22.4.4 Non- Hodgkin lymphoma 5288 Vijaya Raj Bhatt

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section 22 Haematological disorders 5288 22.4.4 Non-Hodgkin lymphoma Vijaya Raj Bhatt and James O. Armitage ESSENTIALS Non-Hodgkin lymphomas comprise precursor lymphoid neo- plasms, mature B-cell neoplasms, and mature T-cell neoplasms. The aetiology of most cases is unknown, but increased risk is as- sociated with immune deficiencies, agricultural chemicals, auto- immune disorders, treated Hodgkin disease, and some infectious agents (e.g. Helicobacter pylori, human T-cell lymphoma/leu- kaemia virus-1, HIV, Epstein–Barr virus, and human herpesvirus-8). Incidence varies from 10 to 22 cases per 100 000 per year in dif- ferent populations. Presentation and diagnosis Patients with non-Hodgkin lymphoma most commonly present with lymphadenopathy, but other presentations include systemic symp- toms or those attributable to mediastinal or retroperitoneal masses or involvement. Diagnosis is typically based on expert evaluation of an adequate lymph node biopsy. Staging depends largely on deter- mining the anatomical extent of disease, with FDG positron emission tomography/CT scanning generally the preferable imaging modality. Treatment and prognosis For most patients, the goal of therapy is to achieve a complete remis- sion. Patients with definitely curable lymphomas, such as diffuse large B-cell lymphoma and Burkitt lymphoma, are almost always treated promptly with intensive regimens, for example, chemotherapy with CHOP (cyclophosphamide, doxorubicin, vincristine (Oncovin), and prednisone) plus the anti-CD20 monoclonal antibody rituximab. By contrast, follicular lymphoma is often not curable and the best treat- ment is not clear, with many physicians favouring no initial therapy in an asymptomatic patient. Patients who are not cured with initial therapy are candidates for what has been termed ‘salvage therapy’. For most patients, the only curative approach in this setting is haematopoietic stem cell trans- plantation, the toxicity of which

means that it is only sensibly offered to carefully selected patients. Various new agents, such as small mol- ecule kinase and BCL-2 inhibitors, and immune checkpoint inhibi- tors, offer hope for the future. Introduction Lymphomas are malignancies of lymphoid cells and almost al- ways present as solid tumours. They frequently respond to avail- able therapies, and a significant subset of patients who develop lymphomas can be cured. Lymphomas are usually divided into Hodgkin lymphoma and non-Hodgkin lymphoma (NHL). NHL consists of indolent lymphomas that grow slowly and are often asymptomatic until they reach an advanced stage, and aggres- sive lymphomas that can be life-threatening if not treated on a timely fashion. Epidemiology NHL is much more frequent than Hodgkin lymphoma, with more than 70 000 new cases being diagnosed in the United States of America each year, and about 12 000 in the United Kingdom. NHL increased in incidence at a higher rate than almost all other malignancies from 1950 to 2000, but recent data suggests that the incidence is stabilizing. In much of the world, it appears that the incidence of NHL is increasing, but the incidence still varies widely between countries. The incidence appears to be approximately 10 cases per 100 000 per year worldwide, 22 per 100 000 per year in the United Kingdom, and more than 19 per 100 000 per year in the United States of America. In the United States, the disease increased in frequency in patients of all ages, but more strikingly in elderly people, by approximately 4% per year between 1950 and the mid 1990s, although recent data suggest that the rate of increase may be stabilizing. The specific types of NHL vary in occurrence between coun- tries. For example, follicular lymphoma is more common in North America than in Europe or Asia. T-cell lymphomas have been seen more frequently in Asia, and certain types of T/natural killer (NK)-cell lymphomas such as angiocentric nasal lymphomas are common only in a few countries in Asia and Latin America. The explanation for this geographical difference is unclear. Aetiology The aetiology of most NHL is unknown. Various aetiological fac- tors, either proven or suggested to be associated with the develop- ment of NHL, are listed in Box 22.4.4.1. It is now clear that exposure to certain agriculture chemicals does increase the risk of this dis- ease. A variety of immune deficiencies, such as those associated with immunosuppression following organ transplantation and various hereditary immune deficiencies, are also associated with an increased risk of developing NHL. Patients with disorders of the immune system such as rheumatoid arthritis and systemic lupus erythematosus also appear to be at increased risk. A variety of infectious agents have been shown to be associated with the development of NHL. Gastric Helicobacter pylori infection is associated with the development of gastric mucosa-associated Box 22.4.4.1 Factors predisposing to the development of NHL • Immune deficiencies:

— Organ transplantation

— Inherited immune deficiencies

— AIDS • Agricultural chemicals • Autoimmune disorders:

— Rheumatoid arthritis

— Lupus erythematosus • Treated Hodgkin lymphoma • Infectious agents:

— Viruses: EBV, HTLV-1, HIV, HHV-8, HCV

— Bacteria: Helicobacter pylori, Chlamydia psittaci, Borrelia burgdorferi, Campylobacter jejuni EBV, Epstein–Barr virus; HCV, hepatitis C virus; HHV-8, human herpesvirus-8; HTLV-1, human T-cell leukaemia virus-1.

5289 22.4.4 Non-Hodgkin lymphoma lymphoid tissue (MALT) lymphoma, and eradication of the infec- tion by antibiotics can lead to regression of the lymphoma. Human T-cell lymphoma/leukaemia virus-1 (HTLV-1) appears to be the cause of a specific type of NHL, seen predominantly in southern Japan and the Caribbean, called adult T-cell lymphoma/leu- kaemia. Epstein–Barr virus (EBV) has been associated with Burkitt lymphoma in Africa, the development of aggressive B-cell lymph- omas in immunosuppressed patients, and certain aggressive T-cell lymphomas. Human herpesvirus-8 (HHV-8) has been closely asso- ciated with a rare diffuse large B-cell lymphoma called primary effu- sion lymphoma that is most frequently seen in immunosuppressed patients. HIV infection can lead to the development of aggressive B-cell lymphomas that are often EBV positive. An association be- tween hepatitis C virus (HCV) infection and the development of splenic or large B-cell lymphomas has been suggested. Similarly, the association of Chlamydia psittaci and ocular adnexal lymphomas has been reported. Other bacteria that have been associated with MALT lymphomas include Campylobacter jejuni (i.e. small bowel) and Borrelia burgdorferi (skin). Pathology The classification of NHL changed several times during the 20th cen- tury. The first popular classification proposed by Gall and Mallory divided lymphomas into giant follicular lymphoma, reticulum cell sarcoma, and lymphosarcoma. Both the lack of adequate clinical cor- relation and clear definitions of the entities led to further proposals. Henry Rappaport recognized the importance of growth pattern in the prognosis of NHL, and put forward his system that divided pa- tients into those with nodular (i.e. follicular) or diffuse lymphomas and those with large or small cell lymphomas. However, this system was proposed before the recognition that lymphomas were all ma- lignancies of lymphocytes and before the discovery of the existence of subtypes of lymphocytes. The advent of modern immunology led to new classification systems proposed by Lennert and colleagues in Europe and Lukes and Collins in the United States of America. The Kiel classification proposed by Lennert and colleagues became the most widely used system in Europe. An attempt to unify the clas- sifications of lymphomas led to the development of the Working Formulation. This is a compromise system taking major elements from the Rappaport classification, the Kiel classification, and the Lukes/Collins classification. It became widely used in the United States of America but less so in Europe. In the 1990s, a group of haematopathologists from Europe, North America, and other parts of the world proposed a new system not just based on morphology and immunophenotyping, but taking into account other genetic and biological information that had be- come available. In the 1990s, a number of ‘new’ lymphomas were discovered that did not fit into previous classification systems. These included mantle cell lymphoma, anaplastic large cell lymphoma, and MALT lymphomas. The Revised European/American Lymphoma (REAL) classification classified lymphomas based on clinical pathological syndromes (in other words, ‘real’ diseases) rather than simply morphology. This system was tested in a large inter- national study and shown to be more accurate than previous sys- tems and to have high clinical relevance. Leaders in the fields of both haematopathology and clinical haematology/oncology agreed on a modified REAL classification to be endorsed by the World Health Organization (WHO) and published as the WHO classification (Box 22.4.4.2). This, with some minor modifications published in 2016, is likely to be the major lymphoma classification for at least the next decade. The incidence of major lymphoma subtypes according to the WHO classification is listed in Table 22.4.4.1. Knowledge of Box 22.4.4.2 WHO classification

of NHL (2016) • Precursor lymphoid neoplasms:

— B-lymphoblastic leukaemia/lymphoma

— T-lymphoblastic leukaemia/lymphoma • Mature B-cell neoplasms:

— Chronic lymphocytic leukaemia/small lymphocytic lymphoma

— Splenic marginal zone lymphoma

— Lymphoplasmacytic lymphoma

— Extranodal marginal zone lymphoma of MALT

— Nodal marginal zone lymphoma

— Follicular lymphoma

— Primary cutaneous follicle centre lymphoma

— Mantle cell lymphoma

— Diffuse large B-cell lymphoma (DLBCL) of ABC and GC type: • T-cell/histiocyte-rich DLBCL • Primary cutaneous DLBCL leg type • Intravascular DLBCL • Plasmablastic lymphoma • Primary effusion lymphoma

— Primary mediastinal (thymic) DLBCL

— Burkitt lymphoma • Mature T-cell neoplasms:

— Adult T-cell leukaemia/lymphoma

— Extranodal NK/T cell lymphoma, nasal type

— Enteropathy associated T-cell lymphoma

— Hepatosplenic T-cell lymphoma

— Subcutaneous panniculitis-like T-cell lymphoma

— Mycosis fungoides

— Sézary’s syndrome

— Primary cutaneous CD30-positive T-cell lymphoproliferative disorders

— Peripheral T-cell lymphoma, not otherwise specified (NOS)

— Angioimmunoblastic T-cell lymphoma/T-follicular helper cell lymphomas

— Anaplastic large cell lymphoma, ALK positive

— Anaplastic large cell lymphoma, ALK negative Table 22.4.4.1 Worldwide relative frequency of occurrence of major subtypes of NHL Type of NHL Percentage of all NHL Diffuse large B cell 31 Follicular 22 Small lymphocytic/chronic lymphocytic leukaemia 6 Mantle cell 6 Peripheral T cell 6 MALT 5 Anaplastic large cell lymphoma 2 Lymphoblastic 2 Burkitt <1 MALT, mucosa-associated lymphoid tissue.

section 22 Haematological disorders 5290 10 to 12 specific subtypes of NHL will allow a clinician to care for almost all patients with NHL. Pathobiology of lymphoma Increased understanding of the biology of the immune system has allowed the improved classification of lymphomas, and provided new prognostic information and new potential targets for therapy. Lymphomas are malignancies of lymphocytes in which the surface proteins involved in cell recognition and intracellular signalling are important in diagnosis, predicting clinical course, and therapy. Although the genetics of lymphomas are complicated, they too are beginning to be unravelled. Information gleaned from all these studies is likely to further change both the classification and therapy of the lymphomas. Immunology The recognition of new surface antigens has improved the ability to recognize specific subtypes of lymphoma. For B-cell NHL it is possible to use immunophenotyping to help identify the cell of origin of the lymphoma. For example, Burkitt lymphoma, follicular lymphoma, and some diffuse large B-cell lymphomas arise from germinal centre B cells. Other diffuse large B-cell lymphomas arise from postgerminal centre B-cells, demonstrating the biological variability of tumours that can be morphologically similar. Further insights into such phenomena are presented in the later section on genetics of lymphomas. The recognition of specific antigens by standardized antibodies has improved the accuracy of diagnosis. Some of the more com- monly recognized antigens are presented in Table 22.4.4.2. A char- acteristic pattern of occurrence can be a key factor in making an accurate diagnosis. Some types of lymphoma, such as follicular lymphoma, can be diagnosed accurately without immunological studies. Others such as all T-cell lymphomas, diffuse large B-cell lymphoma, and mantle cell lymphoma can only be accurately diag- nosed when immune markers are combined with traditional histo- logical evaluation. Genetics A theme common to malignant disorders is the abnormal ex- pression of specific genes. The search for these genes was facili- tated by the frequent occurrence of chromosomal abnormalities detectable by cytogenetic studies. These abnormalities include chromosomal deletions or deletions of parts of a chromosome, chromosomal duplications, and translocation of genetic material from one chromosome to another. Chromosomal translocations, through studying the sites of chromosome breakage, led to the discovery of a number of genes that appear to be important in lymphomagenesis or in determining the character of a particular lymphoma. The best-documented chromosomal abnormalities associated with lymphomas, along with the involved oncogenes, are presented in Table 22.4.4.3. Specific chromosomal translocations are highly associated with certain subtypes of lymphoma and thus are useful in diagnosis. These include the t(2;5) and anaplastic large cell lymphoma; the t(14;18) in follicular lymphoma; the t(8;14), t(2;8), and t(8;22) in Burkitt lymphoma; and the t(11;14) in mantle cell lymphoma. Cytogenetic studies in most patients with NHL display a large number of chromosomal abnormalities. However, only a few have been shown to be of diagnostic or prognostic significance. Genetic abnormalities determine the nature of a lymphoma by leading to the overexpression, underexpression, or abnormal expres- sion of specific

genes. The genes involved, frequently termed ‘onco- genes’, are typically those that regulate the cell cycle, differentiation, rate of proliferation, and apoptosis. Since the work of genes is done by the proteins for which they code, the under-, over-, or abnormal translation of specific proteins is an increasing subject for study. In some cases, protein translations might be abnormal despite no obvious translocation. For example, diffuse large B-cell lymphoma displays the t(14;18) in approximately 30% of patients. This trans- location involves the BCL2 gene on chromosome 18, whose protein product is involved in suppressing apoptosis (i.e. the mechanism of cell death usually triggered by chemotherapeutic agents). Tumours can overproduce the BCL-2 protein with or without the t(14;18). Overproduction of BCL-2 protein might be expected to lead to the increased survival of lymphoma cells when they are exposed to therapeutic agents. In patients with diffuse large B-cell lymphoma, poorer outcome has been associated with overproduction of the BCL-2 protein, rather than with the t(14;18). Patients with diffuse large B-cell who have both the t(8;14) and the t(14;18) are com- monly referred to as double-hit lymphomas. These patients have a poor outlook with currently available treatments, Approximately 5 to 10% of patients with diffuse large B-cell lymphoma, a rare patient with follicular lymphoma, and more than 50% of patients with the Table 22.4.4.2 Immunological markers and their targets useful in the diagnosis or management of lymphomas Marker Target CD3 T cells CD4 Helper/inducer T cells CD5 T cells, early B cells CD8 Cytotoxic/suppressor T cells and NK cells CD10 CALLA CD15 Lewis-X CD19 B4(leuk 12) CD20 B cells CD23 IgE receptor CD25 IL-2 receptor CD30 Ki-1 CD57 HNK-1 Characteristic immunophenotype of selected lymphomasa Subtype Characteristic immunophenotype Diffuse large B cell CD5− CD10+/− CD20+ CD23+/− Follicular CD5− CD10+ CD20+ CD23+/− BCL6+ Small lymphocytic/chronic lymphocytic leukaemia CD5+ CD10− CD20+ (dim) CD23+ Mantle cell CD5+ CD10− CD20+ CD23− cyclic D1+ CALLA, common acute lymphoblastic leukaemia antigen; IL-2, interleukin-2; NK, natural killer. a It is important to remember that not all cases of a particular type of lymphoma will have exactly the characteristic immunophenotype, and this does not invalidate the diagnosis.

22.4.4 Non-Hodgkin lymphoma 5291 unusual subtype high-grade B-cell lymphoma with features inter- mediate between diffuse large B-cell and Burkitt lymphoma have ‘double hits’. The discovery of genetic abnormalities in lymphomas can be ac- complished with cytogenetic analysis, fluorescent in situ hybridiza- tion (FISH), by gene arrays, and more detailed genome sequencing. Cytogenetic studies require fresh tissue. FISH studies can be done on fixed tissue, but only specific abnormalities for which probes are available can be investigated. Gene array studies are currently a research technique that allows identification of genes that are over- or underexpressed in specific specimens. They allow the ana- lysis of thousands of genes simultaneously and have shown that histologically identical groups of lymphomas can be subdivided into clinically relevant subgroups on the basis of their gene ex- pression patterns. For example, diffuse large B-cell lymphoma can be subdivided into at least three subgroups using gene expression patterns that have different clinical characteristics and/or treat- ment outcome. Similar studies have been done in other subtypes of lymphoma. At least one report of patients with follicular lymphoma suggested that survival might be more affected by the gene expres- sion pattern of infiltrating normal immune cells (i.e. a pattern char- acteristic of T lymphocytes versus one characteristic of macrophage/ dendritic cells) than by the gene expression pattern in the tumour cells themselves. Clinical features Patients with lymphoma most commonly present with lymphaden- opathy, but a variety of presentations are possible. These include systemic symptoms such as fevers, night sweats, weight loss, and pruritus, which are believed to be the result of the release of cytokines by normal or malignant cells.

Patients can present with symptoms secondary to a mediastinal or retroperitoneal mass such as superior vena cava obstruction, pleural effusion, pericardial tamponade, ab- dominal or back pain, intestinal obstruction or perforation, gastro- intestinal bleeding, or renal failure from urethral obstruction. Central nervous system (CNS) presentations include primary brain tumours, signs of meningeal involvement and spinal cord compres- sion. Patients might present with cytopenia secondary to either bone marrow involvement or autoimmune destruction of the formed elements of the blood. Symptoms secondary to the overproduction of a monoclonal immunoglobulin or hypogammaglobulinaemia can be seen. In short, the possible presentations of lymphomas are so varied that the diagnosis should be considered in many patients, and not just those presenting with lymphadenopathy or splenomegaly. Diagnosis and evaluation The diagnosis of lymphoma should always be based on evaluation by an expert haematopathologist of an adequate biopsy of a lymph node, or of an extranodal tumour mass if lymph nodes are unavailable. It is important not to handicap the haematopathologist by providing inadequate material. Needle aspirates or small biopsies should be avoided as the basis for diagnosing lymphoma whenever possible. The differential diagnosis that the pathologist considers when diag- nosing a lymphoma includes benign proliferations of lymphoid tissue, malignancies of myeloid cells, nonhaemopoietic malignan- cies, viral infections, and unusual disorders such as Castleman dis- ease and giant lymph node hyperplasia. Having tissue available for immunological studies and/or genetic studies will frequently help to confirm the diagnosis. Once the diagnosis of a type of lymphoma has been established, a series of studies should be carried out to determine the extent of dis- ease and prognosis (Box 22.4.4.3). The anatomical spread of disease is usually expressed as an Ann Arbor stage (Table 22.4.4.4). This sta- ging system was originally developed for Hodgkin lymphoma and divides patients into those with disease confined to one lymphatic site, multiple lymphatic sites on one side of the diaphragm, lymph- atic involvement on both sides of the diaphragm, and those with bone marrow involvement, liver involvement, or other extensive extranodal disease. The Ann Arbor stage also includes a suffix A or B indicating the absence (A) or presence (B) of unexplained fevers above 38°C, weight loss of more than 10% of the body weight in the preceding 6 months, or drenching night sweats. A more recent staging system has suggested removing the classification A and B for NHL. A revised classification includes stage II bulky disease defined as a single nodal mass of 10 cm or greater than a third of the transthoracic diameter at any level of thoracic vertebrae. A fluorodeoxyglucose positron emission tomography (FDG-PET)/CT scan is the

Table 22.4.4.3 Chromosomal translocations characteristic of NHL NHL subtype Translocation Genes involved Frequency Diffuse large B-cell t(3q27) BCL-6 35% t(14;18)(q32;q21) IqH, BCL-2 15–20% t(8;14)(q24;q32) MYC, IgH <5% Burkitt t(8;14)(q24;q32) MYC, IgH 100% have one of these; most commonly t(8;14) t(8;22)(q24;q11) MYC, IgL t(2;8)(p12;q24) IgK, MYC Follicular t(14;18)(q32;q21) IgH, BCL-2 c.90% Mantle cell t(11;14)(q13;q32) BCL-1, IgH

> 90% ALCL t(2;5)(p23;q35) ALK, NPM 80% of ALK + ALCLs MALT t(11;18)(q21;q21) API 2, MALT1 35% t(14;18)(q21;q32) IgH, MALT1 20% t(1;14)(p22;q32) BCL-10, IgH 10%

 preferable imaging modality for staging most lymphomas (though it is less useful in MALT and small lymphocytic lymphoma). If PET/ CT is not available, a CT can be used. At the completion of therapy, where a repeat CT may show a partial

regression of a mediastinal or retroperitoneal mass (because of a sclerotic reaction to the tumour), a PET/CT will often show a complete metabolic response. Determining how much improvement in a PET scan was required to document a complete remission limited the utility of this procedure until the development of the Deauville, or 5-point, score, which is discussed in more detail in Chapter 22.4.3. Prognostic factors Knowledge of the specific subtype of NHL is only one of two pieces of information necessary to plan the intelligent management of patients with these disorders. The other that must be available in- volves the delineation of the prognostic characteristics of the indi- vidual patient. Although it is true that follicular lymphoma has a higher median overall survival than diffuse large B-cell lymphoma, individual patients with follicular lymphoma might have a much worse survival because of adverse prognostic characteristics than an individual patient with diffuse large B-cell lymphoma who has good prognostic characteristics. Codification of these prognostic characteristics into a practical clinical tool was accomplished by a large international study that yielded the International Prognostic Index (IPI) (Table 22.4.4.5). The IPI is a summation of a number of specific adverse prognostic factors in an individual patient. The important factors include age greater than 60 years, Ann Arbor stage III/IV, serum lactate dehydrogenase (LDH) level greater than normal, reduced performance status, and multiple extranodal sites of involvement by lymphoma. The IPI is useful in essentially all types of NHL, although it was developed using patients with dif- fuse large cell lymphoma of both T- and B-cell origin. A new index for use in patients with follicular lymphoma has been developed and referred to as the FLIPI (i.e. follicular lymphoma International Prognostic Index), and others are available for mantle cell and T- cell lymphomas. The treatment plan for any individual patient with lymphoma must always include knowledge of the specific subtype of lymphoma and the patient's prognostic characteristics It is increasingly apparent that the genetic abnormalities in lymph- omas represent an important prognostic factor. It has been known for more than a decade that diffuse large B-cell lymphoma can be subdivided into two different subtypes based on patterns of gene expression, with the germinal centre B-cell subtype having a better prognosis than the activated B-cell subtype in some studies. Specific genetic abnormalities that can be recognized by FISH studies (i.e. considerably easier to perform than gene profiling) also appear to be important. For example, diffuse large B-cell lymphoma tumours that have both MYC and BCL-2 (double–hit) rearrangements have a particularly poor prognosis with currently available therapies. Box 22.4.4.3 Staging evaluation for a new patient with lymphoma • Complete history and physical examination. • Haematological studies:

— Full blood count. • Chemistry studies to measure normal organ function:

— Serum creatinine, liver function studies.

— Serum lactate dehydrogenase, β2-microglobulin and protein electrophoresis. • Imaging studies:

— Chest radiograph.

— PET/CT scan or, if not available, contrast-enhanced CT of the chest, abdomen, and pelvis. • Bone marrow biopsy. • Pregnancy test in women of child-bearing age. • Fertility counselling. • Other studies as appropriate to evaluate specific complaints and to follow up abnormal results found from the studies previously listed:

— Not appropriate if CT chest is performed. However, if performed, a chest radiograph offers an easy way to follow mediastinal or pul- monary involvement.

— Bone marrow biopsy may be omitted in diffuse large B-cell lymphoma, particularly in early stage disease, if a PET is performed because of the sensitivity of PET to detect marrow involvement.

— Other studies can be useful in particular situations. Magnetic res- onance imaging studies are particularly useful in evaluating sus- pected bone or CNS sites of involvement. Cerebrospinal fluid cytology and flow cytometry may be necessary in evaluating sus- pected CNS sites of involvement. In some patients, abdominal ultrasonography will provide a more economical way to follow intra-abdominal disease. The use of rituximab can increase the risk of hepatitis reactivation. Hepatitis B and C serologies should be performed if rituximab is being considered as a part of therapy. Baseline echocardiogram if there is a history of cardiac disease and is often performed before initiation of anthracycline. Table 22.4.4.4 The Ann Arbor staging system Stage Characteristics I 1 nodal site involved IE 1 site of localized extranodal involvement II 2 or more nodal sites involved, but only on 1 side of the diaphragm IIE 1 site of localized extranodal involvement plus regional nodes involved—all on 1 side of the diaphragm III Nodal involvement (i.e. spleen counts as a nodal site) on both sides of the diaphragm IV Bone marrow, liver, or other extensive extranodal involvement (e.g. multiple pulmonary nodules) Table 22.4.4.5 International Prognostic Index Full index Age adjusted (i.e. for patients <60 years) Prognostic factors (APLES) Prognostic factors (PLS) Age >60 years Performance status >1 Performance status ≥2 LDH >1 × normal LDH >1 × normal Stage III or IV Extranodal sites ≥2 Stage III or IV Risk category factors Risk category factors Low 0 or 1 Low 0 Low–intermediate 2 Low–intermediate 1 High–intermediate 3 High 4 or 5

22.4.4 Non-Hodgkin lymphoma 5293 General principles of lymphoma treatment Types of treatment Those treatments effective in the management of patients with cancer include surgery, radiotherapy, cytotoxic chemotherapy, and a variety of new approaches developed through increasing under- standing of the biology of the immune system. The latter include cytokines, antibodies, and attempts to direct an immune reaction against cancer. As few patients with lymphoma have truly localized disease, sur- gery has not been a major treatment modality, except for selected patients with extranodal MALT lymphomas. Since its utilization in medicine in the first part of the 20th century, radiotherapy has been a major treatment modality for patients with lymphoma, but is limited in its application by toxicity. Its curative potential depends upon being able to achieve a tumouricidal dose (typically 30–40 Gy) without irreversibly injuring normal organs. Thus, the ana- tomical site of involvement, as well as the number of sites involved, can limit the effectiveness of this treatment, since toxicity increases with the volume of tissue irradiated. If a lymphoma is truly local- ized, radiotherapy is often curative. However, most patients have oc- cult metastatic disease and cure rates are often higher when a brief course of chemotherapy precedes the radiation. Two approaches have been utilized to make radiotherapy a ‘systemic’ treatment. One involves radiation of the total body. When this is part of a haem-atopoietic stem cell transplant regimen, a total dose of 10 to 12 Gy can be administered. More recently, it has been demonstrated that it is possible to give higher doses of radiotherapy to multiple areas by attaching radioactive molecules to antibodies that home to sites of involvement by lymphoma. For example, radioimmunotherapy such as 131I-tositumomab or 90Y-ibritumomab tiuxetan have dem- onstrated significant response in patients with follicular lymphoma. Cytotoxic chemotherapeutic agents were first discovered in the 1940s when mechlorethamine (i.e. the

nitrogen mustard gas used in warfare), and subsequently methotrexate, were found to cause regressions in immune-system malignancies. A wide variety of agents have since been shown to be able to cause disease regression in many patients with lymphomas. Unfortunately, early studies showed that regressions induced by single agents were almost invariably fol- lowed by regrowth of the tumour and eventual death of the patient. In an attempt to circumvent this, combinations of chemotherapeutic agents were first utilized in the 1960s and early 1970s. The drugs were combined by attempting to choose agents with different mech- anisms of action and nonoverlapping toxicities to allow the admin- istration of doses that were near to the maximum tolerated dose with an individual agent. In both childhood acute leukaemia and Hodgkin's lymphoma, this approach was validated by the cure of a significant number of patients. Today, several combination chemo- therapy regimens with acceptable toxicity have been shown to be effective and are widely used worldwide (Table 22.4.4.6). All regimens are not equally good for treating all types of lymphoma. Very high doses of cytotoxic chemotherapeutic agents with or without radiotherapy and biologically active molecules have been utilized in the treatment of patients with lymphomas as part of the haematopoietic stem cell transplantation procedure. This involves the administration of very high doses of antilymphoma therapy in Table 22.4.4.6 Common combination chemotherapy regimens used in treating patients with non-Hodgkin lymphoma Regimen Drug Dose (mg/m2) Route Schedule CVP-R 21-day cycles Cyclophosphamide 750–1200 IV D1 Vincristine 1.4 (max. 2) IV D1 Prednisone 100 total dose (not by m2) PO D1–5 Rituximab 375 IV D1 CHOP-R 21-day cycles Cyclophosphamide 750 IV D1 Doxorubicin 50 IV D1 Vincristine 1.4 (max. 2) IV D1 Prednisone 100 total (not by m2) PO D1–5 Rituximab 375 IV D1 BR 28-day cycles Bendamustine 90 IV D1 and 2 Rituximab 375 IV D1 FCR 28-day cycles Fludarabine 25 IV D1–3 Cyclophosphamide 250 IV D1–3 Rituximab 375 IV D1 EPOCH-R 21-day cycles Rituximab 375 IV D1 Etoposide 50 IV infusion D1–4 Doxorubicin 10 IV infusion D1–4 Vincristine 0.4 IV infusion D1–4 Cyclophosphamide 750 IV D5 Prednisone 60 PO D1–5 D, day(s); IV, intravenously; PO, orally.

 an attempt to overcome presumed treatment resistance. Patients are rescued from the toxicity of treatment by the reinfusion of haemo- poietic stem cells. The patient's own haemopoietic stem cells (an autologous transplant) or those from another individual with iden- tical HLA genes (an allogeneic transplant) can be utilized. Cells for this procedure can be obtained from either bone marrow or per- ipheral blood. Autologous transplantation has been widely used for patients with lymphoma and shown to be able to cure patients with aggressive NHL. Transplantation is generally reserved for relapsed or refractory lymphoma. In aggressive NHL, a possible increased cure rate has been demonstrated by utilizing adjuvant autologous transplantation following initially effective standard chemotherapy in patients with a poor prognosis. Allogeneic transplantation, while apparently curative, has a high mortality rate. Allogeneic transplant- ation is considered in the management of high-risk chronic lymphocytic leukaemia, or in other high-risk NHLs frequently after the failure of autologous transplantation. Increasing knowledge of the immune system has further led to the recognition that a number of biologically active molecules can cause regression of lymphomas and, in some cases, impact survival. In B-cell NHL, antibodies directed against the CD20 molecule have been incorporated into clinical practice. Rituximab, obinutuzumab, and ofatumumab are commonly utilized anti-CD20 monoclonal antibodies that have been shown to be active in a variety of B-cell lymphomas. The combination of lenalidomide and rituximab has demonstrated efficacy against a variety of B-cell lymphomas. The antibody conjugate brentuximab vedotin has shown significant responses in CD30-expressing tumours. Ibrutinib is an oral irreversible inhibitor of Bruton's tyrosine

kinase (BTK), an integral component of the B-cell receptor. Ibrutinib has single-agent activity against chronic lymphocytic leukaemia, mantle cell lymphoma, and Waldenström macroglobulinaemia. Idelalisib is an oral small-molecule inhibitor of the phosphatidylinositol 3-kinase (PI3Kδ) that is highly expressed in B-cell lymphomas. Idelalisib, combined with rituximab, is active against chronic lymphocytic leukaemia/small lymphocytic lymphoma and follicular lymphoma. Venetoclax or ABT-199 is a small molecule inhibitor of BCL-2 and active against chronic lymphocytic leukaemia/small lymphocytic lymphoma. Several other agents are in development. Promising drugs include an antibody–drug conjugate (polatuzumab vedotin containing an anti-CD79B monoclonal antibody), immune checkpoint inhibitors, and anti-CD19 chimeric antigen receptor (CAR) T cells. General strategy of treatment A number of factors need to be taken into account when formu- lating a treatment recommendation for a patient with lymphoma (Box 22.4.4.4). This decision should be made in conjunction with the patient, and requires good judgement in addition to technical knowledge. The aggressiveness of the treatment that is finally chosen will often depend upon the physician's interpretation of the chances for cure. It is obvious that more toxicity will be acceptable if the goal is cure rather than palliation. For this reason, patients with defin- itely curable lymphomas, such as diffuse large B-cell lymphoma and Burkitt lymphoma, are almost always treated promptly with in- tensive regimens. By contrast, the best treatment for patients with follicular lymphoma remains a point for intense debate. Since the curability of this disease is less clear, many physicians would favour no initial therapy in an asymptomatic patient, but—as discussed later—this is not a simple decision. For most patients, the goal of therapy is to achieve a complete remission. This implies the disappearance of all symptoms and ob- jective evidence of lymphoma. In practice, a complete remission is documented by repeating all abnormal staging studies after sev- eral cycles of therapy or at the completion of the planned therapy. Documentation of complete remission is important. Patients who achieve a complete remission have a chance for cure; those who do not achieve a complete remission with initial therapy will often go directly to second-line treatments. Patients who are not cured with initial therapy, either because they do not achieve an initial remission or because they relapse from remission, are candidates for what has been termed 'salvage therapy.' These second-line regimens can regularly cause tumour re- gression in most patients with lymphoma and can occasionally pro-duce long-term, disease-free survival. However, for most patients, the only curative approach in this setting is haematopoietic stem cell transplantation. The toxicity of haematopoietic stem cell trans- plantation limits its use to patients less than 70 to 75 years of age, who have a good performance status, without serious compromise of major organ function; and to patients who do not have bulky/ chemotherapy-refractory disease. Precursor B- and T-cell lymphomas Lymphoblastic lymphoma of B-cell or T-cell origin Lymphoblastic lymphoma is a tumour of the precursor cells of T- and B-lymphocytes. It is intimately related to the acute lymphoid leukaemias, with the difference being the method of presentation. Lymphoblastic lymphoma is diagnosed when the lymphoblasts are undetectable in blood and consist of less than 25% of marrow cells. Sometimes it is difficult to determine when a patient should be said to have acute lymphoid leukaemia or lymphoblastic lymphoma, since bone marrow involvement is frequent with a lymphomatous presentation and lymphadenopathy and mediastinal mass are common in patients who present with leukaemia. Most patients with lymphoblastic lymphoma have tumours de- rived from T lymphoblasts, but approximately 15% are B cell in origin. The differential diagnosis of lymphoblastic lymphoma includes a blastic variant of mantle cell lymphoma, acute mye- loid leukaemia, and peripheral T-cell lymphoma in children and Box 22.4.4.4 Factors to consider in therapy for a patient with lymphoma • Specific type of lymphoma • Age • Performance status •

Presence of other diseases • Stage • Systemic symptoms • Pace of disease • Potential side effects • Likelihood of cure • Patient's concerns about specific treatments • Convenience • Patient's immediate and long-term goals • Quality of life

22.4.4 Non-Hodgkin lymphoma 5295 young adults. When a mediastinal mass is present in lymphoblastic lymphoma, the differential diagnosis also includes Hodgkin lymphoma, primary mediastinal B-cell lymphoma, thymoma, and germ-cell tumour. The median age of patients with lymphoblastic lymphoma is the late twenties; most patients are male with widely disseminated dis- ease and an elevated serum LDH level, and about 50% will have bone marrow involvement. In young men, testicular involvement should be ruled out with ultrasonography. Patients with lymphoblastic lymphoma who present with stage IV disease, elevated LDH levels, and bone marrow or CNS involvement have a poorer prognosis than adult patients who do not have these adverse characteristics. Patients with none of these adverse characteristics have a high cure rate with regimens such as those used for acute lymphoblastic leu- kaemia. Some patients with stage IV disease, elevated LDH levels, and bone marrow and CNS involvement can also be cured, but this is less likely. Treatment in both groups of patients should include high-dose multiagent induction, consolidation/intensification and maintenance chemotherapy, and CNS prophylaxis or treatment. Adolescents and young adults treated with paediatric acute lympho- blastic leukaemia regimens have improved survival than those treated with adult or NHL regimens. Patients with high-risk charac- teristics, or those who relapse after initial therapy, are candidates for allogeneic or autologous haematopoietic stem cell transplantation. Mature B-cell lymphomas Diffuse large B-cell lymphoma Diffuse large B-cell lymphoma is the most common type of NHL, rep- resenting approximately one-third of all patients. It most commonly presents de novo, but can also develop after histological transform- ation of an indolent lymphoma such as follicular, small lymphocytic, or MALT lymphoma. This tumour can arise in lymph nodes or may involve any extranodal site, including the CNS. Rare presentations include pleural effusions from involvement of serosal surfaces (effu- sion lymphoma) and multiple organ system dysfunction secondary to endothelial involvement (intravascular lymphomatosis). Almost all diffuse large B-cell lymphomas display the CD20 antigen, and several cytogenetic abnormalities are frequently asso- ciated (Table 22.4.4.2). The condition can be subdivided using gene microarrays into the germinal centre B-cell type, the activated B-cell type, and the mediastinal large B-cell type. These have different clinical characteristics and response to therapy (Table 22.4.4.7 and Fig. 22.4.4.1). Several other subtypes of diffuse large B-cell lymphoma deserve special mention because of unique treatment considerations. The plasmablastic subtype of diffuse large B-cell lymphoma is usu- ally CD20 negative and thus does not benefit from treatment with rituximab. Diffuse large B-cell lymphoma with rearrangements of both BCL-2 and MYC is a 'double-hit' lymphoma and has a very poor prognosis. Very intensive regimens and bone marrow trans- plantation are often used in management, but the prognosis is still poorer than for other subtypes. Diffuse large B-cell lymphomas ori- ginating in the testes, CNS, and skin require different treatment ap- proaches. Testicular diffuse large B-cell lymphoma, that is, the most frequent testicular tumour in men over the age of 60 years, has fre- quent relapses in the CNS and the contralateral testis. CNS prophy- laxis and irradiation to the opposite testis is required. Primary CNS diffuse large B-cell lymphoma does not benefit from standard re- gimens and requires treatments that penetrate the CNS including high-dose methotrexate. Certain lymphomas that originate in the skin, typically on the scalp or upper trunk, might be called diffuse large B-cell lymphoma but have an indolent course and only require local therapy. The differential diagnosis of diffuse large B-cell lymphoma includes

undifferentiated carcinoma, acute myeloid leukaemia, Hodgkin lymphoma, and extramedullary plasmacytoma. Occasional patients with diffuse large B-cell lymphoma have a large number of infiltrating T cells, and can be confused with a peripheral T-cell lymphoma. Appropriate immunological studies and genetic studies can usually resolve any confusion. The clinical characteristics of patients with diffuse large B-cell lymphoma are presented in Table 22.4.3.8. The median age at pres- entation of patients with diffuse large B-cell lymphoma is approxi- mately 64 years and there is a slight male predominance. About one-half of the patients will have stage I or II disease and about one- half will have a more widely disseminated lymphoma: approximately
Table 22.4.4.7 Recognized molecular subtypes of diffuse large B-cell lymphoma Characteristics Germinal centre B-cell type Activated B-cell type Mediastinal large B-cell lymphoma % of all patients with diffuse large B-cell lymphoma c.60 c.30 7 Median age (years) 58 66 37 % female 50 40 70 % 5-year survival (i.e. with rituximab) 70–90 60–65 80-90 1.0 0.8 0.6 0.4 0.2 0.0 0 2 4 6 8 10 Overall survival (years) Probability PMBL ABC DLBCL GCB DLBCL 5-year survival 64% 59% 30%
Fig. 22.4.4.1 Survival of patients with subtypes of diffuse large B-cell lymphoma (DLBCL) treated largely in the pre-rituximab era. ABC, activated B cell; GCB, germinal centre B cell; PMBL, primary mediastinal B-cell lymphoma.

 two-thirds will have some sign of extranodal involvement, one-third will have B-symptoms at presentation, and one-half have an elevated LDH. Bone marrow involvement is seen in approximately 15% of cases. Since the early 1970s, it has been known that patients with dif- fuse large B-cell lymphoma could sometimes be cured with combin- ation chemotherapy regimens alone—even those with disseminated disease. The most popular regimen in use today is CHOP (cyclo- phosphamide, doxorubicin, vincristine (Oncovin), and prednisone) plus the anti-CD20 monoclonal antibody rituximab. However, a large number of other regimens including ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone) plus rituximab, and EPOCH (etoposide, prednisone, vincristine, cyclo- phosphamide and doxorubicin) plus rituximab, are at least as ac- tive. Today all regimens used to treat diffuse large B-cell lymphoma will include the antibody rituximab unless the patient’s individual tumour has been shown to be CD20 negative. When a staging evalu- ation shows disease confined to one site (i.e. stage I) or two nearby sites (i.e. minimal stage II) a brief course of chemotherapy followed by radiotherapy has been the most popular treatment approach, al- though a complete course of CHOP plus rituximab might be equally effective. In patients with disseminated disease, a complete course of CHOP plus rituximab, or another active regimen plus rituximab, is standard therapy. Local radiotherapy is sometimes added to very bulky (i.e. >7.5 cm) sites of disease. In patients who present with the multiple adverse risk factors listed in the IPI, adjuvant autologous haemopoietic stem cell transplantation after achieving an initial re- mission might benefit selected patients. Lenalidomide and ibrutinib are active against diffuse large B-cell lymphoma of the ABC genetic subtype, and a combination of CHOP plus rituximab, and ibrutinib or lenalidomide appear to improve responses in early studies. Approximately 75 to 85% of patients with localized disease can be cured with CHOP and rituximab with or without radiotherapy. More than 50% of patients with more disseminated disease can be cured with combination chemotherapy regimens including rituximab. Patients who relapse from complete remission can sometimes be cured with autologous haematopoietic stem cell transplantation. Patients who remain chemotherapy sensitive after relapse have been cured approximately 40% of the time (i.e. perhaps less often after the patients has failed rituximab) while chemotherapy-resistant patients are cured only about 10% of the time.
Follicular lymphoma The second most common type of NHL is follicular lymphoma. The clinical

characteristics of patients with this disease are listed in Table 22.4.4.8. The differential diagnosis of follicular lymphoma includes benign follicular hyperplasia and follicular variants of other NHLs. Patients with follicular lymphoma are subdivided based on the number of large cells in the tumour into grade 1 (i.e. those with the least large cells), grade 2, and grade 3 (i.e. those with the most large cells). The method for assigning grade is controversial among patho- logists, whose ability to reproduce grading is much lower than their ability to reproducibly diagnose follicular lymphoma. In general, a higher proportion of large cells is associated with a higher prolif- erative rate, more rapid tumour progression, and perhaps a better response to anthracycline-containing combination chemotherapy regimens. The natural history of follicular lymphoma involves a re- duction in the degree of follicularity in the tumour over time and an increase in the proportion of large cells. Transformation—usually to diffuse large B-cell lymphoma—is recognized in approximately 20 to 40% of patients and is associated with a poor prognosis in most cases. Table 22.4.4.8 Clinical characteristics of the major subtypes of B-cell non-Hodgkin lymphoma Diffuse large B-cell lymphoma Follicular lymphoma MALT lymphoma Small lymphocytic lymphoma Mantle cell lymphoma Median age (years) 64 59 60 65 63 Percentage male 55 42 48 53 74 Stage (%): I 25 18 39 4 13 II 19 15 28 5 7 III 13 16 2 8 9 IV 33 51 31 83 71 B-symptoms (%) 33 28 19 33 28 Elevated LDH (%) 53 30 27 41 40 Reduced performance status (%) 24 9 15 11 21 Tumour mass >10 cm (%) 30 28 8 13 81 Bone marrow involvement (%) 16 47 14 72 64 Gastrointestinal tract involvement (%) 18 4 50 3

> 50 IPI score (%) 0–1 35 45 44 23 23 2–3 46 48 48 64 54 4–5 19 7 8 13 23 IPI, International Prognostic Index.

22.4.4 Non-Hodgkin lymphoma 5297 Follicular lymphomas regularly display the CD20 antigen. Most tumours will have the t(14;18) translocation and express the BCL-2 protein. Transformation to diffuse large B-cell lymphoma is frequently associated with additional cytogenetic abnormalities. Treatment approaches commonly utilized in the management of patients with follicular lymphoma are presented in Box 22.4.4.5. Asymptomatic patients with nonbulky disease and no organ com- promise are often managed with no initial therapy—a strategy that is sometimes called ‘watchful waiting’. When followed in this manner, approximately 10 to 25% of patients will undergo at least a partial spontaneous regression (i.e. what would be called a partial response if a treatment had been utilized), although these regressions are gen- erally not durable. Over time, almost all patients will progress and require therapy. There is no ‘standard’ treatment for patients with follicular lymphoma. The most often utilized initial treatments are single-agent chemotherapy including bendamustine, CVP (cyclo- phosphamide, vincristine, and prednisone), and CHOP. With few exceptions, each of these regimens will be combined with the anti- body rituximab. An increasingly popular treatment approach, and one that is sometimes utilized instead of watchful waiting, is single- agent therapy with rituximab which has been shown to delay time to starting chemotherapy, but which does not improve overall sur- vival. Recently, the combination of bendamustine and rituximab has become popular as a therapy for patients with low-grade follicular lymphoma. Although an initial study suggested this approach might be superior to CHOP and rituximab, more recent studies suggest that the two regimens have comparable outcomes. Most patients re- spond, although many will not achieve a complete remission. When ongoing or ‘maintenance’ treatment with the antibody is continued after the initial induction therapy, more

patients achieve a com- plete remission and the duration of remissions is prolonged. It is now clear that when combinations of traditional chemotherapeutic agents are combined with rituximab as initial therapy, then patients have a longer survival than when combination chemotherapy alone is utilized. Maintenance rituximab for patients achieving a remis- sion with combined chemotherapy/rituximab regimens has been shown to prolong remission duration but not overall survival. Particular treatment approaches are more appropriate for certain subsets of patients with follicular lymphoma. The rare patients with localized follicular lymphoma can be managed with radiotherapy alone. These patients have an excellent outlook with a 10-year sur- vival of 70 to 90% in most series, and approximately 40 to 50% of patients not relapsing after 10 years of follow-up. Patients with grade 3 follicular lymphoma often respond to treatments used for diffuse large B-cell lymphoma, and many physicians would favour CHOP plus rituximab (CHOP-R) as the initial treatment for these patients. Bone marrow specimens from patients with follicular lymphoma frequently test positive for the BCL2 gene rearrangement using poly- merase chain reaction (PCR) technology. Some but not all patients who achieve a complete remission will revert to a BCL-2-negative status. This test has not been widely utilized clinically since some patients who remain positive do not relapse, some patients who be- come negative do relapse, and circulating lymphoid cells in normal patients sometimes have the BCL2 gene rearrangement. This pre- sumably reflects that rearrangement of the BCL2 gene is a very early step in lymphomagenesis. Most patients with follicular lymphoma will eventually fail their initial treatment regimen, with this being especially true for pa- tients with follicular lymphoma grade 1 and grade 2. Subsequent treatments have included single drugs such as chlorambucil or fludarabine, a variety of combination chemotherapy regimens, and new drugs such as bortezomib, interferon, monoclonal antibodies (e.g. rituximab), radiolabelled antibodies, and both allogeneic and autologous haematopoietic stem cell transplantation. Several new drugs have activity in patients with follicular lymphoma. The new B-cell receptor inhibitors, idelalisib and ibrutinib, both have activity; the combination of rituximab and idelalisib appears to be particu- larly active, though with significant associated toxicities including colitis and pneumonitis. Ibrutinib has also been associated with bleeding, and this drug should be withheld in the context of sur- gical intervention. There is a 10–15% risk of developing atrial fib-rillation on ibrutinib, with older patients being more commonly affected. Both autologous and allogeneic haematopoietic stem cell transplantation can produce long-term disease-free survival in a proportion of patients with follicular lymphoma. Autologous haem- atopoietic stem cell transplantation is more effective when utilized at first relapse. Allogeneic transplantation has a much lower relapse rate than autologous transplantation, but is associated with a higher mortality rate. Overall survival of patients with follicular lymphoma is ap- proaching 20 years. The addition of rituximab to standard chemo- therapy regimens has been instrumental in effecting recent improvements to outcomes for patients with this disease. Some pa- tients survive free of disease for extended periods of time, and hope- fully this proportion will increase with new treatments. MALT lymphoma This lymphoma, also known as the extranodal marginal-zone B- cell lymphoma of MALT type, always presents in extranodal sites. A nodal presentation of a similar lymphoma is referred to as nodal marginal-zone lymphoma (see ‘Less common B-cell lymphomas’). The differential diagnosis of MALT lymphoma includes benign lymphocytic infiltration of extranodal organs and other small cell B-cell lymphomas. MALT lymphomas are tumours of CD5-negative and CD23- negative B cells that express CD20. The commonly seen cytogenetic abnormalities are listed in Table 22.4.4.2. Gastric MALT lymph- omas are associated with infection by Helicobacter pylori, thy- roid MALT lymphomas are frequently associated with Hashimoto thyroiditis, and orbital MALT lymphomas are sometimes asso- ciated with Sjögren syndrome. MALT lymphomas can undergo Box

22.4.4.5 Treatment regimens used for patients with follicular lymphoma • Close observation and no initial therapy • Radiotherapy • Single-agent therapy: chlorambucil, cyclophosphamide, bendamustine— all with rituximab—or rituximab alone • Combination chemotherapy: CHOP-R, CVP-R • Interferon-α • Radioantibodies: tositumomab, ibritumomab • Haemopoietic stem cell transplantation: autologous, allogeneic CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CVP, cyclo- phosphamide, vincristine, prednisone; R, rituximab.

section 22 Haematological disorders 5298 histological transformation to diffuse large B-cell lymphomas. After this transformation, the patient should be treated for diffuse large B-cell lymphoma. MALT lymphomas have a slight female predominance with a me- dian age at presentation of approximately 60 years. The symptoms of the disorder are those associated with involvement of the extranodal site. The disease is usually localized and the presence of systemic symptoms or elevated LDH is unusual. The characteristics of pa- tients with this lymphoma are listed in Table 22.4.4.8. Gastric MALT lymphomas are the first example of a lymphoma that can be treated by eliminating a chronic infection. If the tumour does not transform to a large cell lymphoma, and has not deeply invaded the stomach, then most patients will have their tumour re- gress with the eradication of H. pylori using a combination of two antibiotics (amoxicillin, clarithromycin or metronidazole), and proton pump inhibitors. It appears that in some patients this treat- ment might be curative. However, complete regression following eradication of H. pylori infection may take up to a year. Other local therapies are also effective. Patients with localized MALT lymph- omas can be effectively treated with local radiotherapy or, in some cases, surgery. These lymphomas also respond to rituximab, single- agent chemotherapy, and combination chemotherapy. Patients with disseminated MALT lymphomas usually respond to therapy, but are rarely curable. Most patients with localized MALT lymphoma can be cured, and the 5-year survival in such patients is approximately 90%. However, patients with disseminated disease have a more serious illness and those with a high IPI score have a 5-year survival of only 50%. Small lymphocytic lymphoma/chronic lymphocytic leukaemia Small lymphocytic lymphoma is the tissue manifestation of chronic lymphocytic leukaemia, which is covered in greater detail in Chapter 22.4.5. Patients who present predominantly with blood and bone marrow involvement will be diagnosed with chronic lympho- cytic leukaemia, and those who present with lymphadenopathy as having small lymphocytic lymphoma, although the WHO classifica- tion suggests that all these patients might have chronic lymphocytic leukaemia. Patients with plasmacytoid differentiation and mono- clonal IgM protein in the serum can present with the syndrome of Waldenström’s macroglobulinaemia (see ‘Less common B-cell lymphomas’). Small lymphocytic lymphoma makes up approximately 7% of NHL worldwide, although is more often seen in Western countries. The differential diagnosis includes other small B-cell lymphomas, and patients with small lymphocytic lymphoma can undergo histo- logical transformation to diffuse large B-cell lymphoma. This syn- drome is seen in approximately 3 to 10% of patients and is called Richter’s syndrome. It is associated with a poor prognosis. The lymphoma cells are B cells that are CD5, CD20, and CD23 positive, although the concentration of CD20 on the surface of the tumour cells is less than in most other B-cell lymphomas. Common cytogenetic abnormalities seen in chronic lympho- cytic leukaemia/small lymphocytic lymphoma include trisomy 12, del(11q), del(17p), and del (13q), with del (17p) being particularly associated with a very poor prognosis, and del(13q) as an isolated abnormality being associated with the best prognosis. Other bio- logical measurements to predict outcome in patients with chronic lymphocytic/small lymphocytic lymphoma have included the pro- portion of cells that express CD38, those that express ZAP70, and those with unmutated variable region of

immunoglobulin heavy chain (IgVH) genes. The clinical characteristics of patients with small lympho- cytic lymphoma are listed in Table 22.4.4.8. Patients with chronic lymphocytic leukaemia/small lymphocytic lymphoma some- times have acquired immunological abnormalities including hypogammaglobulinaemia, autoimmune thrombocytopenia, and autoimmune haemolytic anaemia. When present, these immune abnormalities should be treated specifically, in addition to any treatment given for the lymphoma. Hypogammaglobulinaemia accompanied by frequent episodes of serious infection should be treated with intermittent immunoglobulin infusions. Patients with chronic lymphocytic leukaemia/small lymphocytic lymphoma can be followed without therapy when they present with no systemic symptoms or organ compromise. However, most pa- tients will require treatment within the first few years of follow-up. The most popular treatments for patients with chronic lymphocytic leukaemia/small lymphocytic lymphoma contain fludarabine and cyclophosphamide in combination with rituximab. Older, frailer patients are frequently treated with chlorambucil or bendamustine combined with an anti-CD20 antibody such as rituximab, ofatumumab, or obinutuzumab. The patients most likely to respond to fludarabine, cyclophosphamide, and rituximab with long remis- sions are those with the genetic abnormality of either a 13q deletion or trisomy 12 and who have mutated IgHV genes. A number of new agents are changing the treatment paradigm for chronic lymphocytic leukaemia/small lymphocytic lymphoma. Ibrutinib, idelalisib, and venetoclax are all extremely active drugs. Ibrutinib is usually administered alone, and idelalisib is often com- bined with rituximab. Almost all patients respond to ibrutinib, al- though with all drugs of this class, there is an initial lymphocytosis followed by gradual disappearance of the abnormal cells. Most pa- tients with an excellent response to ibrutinib stay in remission for at least a few years as long as they continue taking the drug. For patients with a 17p deletion—the most adverse genetic finding— ibrutinib is the treatment of choice. However, patients treated with any of these approaches will eventually progress and require further treatment. Only a few patients are candidates for allogeneic haem- atopoietic stem cell transplantation, but this can achieve long-term disease-free survival in some cases. Mantle cell lymphoma The clinical characteristics of patients with mantle cell lymphoma are listed in Table 22.4.4.8. This lymphoma was recognized as a specific entity because of its characteristic cytogenetic abnormality, these tumours regularly manifesting the t(11;14) translocation that involves the BCL1 gene on chromosome 11 and leads to overpro- duction of the BCL-1 protein. Indeed, before the recognition of this disorder, patients with mantle cell lymphoma were placed in many other histological categories. The tumours were previously termed centrocytic lymphoma under the Kiel classification. An expert haematopathologist is important in making the diagnosis, since this lymphoma can be confused with small lymphocytic lymphoma, fol- licular lymphoma, and lymphoblastic lymphoma. Extranodal sites of involvement by mantle cell lymphoma are not unusual. Large-bowel involvement can present as the syndrome of

 lymphomatous polyposis. Patients with distal gastrointestinal tract lymphoma often have Waldeyer’s ring involvement in addition. Mantle cell lymphoma has been among the most difficult types of NHL to treat. Using standard chemotherapy regimens such as CHOP, the remission duration has been brief and the median overall survival approximately 3 to 5 years. The addition of the anti- body rituximab, combinations including bendamustine, and the use of very intensive chemotherapy regimens incorporating high doses of cytosine arabinoside have improved the response rate and remission duration. Ibrutinib is a very active drug in mantle cell lymphoma and is now approved for use for patients with re- current disease in many countries. It is likely that this drug will make a contribution to the primary therapy of patients with mantle cell

lymphoma. Other novel agents include idelalisib, bortezomib, lenalidomide, and everolimus. The combination of lenalidomide and rituximab appears to have high response rate for untreated patients in early studies. Maintenance therapy with rituximab fol- lowing the completion of initial therapy may improve survival. However, the cure of these patients with standard chemotherapy re- gimens is still uncertain, hence many patients receive autologous or allogeneic transplantation in first remission. Allogeneic transplant- ation can occasionally cure patients who have failed their primary regimen. As most patients with mantle cell lymphoma are elderly, these more aggressive treatment approaches are often inappropriate or impractical. Less common B-cell lymphomas Burkitt lymphoma was originally described by Denis Burkitt while studying an aggressive lymphoma that occurred in the jaw of children in Central Africa; the disease can also present as acute leukaemia. An association has been demonstrated between EBV infection and this lymphoma, which is much more frequent in children and young adults and in patients infected by HIV. The condition is associated with specific chromosomal translocations involving the heavy-chain immunoglobulin gene on chromosome 14 or the light-chain im- munoglobulin genes on chromosomes 2 and 22. In each case, the associated oncogene is the MYC gene on chromosome 8 (namely, t(8;14), t(2;8), and t(8;22)). The condition can frequently be cured utilizing short courses of very intensive regimens that incorporate high doses of cyclophosphamide, and with the EPOCH-R regimen. Hence the distinction between Burkitt lymphoma and diffuse large B-cell lymphoma is extremely important. The WHO now recognizes that there are some lymphomas with characteristics that are intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma where this distinction cannot be made. These lymphomas typically have a high proliferative rate and are usually treated like Burkitt lymphoma. These lymphomas often have a double hit (i.e. the presence of both the t(8;14) and the t(14;18) translocations) and have a much poorer response to therapy than either Burkitt lymphoma or diffuse large B-cell lymphoma. Nodal marginal-zone lymphoma is immunologically related to MALT lymphoma (mentioned earlier), but presents in a manner similar to follicular lymphoma. These patients respond to therapy and have an overall survival similar to those with follicular lymphoma. Splenic marginal-zone lymphoma is a rare disorder, also known as splenic lymphoma with villous lymphocytes. It is typically an in- dolent condition involving the spleen, marrow, and blood without palpable lymphadenopathy, and can be treated with splenectomy but often also responds dramatically to single-agent rituximab, now the treatment of choice. Primary mediastinal diffuse large B-cell lymphoma varies from other diffuse large B-cell lymphomas in that it occurs at a younger age and has a striking female predominance. Gene expression profiling has shown that these tumours are genetically distinct and have some similarities to nodular sclerosing Hodgkin lymphoma. However, the treatment and response to therapy are similar to that seen in the germinal centre B-cell type of diffuse large B-cell lymphomas (Table 22.4.4.7 and Fig. 22.4.4.1). Primary mediastinal lymphomas can usually be cured with treatment utilizing the CHOP-R regimen and radiotherapy to the large mediastinal mass, but the EPOCH-R regimen has a high rate of complete remission, and patients who achieve a complete remission by PET appear to not require radio- therapy. The WHO now also recognizes lymphomas whose char- acteristics are intermediate between primarily mediastinal diffuse large B-cell lymphoma and Hodgkin lymphoma, termed grey zone lymphoma. Lymphoplasmacytic lymphoma, a subtype of small lympho- cytic lymphoma (see ‘Small lymphocytic lymphoma/chronic lymphocytic leukaemia’), is the histological subtype of lymphoma seen in lymph nodes biopsied in patients with Waldenström macroglobulinaemia. The syndrome of Waldenström macro globulinaemia is characterized by excessive IgM monoclonal gammopathy and features of hyperviscosity syndrome such as blurred vision, headaches, dizziness, retinal vein engorge- ment,

epistaxis, dyspnoea, and paraesthesiae. All patients with Waldenström's macroglobulinaemia have a lymphoplasmacytic lymphoma, but all patients with lymphoplasmacytic lymphoma will not manifest the syndrome of Waldenström macroglobulinaemia. Patients with lymphoplasmacytic lymphoma can have the t(9;14) cytogenetic abnormality. More recently, a MYD88 mutation has been noted in the majority of patients. Treatment in symptom- atic patients often includes alkylator such as cyclophosphamide or bendamustine, fludarabine-based regimens or bortezomib, frequently combined with rituximab, or rituximab as a single agent. Ibrutinib has shown significant response, particularly in patients harbouring a MYD88 mutation and wild-type CXCR4. Patients with symptoms from a very high IgM level will also re- quire plasmapheresis. Mature T-cell lymphomas T-cell lymphomas are much less common than their B-cell coun- terparts, accounting for about 10% of NHL in Western countries. Mature T-cell lymphomas are frequently called 'peripheral T-cell lymphoma'. This refers not to the site of origin of the disease, but to the mature T-cell immunophenotype. Pathologists have been less accurate in diagnosing T-cell lymphomas than B-cell lymph- omas, which in part might relate to the absence of a characteristic immunophenotype for most diseases, and only a few subtypes having consistent genetic abnormalities. For T-cell lymphomas, but not for NK cell lymphomas, demonstration of rearrangements of the T-cell receptor gene will sometimes help solve difficult diagnostic dilemmas. The differential diagnosis of peripheral T-cell lymphomas includes diffuse large B-cell lymphoma and T-cell hyperpla- sias, such as are seen in viral infections and drug reactions. The

section 22 Haematological disorders 5300 characteristics of the mature T-cell lymphomas are presented in Table 22.4.4.9. Nodal T-cell lymphomas The nodal T-cell lymphomas recognized in the WHO classification in- clude peripheral T-cell lymphoma unspecified, angioimmunoblastic T-cell lymphoma, and anaplastic large cell lymphoma. Patients with peripheral T-cell lymphoma unspecified represent a heterogeneous group of NHL and are the largest subgroup of peripheral T-cell lymphomas. These tumours are generally CD3 and CD4 positive, al- though a few will be CD8 positive. Although cytogenetic abnormal- ities are frequent, there is no consistent abnormality. Most patients have widespread disease and systemic symptoms are frequent. Angioimmunoblastic T-cell lymphoma is the second most common subtype. These patients typically present with widespread disease, systemic symptoms, and frequently skin rashes, and features of immune dysregulation such as haemolytic anaemia and poly- clonal hypergammaglobulinaemia. This type of peripheral T-cell lymphoma seems somewhat more frequent in northern Europe. Anaplastic large cell lymphoma has a characteristic histological ap- pearance and consistently overexpresses the CD30 antigen. Many of the tumours have the t(2;5) translocation and overproduction of the ALK protein (in c.50% of cases), and are responsive to ALK inhibitors such as crizotinib. Patients whose tumours are ALK positive are younger, pre- dominantly male, and might have a better outlook than those whose tumours are ALK negative. Some patients have lymphoma with the histological appearance of anaplastic large cell lymphoma, but with the disease confined to the skin: these are one part of an entity that has been referred to as CD30-positive cutaneous lymphoproliferative disorders. The treatment of patients with nodal peripheral T-cell lymph- omas has been largely unsatisfactory. Localized disease is unusual and patients with disseminated disease are treated with combination chemotherapy regimens such as CHOP with or without etoposide. There is no consistently effective approach for patients with periph- eral T-cell lymphoma unspecified and angioimmunoblastic T-cell lymphomas. Novel drugs such as pralatrexate (folate analogue) and histone deacetylase inhibitors (e.g. romidepsin) have been devel- oped and are effective for a subset of patients. Patients with anaplastic large cell lymphoma are more likely to re- spond to

anthracycline-containing combination chemotherapy regi- mens. Young patients whose tumours overexpress the ALK protein are cured in more than 50% of cases. Patients with anaplastic large cell lymphoma that is either ALK positive or ALK negative usually respond to the anti-CD30 antibody conjugate brentuximab vedotin. Patients with cutaneous anaplastic large cell lymphoma have a particu- larly indolent course and often do not need to be treated aggressively. Extranodal peripheral T-cell lymphomas Mycosis fungoides or cutaneous T-cell lymphoma is an indolent lymphoma of mature T cells predominantly involving the skin. Patients who present with circulating, atypical cells (Sézary cells) and erythroderma are said to have Sézary syndrome. The median age is approximately 50 years and the disease is more common in males and black individuals. Mycosis fungoides often presents with eczematous or dermatitic skin lesions for many years, and patients will often have several skin biopsies before the diagnosis is confirmed. Lymphoma first manifests itself as superficial lesions in the skin that thicken and eventually ulcerate. In the late stages of the illness, lymphoma can metastasize to lymph nodes and visceral organs. Treatments utilized for mycosis fungoides include topical cor- ticosteroids, topical nitrogen mustard, phototherapy, psoralen ultraviolet A-range (PUVA) therapy, electron-beam radiation, interferon, vorinostat, bexarotene, and systemic cytotoxic therapy among others. Recently, brentuximab vedotin has shown improved response rates compared with methotrexate of bexarotene. Some patients with localized mycosis fungoides can be cured with radio- therapy, but most will progress. In the end stages of this disease, management of ulcerating cutaneous lesions may be difficult. The median survival from diagnosis averages over 10 years. Table 22.4.4.9 Clinical characteristics of T-cell lymphomas PTCL— unspecified ATL Angioimmunoblastic ALCL ALK+ ALCL ALK− Nasal NK/T Subcutaneous panniculitis-like Hepatosplenic Enteropathy associated Median age (years) 60 62 65 33 58 49 33 34 61 Percentage male 66 55 56 63 61 65 75 68 53 Stage (%): I 13 5 1 12 19 48 17 5 10 II 17 5 10 23 22 20 0 0 21 III 26 18 41 29 21 4 0 0 5 IV 43 73 48 36 38 33 83 95 64 B-symptoms (%) 35 31 69 60 57 46 67 84 63 Elevated LDH (%) 47 40 62 36 44 49 75 84 32 IPI score (%): 0/1 27 19 13 49 41 44 42 5 25 2/3 57 64 58 37 44 50 42 47 62 4/5 15 16 28 14 14 6 17 47 12 % 5-year survival 31 14 32 70 49 32 64 7 20 ALCL, anaplastic large cell lymphoma; ALK+/−, ALK protein positive/negative; ATL, angioimmunoblastic T-cell lymphoma; IPI, International Prognostic Index; PTCL, peripheral T-cell lymphoma; nasal NK/T, angiocentric nasal NK cell lymphoma.

22.4.4 Non-Hodgkin lymphoma 5301 A number of distinctive but unusual clinical syndromes are grouped in the category of extranodal peripheral T-cell lymphomas. These include angiocentric nasal NK cell lymphoma, which often presents with necrotic nasal or facial lesions. These patients are most often seen in South-East Asia and certain parts of Latin America. Radiotherapy is often an important part of the management of this disease. Enteropathy-type T-cell lymphoma is a rare disorder that some- times occurs in patients with gluten enteropathy. Patients are frequently malnourished, sometimes present with intestinal perfor- ation, and have a particularly poor outlook. Hepatosplenic γδ T-cell lymphoma presents as a systemic illness with sinusoidal infiltration of the liver, spleen, and bone marrow by malignant T-cells. These patients often present a diagnostic di- lemma, and treatment results have been poor. Subcutaneous panniculitis-like T-cell lymphoma is a rare disorder that presents with subcutaneous nodules and is frequently confused with panniculitis. This is true even on biopsy if the slides are not re- viewed by an expert haematopathologist. This frequently has a more indolent course than some other types of extranodal peripheral T- cell lymphoma. Adult T-cell lymphoma/leukaemia The two major manifestations of infection by HTLV-1 are tropical spastic paraparesis and adult T-cell

lymphoma/leukaemia. Patients can be in- fected with HTLV-1 through sexual transmission, blood transmission, or through breast milk. The risk of developing lymphoma in a patient infected with HTLV-1 is between 1 and 7% according to various studies. The latency between infection and the development of lymphoma aver- ages approximately 20 years. The diagnosis is established by review of an adequate biopsy by an expert haematopathologist, demonstration of a T-cell immunophenotype, and demonstration of antibodies to HTLV-

1. Most patients will have circulating tumour cells with a characteristic pleomorphic histology (flower-like or clover leaf cells). Adult T-cell lymphoma/leukaemia is most frequently seen in the southern islands of Japan and in the Caribbean. Most patients seen in Europe and North America are immigrants from those re- gions. Blood transfusion provides a possible source for infection, but screening for HTLV-1 has reduced the risk. The clinical characteristics of patients with adult T-cell lymphoma/ leukaemia vary considerably. Some patients present with an indolent disease manifested by lymphadenopathy and skin lesions and survive for extended times without specific therapy. Others present with pro- gressive lymphadenopathy, hepatosplenomegaly, skin infiltration, hypercalcaemia, lytic bone lesions, and elevated LDH levels. Although patients sometimes respond to combination chemotherapy regi- mens, complete remissions are unusual and survival is poor. Newer therapies include zidovudine and interferon, and mogamulizumab (a humanized monoclonal antibody against chemokine receptor 4). Lymphoma-like disorders Lymphadenopathy caused by infectious mononucleosis, drug re- actions to diphenylhydantoin or carbamazepine, autoimmune disorders such as rheumatoid arthritis and systemic lupus erythematosus, and bacterial infections, such as cat-scratch disease, can all be confused on biopsy with lymphoma. Castleman disease is a specific condition that can present with localized or disseminated lymphadenopathy and systemic symp- toms. The disease appears to be related to an overproduction of interleukin-6 (IL-6) and is frequently associated with infection by HHV-8. The disseminated form of Castleman disease is frequently ac- companied by anaemia and polyclonal hypergammaglobulinaemia. Patients with localized disease can frequently be treated with local therapy, while systemic disease sometimes responds to systemic glucocorticoids, combination chemotherapy regimens, autologous or allogeneic haematopoietic stem cell transplantation, rituximab, and siltuximab (antibody against IL-6). Sinus histiocytosis with massive lymphadenopathy (Rosai– Dorfman disease) typically presents with bulky lymphadenopathy in children or young adults. The disease is usually nonprogressive and self-limited. Lymphomatoid papulosis is a cutaneous lymphoproliferative disorder that can be confused with T-cell lymphoma in the skin. It is one of the CD30-positive cutaneous lymphoproliferative dis- orders. The cells in lymphomatoid papulosis stain for CD30 and have a monoclonal T-cell receptor gene rearrangement. The con- dition is characterized by waxing and waning skin lesions that usually heal leaving small scars. Although these patients have an increased risk of developing lymphoma, aggressive therapy is inappropriate. FURTHER READING Ardeshna K, et al. (2014). Rituximab versus a watch-and-wait ap- proach in patients with advanced-stage, asymptomatic, non-bulky follicular lymphoma: an open-label randomised phase 3 trial. Lancet Oncol, 15(4), 424–35. Armitage JO (2007). How I treat patients with diffuse large B-cell lymphoma. Blood, 110, 29–36. Armitage JO (2015). The aggressive peripheral T-cell lymph- omas: 2015. Am J Hematol, 90, 665–73. Barrington SF, et al. (2014). Role of imaging in the staging and re- sponse assessment of lymphoma: consensus of the International Conference on

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