever rules printed on a red "Chemo card" along with an emergency contact phone number, which allows emergency admission to the haematology unit (fig 4).

Long term side effects include peripheral neuropathy, which can occasionally be disabling. Cardiomyopathy is a specific complication of the anthracycline component of R-CHOP. Hypogammaglobulinaemia is commonly seen after treatment with rituximab; rarely this is associated with symptomatic infections. Renal damage may result from nephrotoxic chemotherapy, such as the platinum based drugs, as well as from tumour lysis syndrome that may complicate the treatment of some high grade lymphomas. Fertility may be reduced.[33] Where relevant, male patients are offered sperm banking and female patients should be offered urgent consultation with a fertility specialist. Both chemotherapy and radiotherapy may increase the risk of secondary malignancy.[33]

What new treatments can we expect?

Improved understanding of the molecular and genetic pathogenesis of lymphoma[7] has led to development of newer drugs targeted to genetic subtypes of lymphoma. Early phase I and II clinical trials have shown beneficial effects, such as for ibrutinib in treating mantle cell lymphoma.[34] However, acquired resistance and unexpected toxicities are common, and there is still much to learn in terms of how these drugs should be used. Other agents in clinical trials include patients' T cells that have been genetically modified to recognise lymphoma cells and antibody-drug conjugates that deliver chemotherapy directly to tumour cells.

How to support patients once diagnosed

Patients with lymphoma face particular challenges. Those with newly diagnosed indolent lymphoma often struggle with being told they have a malignant disease but that initial treatment will merely be observation. Patients in remission after treatment may live in fear that each new symptom they develop could represent a recurrence of their disease (see patient perspective).

Patient education and emotional support can help with this. Patients should be given detailed written information about the risks and benefits of their proposed chemotherapy. Patients may want to discuss the effects of chemotherapy with their GP when deciding whether to undergo treatment. Patients may also present to their GP with complications arising during chemotherapy.

Specialist nurses play an essential role, both during clinic visits and as a point of contact should help or advice be needed between visits.

Several patient groups and charities provide excellent educational and emotional support free of charge for patients, carers, and families.

Sources of information and support for patients with lymphoma

- Lymphoma Action (https://lymphoma-action.org.uk/) provides information literature and support to patients with lymphoma and runs a "buddy" scheme that matches newly diagnosed patients with a patient who has already been through a similar diagnosis
- Macmillan Cancer Support (www.macmillan.org.uk) offers medical, psychological, and financial support to patients diagnosed with cancer
- Several helpful patient groups exist, such as "Living with follicular lymphoma" on Facebook (www.facebook.com/follicularlymphoma1/)
- Cancer Research UK (www.cancerresearchuk.org/about-cancer/non-hodgkin-lymphoma) provides information about symptoms, risk factors, incidence statistics, treatment, and trials for non-Hodgkin lymphoma

Questions for future research

- How should we manage patients who relapse early or fail to respond to chemotherapy?
- How should we manage older or comorbid patients who cannot tolerate chemotherapy?
- How to prospectively identify and manage patients at high risk of treatment failure?
- How to provide optimal prophylaxis against central nervous system relapse?
- What is the role of genomic medicine, novel antibodies, and small molecules in treatment of lymphoma?

Further educational resources

These organisations publish practice guidelines for the management of patients with lymphoma. The guidelines are available on online and can be accessed free of charge

- British Society for Haematology. BSH guidelines. www.b-s-h.org.uk/guidelines
- European Society for Medical Oncology. ESMO clinical practice guidelines: haematological malignancies. www.esmo.org/Guidelines/Haematological-Malignancies
- National Comprehensive Cancer Network. NCCN guidelines. www.nccn.org/professionals/physician_gls/default.aspx
- National Institute for Health and Care Excellence. Non-Hodgkin's lymphoma: diagnosis and management (NICE guideline NG52). 2016. www.nice.org.uk/guidance/ng52

A patient's perspective

After about two years of ongoing discomfort and lingering pain in the left side of my face and a hard swelling in my left groin, I was finally referred to the hospital by my GP. The first biopsy of the swelling of my cheek was inconclusive, and an operation to remove the lump followed. I was diagnosed with follicular lymphoma and immediately referred to the oncology clinic. I started chemotherapy with R-CVP. The side effects of the chemotherapy set in quickly—nausea, vomiting, constipation, weakness, and hair loss. Hair loss was my least concern, it will grow again. After six sessions of chemotherapy, a CT scan showed clearance of the disease. I was in remission.

From then on, I had regular checks. In the run-up to each, I was terrified that I would find out my lymphoma had returned. In 2011 it did. I had noticed for some time a swollen leg. I also had a skin rash on hands and lower arms. My GP had no explanation for it and suggested medication that might make me feel better. Since the next oncology check was due, I decided to wait until then. A CT scan and a biopsy were arranged.

This time the diagnosis was high grade lymphoma. My previous follicular lymphoma had now "transformed" into something more aggressive, a large mass in the right side of my pelvis near the uterus. R-CHOP was prescribed. It was a severe treatment. I had two blood transfusions during the treatment, followed by a course of radiotherapy. The side effects seemed much worse, but I was in remission again. This time it lasted over five years. The consultant suggested discharge, which I declined. I was paranoid and I was watching every slight difference in my body.

Then I detected a lump in my neck under my chin. Another CT scan and a biopsy confirmed the original follicular lymphoma was back, but just in one place. This time I had radiotherapy. The lump disappeared, but a new one on my upper gum started to grow. It was cut out, and now it was high grade lymphoma again. One shot of radiotherapy seems to have done the trick. My last check was clear, and I am in remission again and dealing with my paranoia.

Education into practice

- When you last saw, for an unrelated reason, a patient who had been treated for lymphoma, to what extent did you consider their fear of relapsing lymphoma when discussing their current presenting symptoms?

How patients were involved in the creation of this article

When designing the content of this article, we sought input from the patient group "Living with Follicular Lymphoma" and posed the question: "What do non-specialist doctors need to know about lymphoma?" We received over 70 responses from patients, relatives, and carers. These indicated a need for information on the disease, how it presents, and treatment options. They also suggested emphasising the emotional impact of the diagnosis, and where to get help, support, and education. We have attempted to address these points.

The manuscript was reviewed by a patient who had received treatment for high grade lymphoma and by a general practitioner. Their comments were incorporated into the final version, and the patient provided "A patient's perspective."

Contributors: All authors were involved in the design and writing of this manuscript.

Competing interests: We have read and understood the BMJ Group policy on declaration of interests and declare the following: DJH has received funding from Gilead Sciences for research on tumour biology and preclinical models of non-Hodgkin lymphoma.

Patient consent obtained.

Provenance and peer review: Commissioned; externally peer reviewed.

1 Swerdlow SH, Campo E, Pileri SA, etal . The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood* 2016;127:2375-90. 10.1182/blood-2016-01-643569 26980727
2 Cancer Research UK (CRUK). Non-Hodgkin lymphoma statistics. www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/non-hodgkin-lymphoma.
3 Smith A, Howell D, Patmore R, Jack A, Roman E. Incidence of haematological malignancy by sub-type: a report from the Haematological Malignancy Research Network. *Br J Cancer* 2011;105:1684-92. 10.1038/bjc.2011.450 22045184
4 Smith A, Crouch S, Lax S, etal . Lymphoma incidence, survival and prevalence 2004-2014: sub-type analyses from the UK's Haematological Malignancy Research Network. *Br J Cancer* 2015;112:1575-84. 10.1038/bjc.2015.94 25867256
5 International Agency for Research on Cancer. GLOBOCAN 2012: estimated cancer incidence, mortality and prevalence worldwide in 2012. 2013. http://globocan.iarc.fr.
6 Müller AM, Ihorst G, Mertelsmann R, Engelhardt M. Epidemiology of non-Hodgkin's lymphoma (NHL): trends, geographic distribution, and etiology. *Ann Hematol* 2005;84:1-12. 10.1007/s00277-004-0939-7 15480663
7 Shaffer AL3rd, Young RM, Staudt LM. Pathogenesis of human B cell lymphomas. *Annu Rev Immunol* 2012;30:565-610. 10.1146/annurev-immunol-020711-075027 22224767
8 Parkin DM. 11. Cancers attributable to infection in the UK in 2010. *Br J Cancer* 2011;105(Suppl 2):S49-56. 10.1038/bjc.2011.484 22158321
9 Morton LM, Slager SL, Cerhan JR, etal . Etiologic heterogeneity among non-Hodgkin lymphoma subtypes: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. *J Natl Cancer Inst Monogr* 2014;2014:130-44. 10.1093/jncimonographs/lgu013 25174034
10 Brown KF, Rumgay H, Dunlop C, etal . The fraction of cancer attributable to modifiable risk factors in England, Wales, Scotland, Northern Ireland, and the United Kingdom in 2015. *Br J Cancer* 2018;118:1130-41. 10.1038/s41416-018-0029-6 29567982
11 Gurney KA, Cartwright RA. Increasing incidence and descriptive epidemiology of extranodal non-Hodgkin lymphoma in parts of England and Wales. *Hematol J* 2002;3:95-104. 10.1038/sj.thj.6200154 12032871
12 Chaganti S, Illidge T, Barrington S, etal. British Committee for Standards in Haematology. Guidelines for the management of diffuse large B-cell lymphoma. *Br J Haematol* 2016;174:43-56. 10.1111/bjh.14136 27196701
13 Lister TA, Crowther D, Sutcliffe SB, etal . Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. *J Clin Oncol* 1989;7:1630-6. 10.1200/JCO.1989.7.11.1630 2809679
14 Sehn LH, Berry B, Chhanabhai M, etal . The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. *Blood* 2007;109:1857-61. 10.1182/blood-2006-08-038257 17105812
15 National Institute for Health and Care Excellence. Suspected cancer: recognition and referral (NICE guideline NG12). Chapter 1: Recommendations organised by site of cancer. 2015. www.nice.org.uk/guidance/ng12/chapter/1-Recommendations-organised-by-site-of-cancer.
16 Coiffier B, Lepage E, Briere J, etal . CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med* 2002;346:235-42. 10.1056/NEJMoa011795 11807147
17 Pfreundschuh M, Trümper L, Osterborg A, etal. MabThera International Trial Group. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. *Lancet Oncol* 2006;7:379-91. 10.1016/S1470-2045(06)70664-7 16648042
18 Cunningham D, Hawkes EA, Jack A, etal . Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: a phase 3 comparison of dose intensification with 14-day versus 21-day cycles. *Lancet* 2013;381:1817-26. 10.1016/S0140-6736(13)60313-X 23615461
19 Chiappella A, Martelli M, Angelucci E, etal . Rituximab-dose-dense chemotherapy with or without high-dose chemotherapy plus autologous stem-cell transplantation in high-risk diffuse large B-cell lymphoma (DLCL04): final results of a multicentre, open-label, randomised, controlled, phase 3 study. *Lancet Oncol* 2017;18:1076-88. 10.1016/S1470-2045(17)30444-8 28668386
20 Maurer MJ, Ghesquières H, Jais JP, etal . Event-free survival at 24 months is a robust end point for disease-related outcome in diffuse large B-cell lymphoma treated with immunochemotherapy. *J Clin Oncol* 2014;32:1066-73. 10.1200/JCO.2013.51.5866 24550425
21 Young RC, Longo DL, Glatstein E, Ihde DC, Jaffe ES, DeVita VTJr. The treatment of indolent lymphomas: watchful waiting v aggressive combined modality treatment. *Semin Hematol* 1988;25(Suppl 2):11-6.2456618
22 Brice P, Bastion Y, Lepage E, etal . Comparison in low-tumor-burden follicular lymphomas between an initial no-treatment policy, prednimustine, or interferon alfa: a randomized study from the Groupe d'Etude des Lymphomes Folliculaires. Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol* 1997;15:1110-7. 10.1200/JCO.1997.15.3.1110 9060552
23 Ardeshna KM, Smith P, Norton A, etal. British National Lymphoma Investigation. Long-term effect of a watch and wait policy versus immediate systemic treatment for asymptomatic advanced-stage non-Hodgkin lymphoma: a randomised controlled trial. *Lancet* 2003;362:516-22. 10.1016/S0140-6736(03)14110-4 12932382
24 Ardeshna KM, Qian W, Smith P, etal . Rituximab versus a watch-and-wait approach in patients with advanced-stage, asymptomatic, non-bulky follicular lymphoma: an open-label randomised phase 3 trial. *Lancet Oncol* 2014;15:424-35. 10.1016/S1470-2045(14)70027-0 24602760
25 McNamara C, Davies J, Dyer M, etal. Haemato-oncology Task Force of the British Committee for Standards in Haematology (BCSH)British Society for Haematology Committee. Guidelines on the investigation and management of follicular lymphoma. *Br J Haematol* 2012;156:446-67. 10.1111/j.1365-2141.2011.08969.x 22211428
26 Hiddemann W, Kneba M, Dreyling M, etal . Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. *Blood* 2005;106:3725-32. 10.1182/blood-2005-01-0016 16123223
27 Marcus R, Imrie K, Belch A, etal . CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. *Blood* 2005;105:1417-23. 10.1182/blood-2004-08-3175 15494430
28 Salles G, Mounier N, de Guibert S, etal . Rituximab combined with chemotherapy and interferon in follicular lymphoma patients: results of the GELA-GOELAMS FL2000 study. *Blood* 2008;112:4824-31. 10.1182/blood-2008-04-153189 18799723
29 Rummel MJ, Niederle N, Maschmeyer G, etal. Study group indolent Lymphomas (StiL). Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. *Lancet* 2013;381:1203-10. 10.1016/S0140-6736(12)61763-2 23433739
30 Salles G, Seymour JF, Offner F, etal . Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. *Lancet* 2011;377:42-51. 10.1016/S0140-6736(10)62175-7 21176949
31 Casulo C, Byrtek M, Dawson KL, etal . Early relapse of follicular lymphoma after rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone defines patients at high risk for death: an analysis from the National LymphoCare Study. *J Clin Oncol* 2015;33:2516-22. 10.1200/JCO.2014.59.7534 26124482
32 Al-Tourah AJ, Gill KK, Chhanabhai M, etal . Population-based analysis of incidence and outcome of transformed non-Hodgkin's lymphoma. *J Clin Oncol* 2008;26:5165-9. 10.1200/JCO.2008.16.0283 18838711
33 Ahmad SS, Reinius MA, Hatcher HM, Ajithkumar TV. Anticancer chemotherapy in teenagers and young adults: managing long term side effects. *BMJ* 2016;354:i4567. 10.1136/bmj.i4567 27604249
34 Blum KA. B-cell receptor pathway modulators in NHL. *Hematology Am Soc Hematol Educ Program* 2015;2015:82-91. 10.1182/asheducation-2015.1.82 26637705

Figures

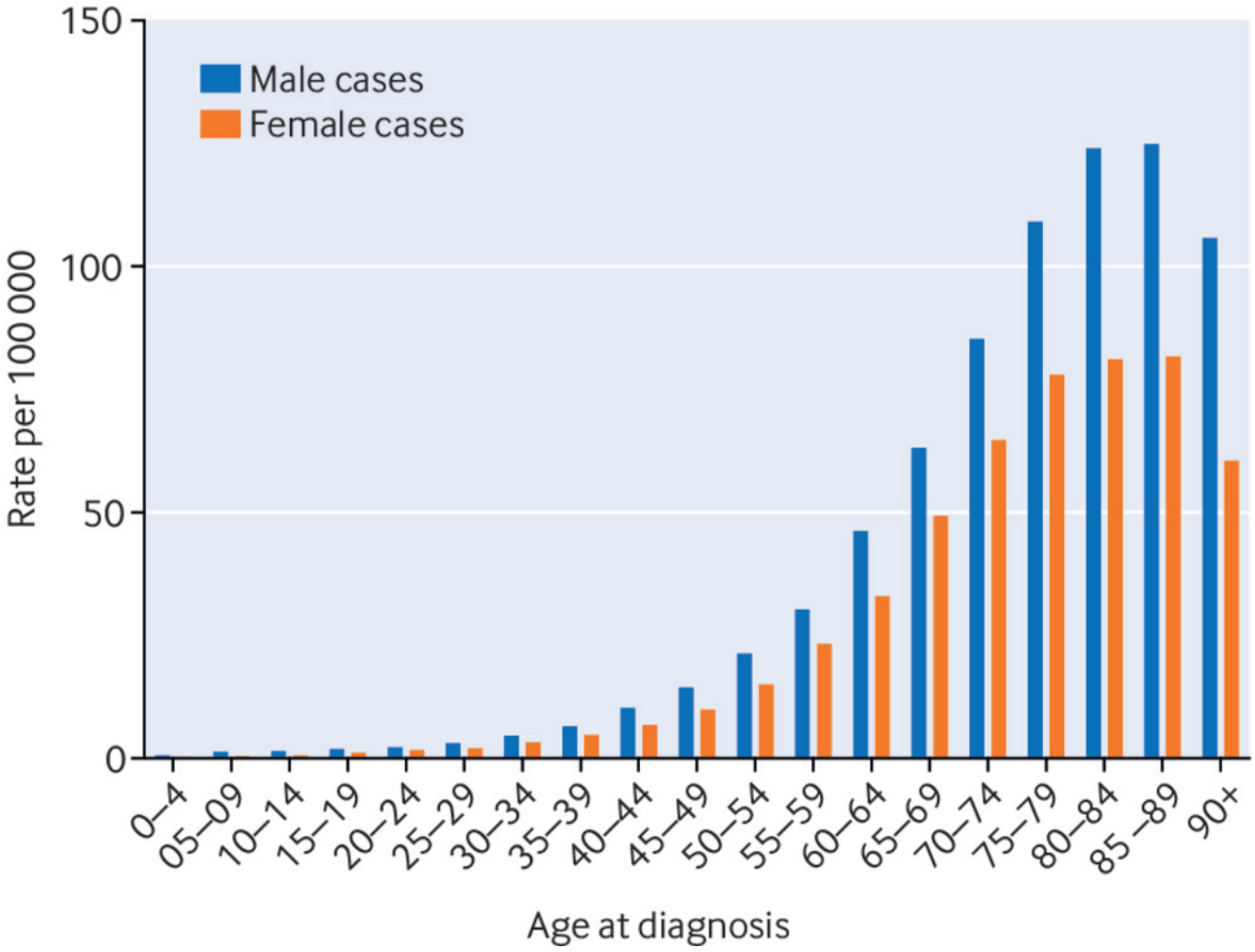

Fig 1 Incidence of non-Hodgkin lymphoma in the UK by age and sex (data modified from Cancer Research UK cancer incidence statistics 2014[2])

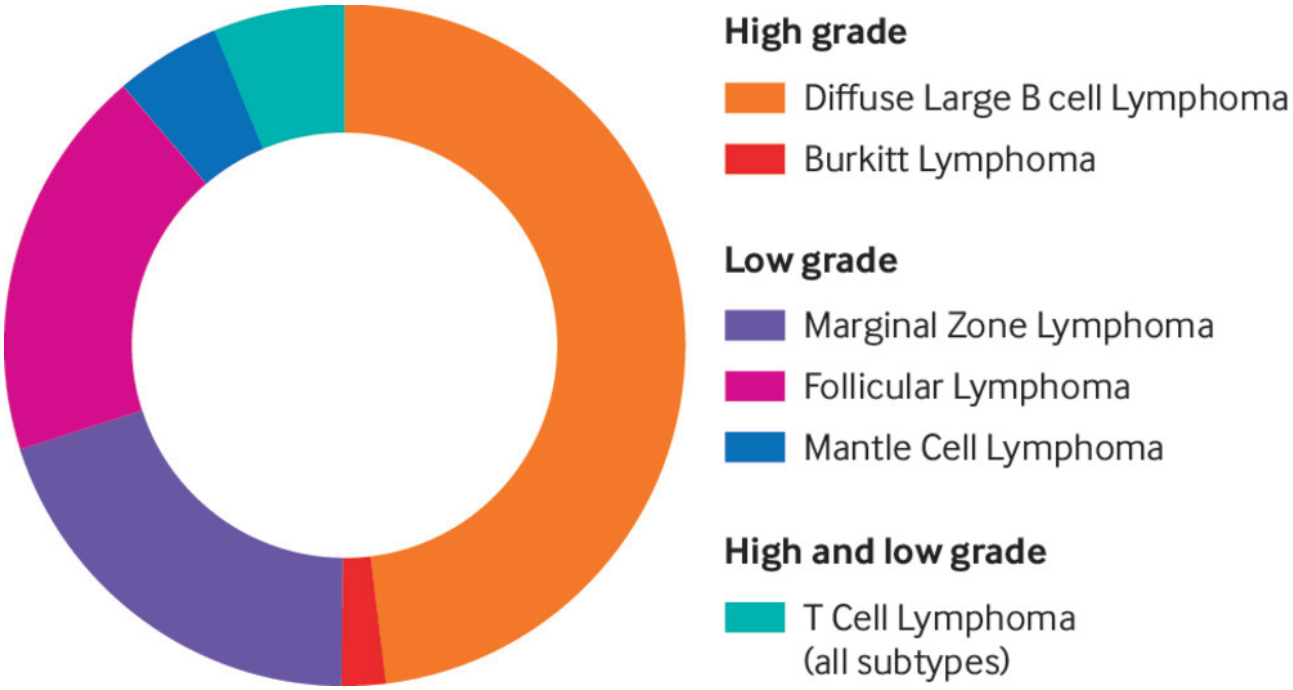

Fig 2 Relative incidence of the major categories of non-Hodgkin lymphoma (based on data from Smith et al[4])

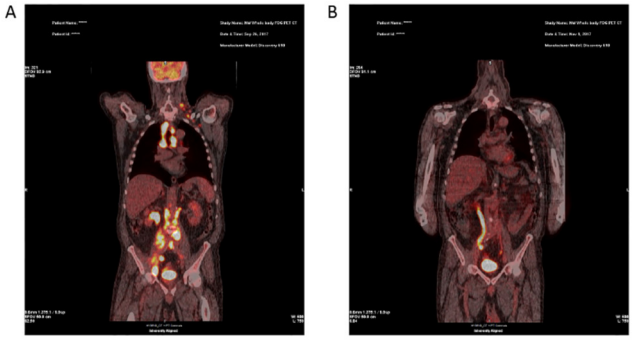

Fig 3 Positron emission tomography-computed tomography image of a patient with diffuse large B cell lymphoma (DLBCL) before (A) and after (B) treatment with two courses of R-CHOP chemotherapy. Areas of high intensity signal are seen in the left neck, mediastinum, and para-aortic and iliac lymph nodes. Resolution is seen in the interim treatment scan. The high intensity seen in the right ureter and bladder represents normal excretion of the tracer

Fig 4 Example of a "Chemo card" provided to patients undergoing chemotherapy. It includes emergency contact details and instructions to follow in the event of fever