Non-Hodgkin lymphoma

Kate R Shankland, James O Armitage, Barry W Hancock

Lymphomas are solid tumours of the immune system. Hodgkin’s lymphoma accounts for about 10% of all lymphomas, and the remaining 90% are referred to as non-Hodgkin lymphoma. Non-Hodgkin lymphomas have a wide range of histological appearances and clinical features at presentation, which can make diagnosis difficult. Lymphomas are not rare, and most physicians, irrespective of their specialty, will probably have come across a patient with lymphoma. Timely diagnosis is important because effective, and often curative, therapies are available for many subtypes. In this Seminar we discuss advances in the understanding of the biology of these malignancies and new, available treatments.

Epidemiology
Since non-Hodgkin lymphoma was last reviewed in The Lancet in 2003,1 biological understanding of these malignancies has advanced and treatments have improved. Around 12 294 people were diagnosed with non-Hodgkin lymphoma in the UK in 2009, and about 4452 people in the UK died of the disease in 2010.2,3 Corresponding numbers in the USA were 65 540 new cases (in 2007) and 20 210 deaths (in 2008).4 More than two-thirds of patients are 60 years and older.2,3 Non-Hodgkin lymphoma is the fifth most frequently diagnosed cancer in the UK, with roughly equal numbers of cases in men and women; however, because the population contains more women than men, the male age-standardised incidence per 100 000 men (17·7) is higher than the female incidence (12·8).2,3,5 The frequency of specific subtypes of lymphoma varies substantially by geographic region. For example, adult T-cell lymphoma associated with infection by human T-cell lymphotropic virus type 1 is much more frequent in east Asia than in other regions, as is nasal natural killer (NK)-cell or T-cell lymphoma associated with Epstein-Barr virus infection, whereas follicular lymphomas are more frequent in western Europe and North America.6 Diffuse large B-cell lymphoma, by contrast, is common worldwide. The incidence of non-Hodgkin lymphoma is increasing in many regions. In England, Scotland, and Wales, the age-standardised incidence has increased by 35% in 30 years (1988–2007).7,13 A similar trend has been recorded in the USA, with a 3·7% yearly percentage increase in the incidence of non-Hodgkin lymphoma between 1975 and 1991, and a 0·3% yearly increase from 1992 to 2007.8 The incidence in Brazil, India, Japan, Singapore, and western Europe has also increased.9,10 The reason for this long-term increase is unclear, although the emergence of HIV caused an additional increase in the incidence of non-Hodgkin lymphoma. Survival in England and Wales has improved substantially during the past four decades, with 50–8% of patients now expected to survive for longer than 10 years, compared with only 21–8% of those diagnosed in the early 1970s.11

Pathophysiology
Non-Hodgkin lymphomas encompass a heterogeneous group of cancers, 85–90% of which arise from B lymphocytes; the remainder derive from T lymphocytes or NK lymphocytes. This diverse group of malignancies usually develops in the lymph nodes, but can occur in almost any tissue, and ranges from the more indolent follicular lymphoma, to the more aggressive diffuse large B-cell and Burkitt’s lymphomas. Several different classification systems have been proposed that have grouped these malignancies according to their histological characteristics. The most recent system is the fourth edition of the WHO classification of tumours of haemopoietic and lymphoid tissues, published in 2008 (table I).9 It built upon the 2001 third edition and applied new findings from clinical and laboratory research to provide guidance on how to recognise early or in-situ lesions by assessment of B-cell

Search strategy and selection criteria
We searched PubMed for articles published in English since 2003, with the search terms “non-Hodgkin lymphoma” and “pathology”, “staging”, “prognosis”, and “treatment”. We searched reference lists of publications identified through the initial search for further citations. Text books were also used, from which we identified further citations.
clonal expansion and less often T-cell expansion, which seem to have a decreased potential for malignant transformation; appreciate patient age as a defining feature of some subtypes (eg, follicular and nodal marginal-zone lymphomas have variants that present almost exclusively in children and are clinically and biologically distinct from their counterparts affecting adults); and recognise borderline categories that share common morphological and immunophenotypical features with other subtypes of lymphoma—eg, primary mediastinal large B-cell lymphoma shares features with mediastinal nodular sclerosing classic Hodgkin’s lymphoma.

Despite this classification refinement, some groups remain heterogeneous, such as diffuse large B-cell lymphoma, not otherwise specified, and peripheral T-cell lymphoma, not otherwise specified. Further subclassification of these entities is a probable focus of future research.

To understand the mechanisms by which lymphomas might develop, the events that occur during normal B-cell maturation should be considered (figure). During normal B-cell development, cells arise from the germinal centre light zone where they become centrocytes (non-dividing B cells with a cleaved nucleus), which remove antigen from follicular dendritic cells and present it to T cells. Centrocytes can revert back to centroblasts, or differentiate into memory B cells or plasma cells. During this germinal centre reaction, cells undergo two distinct modifications to their DNA: class-switch recombination, whereby the immunoglobulin heavy-chain class might change from IgM to IgG, IgA, or IgE; and somatic hypermutation, in which the variable immunoglobulin (IgV) light chain mutates, thus modifying the affinity of a population of B cells for a particular antigen. These normal genetic modifications are a mechanism by which DNA damage can lead to lymphoma, and also allow the subtypes of lymphoma to be divided into non-Hodgkin lymphomas with and without IgV mutations.

Non-Hodgkin lymphomas without IgV mutations consist of pregerminal centre-derived non-Hodgkin lymphomas (eg, most cases of mantle-cell lymphoma) and other tumours arising from B cells that, although derived from the germinal centre, have not undergone somatic hypermutation (applies to about a third of cases of B-cell chronic lymphocytic leukaemia or small lymphocytic lymphoma). Non-Hodgkin lymphomas with IgV mutations that arise from germinal centre or postgerminal-centre B cells include Burkitt’s lymphoma, follicular lymphoma, lymphoplasmacytic lymphoma, mucosa-associated lymphoid tissue lymphoma, and diffuse large B-cell lymphoma.

The developmental biology of peripheral T-cell lymphoma is less well understood, and most subtypes are not

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Table 1: Subtypes of non-Hodgkin lymphoma according to the 2008 WHO classification

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Figure: Cellular origins and therapeutic targets of representative non-Hodgkin lymphomas

(A) B-cell and (B) T-cell. ALCL=anaplastic large-cell lymphoma (activated); BCL=B-cell lymphoma; CLL/SLL=chronic lymphocytic leukaemia/small lymphocytic lymphoma; DLBCL=diffuse large B-cell lymphoma; FL=follicular lymphoma; MCL=mantle-cell lymphoma (pre-germinal centre); MZL=marginal-zone mucosa-associated lymphoid tissue lymphomas (post-germinal centre); PTCL=peripheral T-cell lymphoma; TCL=T-cell lymphoma. Updated version of figure 1 from Evans’ and Hancock’s Seminar on non-Hodgkin lymphoma, published in The Lancet in 2003.

associated with distinct genetic or biological changes. Nevertheless, angioimmunoblastic T-cell lymphoma bears a close relation to the follicular helper T cell of the germinal centre, and the follicular variant of peripheral T-cell lymphoma, not otherwise specified, shares a similar phenotype, although this subtype differs genetically and clinically. Unlike B-cell lymphomas, recurring translocations that activate specific oncogenes are unusual in T-cell lymphomas, apart from the t(2;5) involving ALK seen in anaplastic large cell lymphoma. However, gene expression profiling of peripheral T-cell lymphomas has shown characteristic patterns of gene expression in the major subtypes, with the exception of peripheral T-cell lymphoma, not otherwise specified. Most nodal peripheral T-cell lymphomas seem to be related to effector T cells.6

Unlike most solid tumours, which typically have sub-stantial genetic instability, lymphomas generally have a stable genome. Rather, chromosomal translocations, which typically occur in malignancies of the haemopoietic system, are implicated.2 These translocations typically result in the presence of a proto-oncogene in the proximity of the chromosomal recombination sites. For example, the genetic hallmark of follicular lymphoma is the t(14;18) chromosomal translocation, which causes the juxtaposition of the BCL2 gene on chromosome 18 to the transcriptionally active immunoglobulin heavy-chain region on chromosome 14. This translocation can be detected in 80–90% of cases, and upregulates BCL2, which increases the apoptotic threshold and prevents programmed cell death.14 A similar process occurs in Burkitt’s lymphoma, which is characterised by the dysregulation of MYC on chromosome 8, most often by the juxtaposition of MYC with the immunoglobulin heavy locus on chromosome 14 via a t(8;14) translocation. In mantle-cell lymphoma, the cyclin-D1 region of chromosome 11 translocates to the same immunoglobulin heavy locus on chromosome 14.

Clinical presentation and staging

Clinical presentation is dependent on the site of involvement, natural history of the lymphoma subtype, and presence or absence of B symptoms (weight loss >10%, night sweats, body temperature >38°C). Two-thirds of patients present with painless lymphadenopathy, which is more often generalised than in Hodgkin’s lymphoma.29 Low-grade lymphomas typically present with peripheral lymphadenopathy that can vary in size. The more aggressive lymphomas can cause fulminating symptoms and signs needing prompt assessment and treatment.

In most solid tumours, advanced stage of disease often correlates with poor prognosis, but this association is not always noted with lymphoma. Non-Hodgkin lymphoma is staged with the Ann Arbor classification system, which was originally designed for Hodgkin’s lymphoma in 1971 (table 2).20 CT is the standard means of disease assessment above and below the diaphragm, replacing chest radiography, lymphangiography, and staging laparotomy. MRI is better than CT at detecting CNS and bone diseases.19,2 PET scanning with 2-[18F]fluoro-2-deoxy-D-glucose (FDG), a glucose analogue labelled with a positron emitter, is increasingly being used in the management of lymphomas. Different subtypes of non-Hodgkin lymphoma exhibit varied avidity for FDG, with the most common subtypes (diffuse large B-cell, follicular, and mantle-cell lymphomas) believed to be routinely FDG avid, whereas extranodal marginal-zone, small lymphocytic, and T-cell non-Hodgkin lymphomas are variably FDG avid.19,22,23 In subgroups that are routinely avid, PET scanning detects disease with a sensitivity of 80% and a specificity of 90%.19,22,24,25 Pretreatment PET scans can result in upstaging; however, PET scans are most widely used to assess response to therapy.

Any organ can be the primary site of non-Hodgkin lymphoma. However, the gastrointestinal tract is the most frequent extranodal site in non-Hodgkin lymphoma, and the stomach is the most frequently implicated part of the gastrointestinal tract. Gastric lymphomas are usually mucosa-associated lymphoid tissue lymphomas, or diffuse large B-cell lymphoma on a background of
mucosa-associated lymphoid tissue lymphoma. Endoscopic ultrasound might be used for part of the initial staging. Lymphoma of the stomach often coexists with lymphoma of the Waldeyer’s ring, so this association should also be assessed in patients with gastrointestinal involvement, and vice versa. Mantle-cell lymphomas are associated with the colon in most cases when masked biopsies are done, and occasionally present with lymphomatous polyposis. Non-Hodgkin lymphoma is the most common testicular tumour in men older than 60 years. These testicular tumours are usually aggressive B-cell tumours, and sites of other involvement include the contralateral testis and the CNS.

The International Prognostic Index (IPI) is the most widely used prognostic model for patients with non-Hodgkin lymphoma. First introduced for aggressive non-Hodgkin lymphoma, clinical features independently associated with survival were age (≤60 years vs >60 years), lactate dehydrogenase concentration (normal vs abnormal), Eastern Cooperative Oncology Group performance status (≤2 vs ≥2), Ann Arbor stage (I/II vs III/IV), and number of extranodal sites implicated (≤one vs >one). From this, four risk groups were delineated: low risk (zero to one clinical feature), low-intermediate risk (two features), high-intermediate risk (three features), and high risk (four to five features). When applied to 2031 patients, these risk groups had 5-year survivals of 73%, 51%, 43%, and 26%, respectively. Age is a particularly important prognostic marker, and has been repeatedly associated with poorer outcomes. However, elderly patients who are able to receive full-dose chemotherapy have survival rates similar to their younger counterparts. The advent of the anti-CD20 monoclonal antibody rituximab (figure), the IPI has been revised for diffuse large B-cell lymphoma. The IPI for this lymphoma is still to be validated in large prospective trials, but it seems to be a legitimate prognostic method since the introduction of rituximab, although it does not identify patients with low survival prospects.

Biological heterogeneity within diffuse large B-cell lymphoma is substantial, and gene expression profiling has identified two broad subgroups: those of germinal centre origin, known as germinal centre B-cell like lymphomas (typically CD10+ and BCL6+); and those arising from cells resembling activated B-cells (typically IRF4/MUM1+/- and CD138+). This distinction has clinical relevance, because the 5-year survival for the germinal centre subgroup was 76% versus 16% for the activated B-cell group. This distinction is still relevant in the era of rituximab plus cyclophosphamide, vincristine, doxorubicin, and prednisolone (R-CHOP). An assessment of 153 patients given R-CHOP showed that both subgroups showed increased survival compared with historical controls treated with CHOP, but the germinal centre subgroup had a 3-year overall survival of 86% compared with 68% in the activated B-cell group.

The IPI is less useful in follicular lymphoma, because fewer patients present with high-risk disease, thus prompting the evolution of the Follicular Lymphoma International Prognostic Index (FLIPI). Three of the five prognostic variables are identical to those in the IPI—namely, age, Ann Arbor stage, and serum lactate dehydrogenase concentration. The two other prognostic markers are haemoglobin concentration (<12 g/L vs ≥12 g/L) and number of nodal sites involved (>four vs ≤four). Patients are thus stratified into one of three prognostic groups: low (zero to one variable), intermediate (two variables), or high (three or more). These groups have 10-year survivals of 71%, 51%, and 36%, respectively. The FLIPI has yet to be prospectively assessed in the rituximab era.

**Treatment of B-cell lymphomas**

**Small B-cell lymphocytic lymphoma and chronic lymphocytic leukaemia**

Historically, small B-cell lymphocytic lymphoma and chronic lymphocytic leukaemia were believed to be two distinct diseases, but they are now considered to be different clinical manifestations of the same disease. This non-Hodgkin lymphoma is mainly a disease of elderly people, with a median age of 72 years at diagnosis of chronic lymphocytic leukaemia in the USA. The clinical course of this disease often begins with asymptomatic lymphocytosis, with about a quarter of patients diagnosed after a routine blood count. Other common presentations include painless lymphadenopathy and hepatosplenomegaly. Several randomised trials have compared the efficacy of chlorambucil with combination chemotherapy including anthracycline-containing combinations, but no survival advantage with combination treatment was noted. The purine analogues cladribine and particularly fludarabine have activity against small B-cell lymphocytic lymphoma and chronic lymphocytic leukaemia. Findings from one large trial showed an improvement in overall survival in patients with
previously untreated chronic lymphocytic leukaemia given fludarabine, cyclophosphamide, and rituximab compared with those given fludarabine and cyclophosphamide alone.\textsuperscript{46} Bendamustine is an alternative first-line treatment option for patients for whom fludarabine-containing regimens are not appropriate. Three monoclonal antibody therapies have been approved for use in small B-cell lymphocytic lymphoma and chronic lymphocytic leukaemia. Rituximab is one, but it has shown lower response rates in this disease than in other B-cell lymphomas.\textsuperscript{46–48} Alemtuzumab, an anti-CD52 monoclonal antibody (figure) is approved in the USA and Europe as third-line therapy for cases of small B-cell lymphocytic lymphoma and chronic lymphocytic leukaemia that are fludarabine refractory.\textsuperscript{49} In 2007, the US Food and Drug Administration (FDA) also approved alemtuzumab for previously untreated cases of this disease.\textsuperscript{50} Ofatumumab, a human monoclonal antibody to the CD20 protein, has FDA approval and conditional approval in Europe for the treatment of refractory chronic lymphocytic leukaemia.\textsuperscript{51} Radiotherapy can be used to palliate symptoms of bulky lymphadenopathy in this lymphoma subtype.

**Follicular lymphoma**

Follicular lymphoma is the second most common lymphoma in the USA and western Europe, accounting for about 20% of all non-Hodgkin lymphomas.\textsuperscript{52} The median age at diagnosis is 60 years.\textsuperscript{53} Follicular lymphoma often presents with painless peripheral lymphadenopathy, which may increase and decrease in size. Staging investigations usually identify disseminated disease, with involvement of the spleen (in 40% of cases), liver (50%), and bone marrow (60–70%).\textsuperscript{54} The clinical course can vary—some patients might not need treatment for several years, whereas others have massive nodal or organ involvement needing intervention. Follicular lymphoma has traditionally been graded between 1 and 3 according to the proportion of centroblasts present. However, the clinical significance of the division of grades 1 and 2 is questionable, because clinical outcomes are similar. The 2008 WHO classification therefore combines cases with few centroblasts as follicular lymphoma grade 1–2 (low grade). Grade 3 is subdivided into 3A and 3B according to whether sheets of centroblasts are present (3B). In clinical practice, the ability to separate grades 3A and 3B is a histological challenge. Many oncologists treat all patients with grade 3 follicular lymphoma in a manner similar to those with diffuse large B-cell lymphoma with R-CHOP. However, this method is controversial, and others believe that all patients with follicular lymphoma should be treated in the same way irrespective of grade.

Historically, the median survival of patients presenting with advanced stage follicular lymphoma was 10 years, although since the inclusion of monoclonal antibody treatment, survival seems to have increased.\textsuperscript{55,56} Histological transformation from follicular to a diffuse aggressive lymphoma occurs in 10–70% of cases, and is associated with a poor prognosis.\textsuperscript{57,58}

Despite the fact that prognosis is measured in years, follicular lymphoma is not usually curable with conventional treatment. The exception is the few patients who present with limited-stage disease (stage I or II), who can be cured with radiotherapy, a few patients with exceptional responses to initial chemotherapy regimens, and some patients after autologous or allogeneic haemopoietic stem-cell transplantation as second-line therapy.\textsuperscript{59–61} When to begin treatment is a matter of debate, with quality of life being a major determining factor. No evidence suggests that immediate treatment of asymptomatic patients improves their survival. Before the introduction of rituximab, no therapy had been shown to improve overall survival with advanced disease. Some patients can be treated with rituximab alone. Other treatment regimens include oral chlorambucil, fludarabine, or bendamustine; or combination chemotherapies with cyclophosphamide, vincristine, and prednisolone; or anthracycline-containing regimens such as CHOP. All patients should receive rituximab as part of their initial treatment for advanced stage follicular lymphoma, since findings from phase 3 randomised controlled trials have shown improved overall survival with the addition of this agent to chemotherapy.\textsuperscript{62–64} Maintenance rituximab after induction prolongs remission duration,\textsuperscript{65–67} and future analysis will establish whether this prolonged remission translates into improved overall survival. Radiolabelled monoclonal antibodies are being tested as part of initial treatment regimens for follicular lymphoma. \textsuperscript{68} \textsuperscript{69}⁹⁰Y-ibritumomab tiuxetan combines an anti-CD20 monoclonal antibody and localised yttrium-90 radiation (figure). Its use as consolidation therapy after initial induction chemotherapy has been favourably compared with induction chemotherapy alone.\textsuperscript{62} \textsuperscript{70} ¹³¹I-tositumomab is approved for use in the USA.

No convincing data exist that support myeloablative chemotherapy and autologous stem-cell transplantation in follicular lymphoma in first remission.\textsuperscript{64,71} Palliative radiotherapy might be useful in advanced disease, particularly to relieve pressure symptoms from a localised mass, which might cause spinal cord or nerve root compression, or other local symptoms.

**Mantle-cell lymphoma**

The median age at diagnosis of mantle-cell lymphoma is 58 years. Most patients present with disseminated lymphadenopathy, although gastrointestinal tract involvement is common and mantle-cell lymphoma is the most common lymphoma to cause lymphomatous polypsis. Occasionally patients will present with only blood and bone marrow involvement, which can be confused with chronic lymphocytic leukaemia.

Although classified as indolent, mantle-cell lymphoma has one of the poorest prognoses of the various subtypes of lymphoma.\textsuperscript{73} Most patients are symptomatic and need
treatment at diagnosis, although a few are asymptomatic and can be observed for a period without treatment. Standard treatment is combination chemotherapy with or without rituximab, and median overall survival is around 3 years. Studies assessing the addition of rituximab to standard chemotherapy have shown significant improvements in complete response rates and time-to-treatment failure, but disappointingly this addition has not led to an improvement in overall survival.\textsuperscript{64,65} Regimens incorporating high-dose cytarabine might lead to improved outcomes.\textsuperscript{66} Several studies have assessed the role of high-dose chemotherapy and autologous stem-cell transplantation in patients with mantle-cell lymphoma. The extent of benefit varies between studies, and at present autologous stem-cell transplantation should not be regarded as curative for mantle-cell lymphoma, because late relapses are recorded.\textsuperscript{67} For the rare, young patient with an HLA-matched donor, allogeneic haemopoietic stem-cell transplantation can be curative.

\textbf{Marginal-zone lymphoma}

Mucosa-associated lymphoid tissue lymphoma is the third most common subtype of non-Hodgkin lymphoma. The most frequent site is the stomach, but these extranodal marginal-zone lymphomas can involve almost any organ. \textit{Helicobacter pylori} infection is implicated in the pathogenesis of gastric mucosa-associated lymphoid tissue lymphoma, and remission can be achieved with eradication of the bacteria in many patients, although 30–40\% of cases do not respond to antibiotic therapy.\textsuperscript{68} Localised mucosa-associated lymphoid tissue lymphomas at all sites can sometimes be effectively treated with radiotherapy or surgery. Patients with disseminated disease usually respond to rituximab alone or chemotherapy regimens incorporating rituximab. Patients with widespread marginal-zone lymphoma involving the lymph nodes and bone marrow are usually diagnosed with nodal marginal-zone lymphoma and treated in a similar manner to patients with follicular lymphoma. A rare subtype, splenic marginal-zone lymphoma, involves the spleen, blood, and bone marrow. This subtype has traditionally been treated in the past with splenectomy, but rituximab also seems to be effective.

\textbf{Diffuse large B-cell lymphoma}

Diffuse large B-cell lymphoma is the most common subtype of non-Hodgkin lymphoma, representing about a third of cases. There are many subtypes of diffuse large B-cell lymphoma recognised in the WHO classification (panel). Mediastinal diffuse large B-cell lymphoma presents as a mediastinal mass and most often occurs in young women. Plasmablastic diffuse large B-cell lymphoma is a histological variant that is frequently detected in patients with HIV infection, and involves the head and neck. This subtype does not usually express CD20 and, thus, does not benefit from treatment with rituximab.

Diffuse large B-cell lymphoma is localised in about 25\% of patients. Before 1980, radiotherapy was given to the affected region alone, but several trials in the early 1980s compared radiation alone with radiation plus combination chemotherapy with cyclophosphamide, vincristine, and prednisolone or CHOP.\textsuperscript{70–72} Findings from these trials showed an improvement in overall survival for dual modality therapy, which became the standard treatment.\textsuperscript{70–72} These studies all took place in the prerituximab era. The MabThera International Trial of 824 patients from 18 countries assessed the addition of rituximab to CHOP chemotherapy versus CHOP chemotherapy alone, with radiotherapy allowed in both groups. Trial participants were young with a good disease prognosis, although not all had localised disease. Patients who received R-CHOP had an improved 3-year overall survival compared with those randomly assigned to CHOP (93\% [95\% CI 90–95] vs 84\% [80–88]; log rank \(p=0.0001\)).\textsuperscript{73}

Disseminated disease is the common presentation of diffuse large B-cell lymphoma, and in the prerituximab era more than a third of patients with this form of the disease were cured with chemotherapy alone, most by the CHOP regimen. Again, the most important advance in treatment was the addition of rituximab to chemotherapy. Findings from several randomised trials have shown significant increases in overall survival in patients who received rituximab plus chemotherapy.\textsuperscript{73,74} A retrospective study in British Columbia, Canada, compared outcomes of 140 patients given CHOP-like chemotherapy in the prerituximab era with outcomes of 152 patients treated in the rituximab era. The addition of rituximab to CHOP-like chemotherapy improved overall survival at 2 years from 52\% to 78\%.\textsuperscript{75} Data from the Surveillance, Epidemiology, and End Results (SEER) registry comparing survival in all patients with diffuse large B-cell lymphoma from 1973–2004 show that survival has substantially improved since the advent of rituximab; median overall survival for 1973–79 was 15 months, 1980–89 was 18 months, 1990–99 was 20 months, and 2000–04 was 47 months.\textsuperscript{76} The use of rituximab with increasingly intensive chemotherapy regimens looks promising and is being assessed in randomised trials.

About 30–40\% of patients will relapse after first-line chemotherapy, Salvage chemotherapy regimens are used in combination with rituximab, but rarely lead to longlasting progression-free survival. These salvage regimens are often used to achieve remission before the use of high-dose chemotherapy and autologous stem-cell transplantation. Because this subgroup includes a heterogeneous mix of diseases with varied natural histories, the future is likely to include different primary treatment protocols according to risk of relapse.

\textbf{Burkitt’s lymphoma}

Burkitt’s lymphoma occurs endemically in parts of Africa, and sporadically around the world. Nowadays, most patients with Burkitt’s lymphoma can be cured, but
a shortage of access to health-care resources affects outcomes in developing countries. Burkitt’s lymphoma has a very high proliferation index, which makes prompt diagnosis and initiation of therapy very important to increase chances of survival. Principles of chemotherapy delivery for Burkitt’s lymphoma include maintenance of high dose intensity and the use of alternating non-crossresistant regimens to prevent the emergence of drug resistance. Patients are at risk of CNS relapse, and the use of high-dose methotrexate and cytarabine has helped to reduce this risk.77

Treatment of T-cell lymphomas and precursor B-cell or T-cell lymphomas

Lymphomas of mature T cells are much less common than their B-cell counterparts. A few cutaneous T-cell lymphomas, including mycosis fungoides, cutaneous anaplastic large-cell lymphoma, and lymphomatoid papulosis, are indolent. Other lymphomas of mature T cells (often referred to as peripheral T-cell lymphomas) are aggressive disorders. Some subtypes present rare but interesting clinical syndromes and others (eg, adult T-cell lymphoma and nasal NK-cell or T-cell lymphoma) are common in east Asia but rare in western Europe and North America.78 We discuss three subtypes that are frequently seen in Europe and America: peripheral T-cell lymphoma, not otherwise specified; angioimmunoblastic T-cell lymphoma; and anaplastic large-cell lymphoma.

Peripheral T-cell lymphoma, not otherwise specified, is the most common of the peripheral T-cell lymphomas and is made up of a heterogeneous group of diseases that are usually aggressive. These diseases often present in a manner similar to that of diffuse large B-cell lymphoma, and a diagnosis is established only when the haematopathologist reviews the biopsy sample. Peripheral T-cell lymphomas, not otherwise specified, most commonly present as nodal disease in elderly people, but can be extranodal. Combination chemotherapy can achieve long-term survival in 12–45% of patients.79,80 These neoplasms are often refractory to anthracyclines.78

Angioimmunoblastic T-cell lymphoma is the second largest group of peripheral T-cell lymphomas and usually presents with generalised lymphadenopathy, hepatosplenomegaly, skin rash, and constitutional symptoms in elderly patients. This lymphoma, which seems to arise from follicular helper T cells, often harbours Epstein-Barr virus-infected B cells that can become monoclonal, and occasionally patients develop diffuse large B-cell lymphoma simultaneously. Combination chemotherapy with anthracycline-containing regimens has led to long-term survival in around a third of patients.81,82 Patients with recurrent disease sometimes respond to immune manipulations such as ciclosporin, and a few patients seem to benefit from transplantation.

Anaplastic large-cell lymphoma was first described by Stein and colleagues in 1985.83 Various subtypes have subsequently been described, and overall it accounts for 3–8% of all lymphomas and 10–15% of all childhood lymphomas.84 In North America, treatment is generally the same as that used for diffuse large B-cell lymphoma, whereas in Europe, treatment varies, with some centres mirroring American practice, and others using chemotherapy protocols that are longer.85–87 All anaplastic large-cell lymphomas are CD30 positive. A subset of these lymphomas harbour the t(2;5) translocation and over-express anaplastic lymphoma kinase (ALK). These patients are usually younger and have excellent prognosis with a greater than 50% cure rate. Patients with so-called ALK-negative anaplastic large-cell lymphoma have a better outlook than do those with other subtypes of peripheral T-cell lymphoma, but fewer than half will be cured.88 The FDA has approved the antibody–drug conjugate brentuximab vedotin for the treatment of anaplastic large-cell lymphoma. This agent combines the anti-CD30 monoclonal antibody brentuximab and the antitubulin agent monomethylauristatin E (vedotin)89 (figure). Lymphoblastic lymphoma is a precursor B-cell or T-cell lymphoma and the lymphomatous presentation of acute lymphoblastic leukaemia. This rare subtype of lymphoma is most often seen in children and young adults. Treatment usually includes acute leukaemia-like regimens.89

Reassessment after treatment

PET scanning is more accurate than is CT scanning in the reassessment of patients after completion of treatment because it can distinguish between residual tumour and necrosis or fibrosis. Residual masses after therapy—which are not rare in retroperitoneal and mediastinal lymphomas—are frequently negative on PET scan. Guidelines suggest that these patients should be classed
as being in complete remission.\textsuperscript{91} Findings from prospective studies have shown that PET correlates well with patient outcome.\textsuperscript{92} PET has a positive predictive value of around 85\% in non-Hodgkin lymphoma.\textsuperscript{93–95} This value is higher than that for CT, which has a positive predictive value in aggressive lymphoma of 40–50\%.\textsuperscript{96} The negative predictive value of PET is about 85\% across studies.\textsuperscript{93–94} In practice, PET is a routine part of post-treatment assessment of patients with potentially curable lymphoma because further therapy is often needed if disease is residual—ideally, 6–8 weeks should pass from the completion of treatment to the PET scan to reduce the risk of a false-positive result.\textsuperscript{96}

**Future challenges**

The opportunities to improve the treatment for patients with non-Hodgkin lymphoma are encouraging. Improved use of PET might allow shortening of therapy for patients with very sensitive lymphomas and changing or intensification of treatment for those with more resistant disease. As understanding of the molecules or pathways that are targeted by both old and new drugs improves, regimens for individual patients will become available. A focus of research on T-cell lymphomas, similar to that applied during the past few decades for B-cell lymphomas, might yield similar advances. A review of non-Hodgkin lymphomas in 2022 will probably describe at least as much improvement as has been seen in the past decade.

**Contributors**

All authors took part in the review of published work, the writing and editing of the review, figure creation, and reference selection.

**Conflicts of interest**

JOA has been a consultant for Ziopharm, Seattle Genetics, Eisai, GlaxoSmithKline, Allos Therapeutics, Genentech, and Roche. BWH was, until 2009, taking part in studies done or supported by Seattle Genetics, Roche, and Genentech. KRS declares that she has no conflicts of interest.

**References**


